Carboxylated, Heteroaryl-Substituted Chalcones as Inhibitors of Vascular Cell Adhesion Molecule-1 Expression for Use in Chronic Inflammatory Diseases

Charles Q. Meng,* Liming Ni, Kimberly J. Worsencroft, Zhihong Ye, M. David Weingarten, Jacob E. Simpson, Jason W. Skudlarek, Elaine M. Marino, Ki-Ling Suen, Charles Kunsch, Amy Souder, Randy B. Howard, Cynthia L. Sundell, Martin A. Wasserman, and James A. Sikorski

AtheroGenics, Inc., 8995 Westside Parkway, Alpharetta, Georgia 30004

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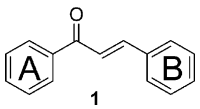
Starting from a simple chalcone template, structure−activity relationship (SAR) studies led to a series of carboxylated, heteroaryl-substituted chalcone derivatives as novel, potent inhibitors of vascular cell adhesion molecule-1 (VCAM-1) expression. Correlations between lipophilicity determined by calculated logP values and inhibitory efficacy were observed among structurally similar compounds of the series. Various substituents were found to be tolerated at several positions of the chalcone backbone as long as the compounds fell into the right range of lipophilicity. The chalcone α,β-unsaturated ketone moiety seemed to be the pharmacophore required for inhibition of VCAM-1 expression. Compound **19** showed significant antiinflammatory effects in a mouse model of allergic inflammation, indicating that this series of compounds might have therapeutic value for human asthma and other inflammatory disorders.

Introduction

VCAM-1 is a key regulator of leukocyte trafficking to sites of inflammation and has been implicated in numerous inflammatory diseases such as asthma, rheumatoid arthritis (RA), and atherosclerosis. While it is endogenously expressed at very low levels in healthy tissues, increased expression of VCAM-1 has been observed in inflammatory disease states in humans and in animal models. Increased plasma levels of soluble VCAM-1 have also been observed in some patient populations. Antibodies directed against VCAM-1 and inhibitors of VCAM-1 expression have shown antiinflammatory effects in animal models.[1−6] Natalizumab, a specific humanized monoclonal antibody to very late antigen-4 (VLA-4, the counter receptor of VCAM-1), showed efficacy in treating patients with multiple sclerosis[7,8] and might also be promising for patients with Crohn's disease.[9,10]

The chalcone class of compounds, with a common 1,3-diphenyl-2-propen-1-one framework (**1**), has been known for over a century. Natural chalcones occur mainly as petal pigments and have also been found in the heartwood, bark, leaf, fruit, and root of a variety of trees and plants. Chalcone-containing plants such as *Glycyrrhiza* species have long been used as folk remedies. Naturally occurring and synthetic chalcone compounds have shown interesting biological activity as antioxidant, antiinflammatory, anticancer, or antiinfective agents.[11] Recently we disclosed the discovery of some chalcone derivatives as inhibitors of VCAM-1 expression.[12] Herein we report on the lead evolution from our initial discovery, subsequent SAR studies, and biological activities of a novel series of carboxylated, heteroaryl-substituted chalcones.



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* Corresponding author. 678-336-2540 (Tel.); 678-336-2501 (Fax); cmeng@atherogenics.com.

Results and Discussion

The chalcone compounds reported herein were synthesized through aldol condensation between properly substituted acetophenones and benzaldehydes. Bromobenzaldehyde **2** was converted to benzothienylbenzaldehyde **3** using a modified Suzuki coupling condition. Compound **3** was then condensed with commercially available 4-acetylbenzoic acid (**4**), affording chalcone **5** after acidification.[13] Derivatization could also be carried out after the aldol condensation step. For example, compound **5** was converted to amide **6** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (Scheme 1).

In addition to the heteroaryl moiety at the 5-position, various substituents were also introduced to the 2- and/or 4-positions of ring B before the aldol condensation step. Benzaldehyde **7**, which was obtained from 5-bromo-2-hydroxy-4-methoxybenzaldehyde and thiophene-2-boronic acid using a Suzuki coupling reaction in the same fashion as in Scheme 1, was treated with mesylate **8**[14] to give aldehyde **9** (Scheme 2). The silyl protecting groups in **9** were removed after the aldol condensation step.

Alternatively, protected benzaldehyde **10** was converted to boronic ester **11** which then underwent a Suzuki coupling to give protected thiazolylbenzaldehyde **12**. Hydrolysis of the ketal of **12** gave benzaldehyde **13** (Scheme 3).

For the introduction of an indolyl group to ring B, an indole synthesis route was developed due to the limited availability of indole-boronic acids or esters for Suzuki coupling. Iodide **14**[15] was coupled using a modified Castro−Stephens reaction with 2-ethynylaniline generated in situ from 2-[(trimethylsilyl)-ethynyl]aniline to give alkyne **15**. A pivaloyl group was introduced to **15** to afford compound **16**. Treatment of compound **15** or **16** with $PdCl_2$ caused indole formation to give compound **17** or **18**, respectively. Aldol condensation of **17** or **18** with 4-acetylbenzoic acid (**4**) gave chalcone **19**. The pivaloyl group in **18** was cleaved during this aldol condensation (Scheme 4). By having the pivaloyl group, compound **16** was less prone to form side products than **15** during the indole formation step.

Compound **20**[12] (Figure 1) exhibits weak inhibitory potency on VCAM-1 expression (IC_{50} = 29 μM). When the methoxy

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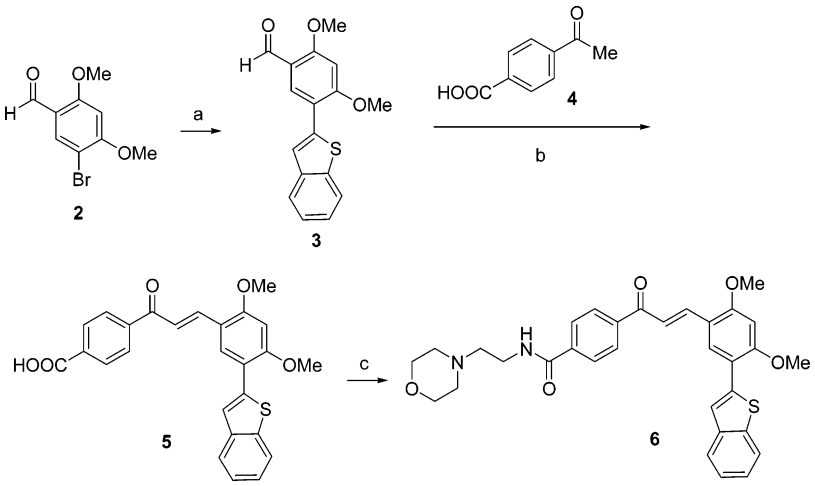
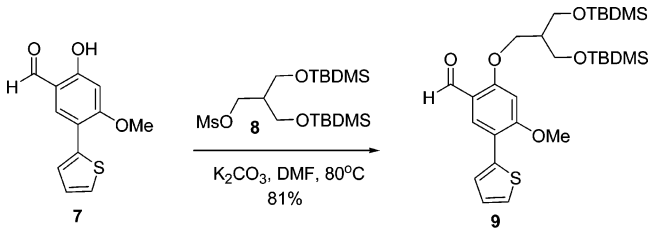
Scheme 1[a]

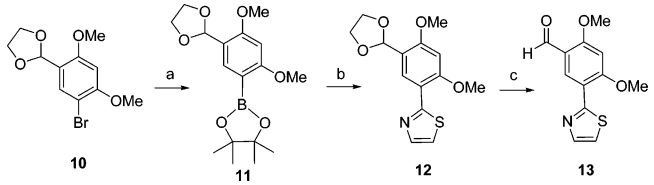


[a] Reagents and conditions: (a) benzo[*b*]thiophene-2-boronic acid, KF, Pd(*t*-$Bu_3P)_2$, THF, reflux, 97%; (b) 1. LiOMe, MeOH, DMF, rt; 2. H_2SO_4, 54%; (c) 2-(morpholin-4-yl)ethylamine, EDCI, CH_2Cl_2, rt, 77%.

Scheme 2

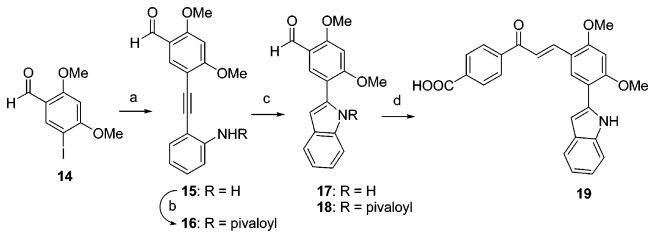


Scheme 3[a]



[a] Reagents and conditions: (a) 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 2-(dicyclohexylphosphino)biphenyl, Pd(OAc)$_2$, Et_3N, dioxane, reflux, 59%; (b) 2-bromothiazole, aqueous Na_2CO_3, $Pd(PPh_3)_4$, DME, reflux, 19% from **10** (one pot); (c) *p*-toluenesulfonic acid, acetone, water, rt, 83%.

Scheme 4[a]



[a] Reagents and conditions: (a) 2-[(trimethylsilyl)ethynyl]aniline, $PdCl_2(PPh_3)_2$, CuI, Et_3N, TBAF, THF, reflux, 92%; (b) pivaloyl chloride, CH_2Cl_2, rt, 79%; (c) $PdCl_2$, acetonitrile or DMF, reflux, 60−72%; (d) 1. **4**, LiOMe, MeOH, DMF, rt; 2. H^+, 66%.

group on ring A is replaced with a carboxy group for potential enhancement of solubility, the potency improves about 2-fold (compound **21**, IC_{50} = 15 μM). When an alkyl group isintroduced to the 5-position of ring B of **21**, the potency drops from IC_{50} of 15 μM to 22 μM (**22**). However, when a heteroaryl group is introduced to the 5-position, the potency is dramatically increased (compound **23**, IC_{50} = 3.8 μM). Thus, the combination of a carboxylic group on ring A and a heteroaryl group on ring B contributes to the observed in vitro efficacy. These findings

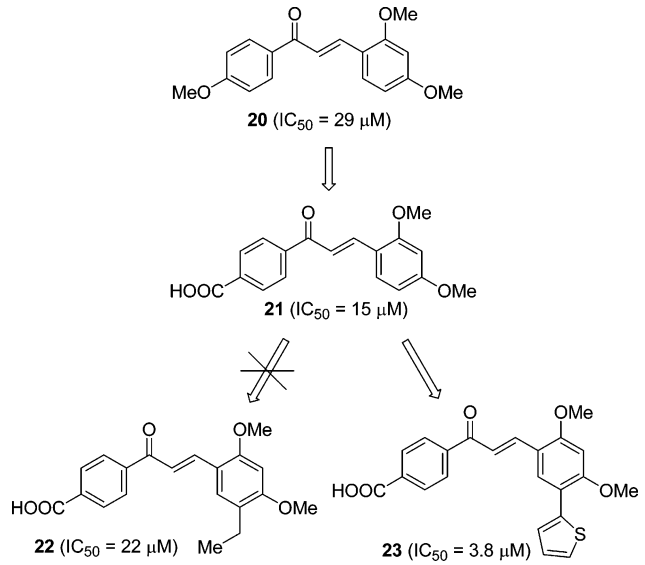
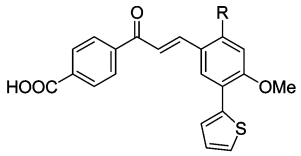


Figure 1. Evolution of carboxylated, heteroaryl-substituted chalcones.

led us to explore chalcone derivatives containing a para-carboxylated ring A and a meta-heteroaryl-substituted ring B for potent inhibitors of VCAM-1 expression.

Using **23** as a template, compounds with various substituents at the 2-position of ring B were prepared to study the SAR of that position (Table 1). When two units of ethylene glycol ether are inserted between the methoxy group and the phenyl ring of **23** at this position, the potency improves by threefold (**24**). However, when a third unit of ethylene glycol ether is added and the lipophilicity further decreased, the potency drops to IC_{50} of 4.0 μM (**25**). When the methoxy group at the 2-position of **23** is replaced with a morpholinoethoxy group the potency increases to IC_{50} of 0.8 μM (**26**), further showing that this position can tolerate bulky groups. When the morpholinoethoxy group is extended by one methylene unit to morpholinopropoxy group (**27**), the potency remains likely because the lipophilicity does not change by much although the spatial requirement is different. However, when a methylene unit of the morpholinoethoxy group of **26** is converted to a carbonyl and hence the lipophilicity is decreased significantly, the potency drops to an IC_{50} of 6.0 μM (**28**). To take advantage of the fact that the 2-position of ring B tolerates a variety of substitution, at least in the context of **23**, a diol was introduced to this position to

Table 1. Inhibiting Profile of 4-[3*E*-(2-Substituted-4-methoxy-5-thien-2-yl)acryloyl]benzoic Acids on TNF-α-Induced VCAM-1 Expression



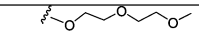
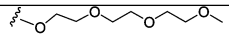
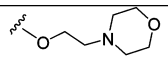
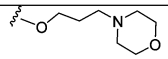
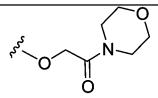
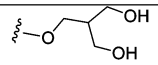
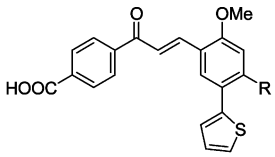
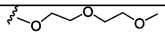
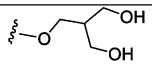
Compd.	R	VCAM-1 IC_{50} (μM)	ClogP
23	OMe	3.8±2.0	4.55
24		1.3±0.9	4.23
25		4.0±2.3	4.08
26		0.8±0.1	4.15
27		0.9±0.8	4.25
28		6.0±2.3	3.23
29		21±1	3.64

Table 2. Inhibiting Profile of 4-[3*E*-(2-Methoxy-4-substituted-5-thien-2-yl)acryloyl]benzoic Acids on TNF-α-Induced VCAM-1 Expression

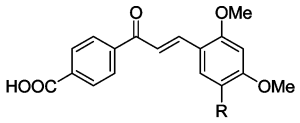


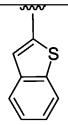
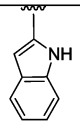
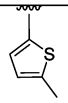
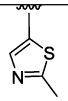
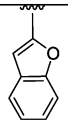
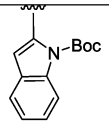
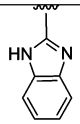
Compd. No.	R	VCAM-1 IC_{50} (μM)	ClogP
23	OMe	3.8±2.0	4.55
30	H	3.1±0.5	4.67
31	OEt	4.9±2.8	4.88
32		6.5±0.8	4.23
33		41±7	3.64

potentially increase solubility of the compound (**29**). However, **29** turned out to be 10-fold less potent, likely due to lowered lipophilicity.

Compounds with various substituents at the 4-position of ring B were also prepared using **23** as a template to probe the SAR of that position (Table 2). Removal of the methoxy group leads to a compound (**30**, IC_{50} = 3.1 μM) with comparable efficacy on VCAM-1 expression. When the methoxy group is replaced with an ethoxy group, the potency drops slightly (**31**, IC_{50} = 4.9 μM). When the length of the 4-substituent is extended to methoxyethoxyethoxy group, the potency further decreases (**32**, IC_{50} = 6.5 μM). Compound **24** (Table 1) is more potent than its regioisomer **32**. Compounds **33** (Table 2) and **29** (Table 1) are another pair of regioisomers with the same lipophilicity but different potencies (IC_{50} = 41 and 21 μM, respectively), indicating that the 2-position of ring B tolerates substitution to a greater degree than the 4-position.

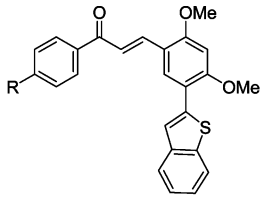
Table 3. Inhibiting Profile of 4-[3*E*-(2,4-Dimethoxy-5-heteroarylphenyl)acryloyl]benzoic Acids on TNF-α-Induced VCAM-1 Expression

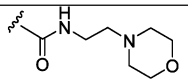
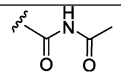
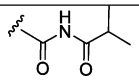


Compd. No.	R	VCAM-1 IC_{50} (μM)	ClogP
5		0.6±0.1	5.60
19		0.9±0.4	4.16
23		3.8±2.0	4.55
34		2.1±1.1	4.55
35		1.0±0.6	4.88
36		2.5±1.7	4.03
37		0.3±0.2	4.23
38		1.2±0.8	5.57
39		4.4±3.4	3.72

Compounds with various heteroaryl groups at the 5-position of ring B were prepared to study the SAR of that position (Table 3). When the thien-2-yl on ring B of **23** is replaced with thien-3-yl, the ClogP value does not change and the potency improves slightly (**34**, IC_{50} = 2.1 μM), indicating that substitution pattern of a thienyl heterocycle on ring B does not affect the efficacy. The introduction of a methyl to the thienyl ring of **23** brings the IC_{50} value from 3.8 μM to 1 μM, presumably due to an increase in lipophilicity (**35**). When a carbon atom of the

Table 4. Inhibiting Profile of 3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-1-(4-substituted-phenyl)propenones on TNF-α-Induced VCAM-1 Expression



Compd. No.	R	VCAM-1 IC_{50} (μM)	ClogP
5	-COOH	0.6±0.1	5.60
6		0.8±0.5	4.78
40	-COOEt	3.1±1.6	6.20
41	$-CONH_2$	0.2±0.1	4.95
42	-CONHOMe	0.5±0.3	5.38
43		0.8±0.6	4.90
44		1.7±1.3	6.12

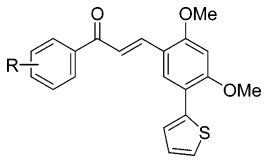
thienyl ring of **35** is replaced with a nitrogen atom (thiazole), the compound is still potent (**36**, $IC_{50} = 2.5\ \mu M$).

When the thienyl group of **23** is fused to a benzene ring, the potency is dramatically enhanced (**5**, $IC_{50} = 0.6\ \mu M$). From **23** to **35** and **5**, the ClogP value increases from 4.55 to 4.88 and 5.60, respectively, indicating a correlation between lipophilicity and potency among these compounds. The potency is retained when the benzothienyl group of **5** is replaced with a benzofuranyl (**37**, $IC_{50} = 0.3\ \mu M$) or an indolyl group (**19**, $IC_{50} = 0.9\ \mu M$). When a Boc group is introduced to the indole nitrogen of **19**, the potency is retained (**38**, $IC_{50} = 1.2\ \mu M$), further indicating that the 5-position of ring B can tolerate a bulky group. The dependence of potency on lipophilicity becomes more obvious when a nitrogen atom is incorporated into the indole ring of **19**, which lowers the ClogP from 4.16 to 3.72 and the potency from $IC_{50} = 0.9\ \mu M$ to $4.4\ \mu M$ (**39**).

To investigate the SAR of the 4-carboxylic group on ring A, compounds with various substituents on the group were prepared using **5** as a template (Table 4). Esterification of **5** increases the lipophilicity and decreases the potency (**40**, $IC_{50} = 3.1\ \mu M$). When **5** is converted to amide **41**, the potency increases ($IC_{50} = 0.2\ \mu M$) presumably due to slight lowering of lipophilicity. N-Substituted amides are also potent as long as they are in the right lipophilicity range, such as **6**, **42**, and **43**. When two additional methyl groups are introduced to the acetyl group of **43** and the lipophilicity increases, the potency decreases (compound **44**, $IC_{50} = 1.7\ \mu M$).

Compounds **23**, **45**, and **46** are regioisomers with a carboxy group at different positions of ring A (Table 5). The potency remains more or less the same when the carboxy group is moved between the 3- and 4-positions (**23**, $IC_{50} = 3.6\ \mu M$; **45**, $IC_{50} = 4.2\ \mu M$). However, with the carboxy group moved to the 2-positon, compound **46** is about 2-fold less potent than **23** or

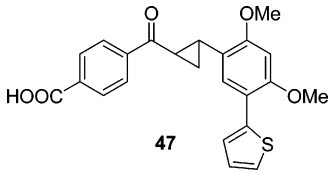
Table 5. Effects of Carboxylic Substitution Positions on TNF-α-Induced VCAM-1 Expression of Chalcone Compounds



compd. no.	R	VCAM-1 IC_{50} (μM)	ClogP
23	4-COOH	3.8 ± 2.0	4.55
45	3-COOH	4.2 ± 1.5	4.55
46	2-COOH	8.6 ± 1.5	4.55

45 although the three compounds have the same ClogP value. This shows again that spatial configuration prevails over lipophilicity in determining efficacy of compounds and the lipophilicity−potency trends are only true within *certain* closely related structures.

The α,*β*-unsaturated ketone portion of the chalcone structure is most likely the pharmacophore of this class of compounds as inhibitors of VCAM-1 expression since its reduction to the corresponding saturated ketone leads to complete loss of activity.[12] When the olefinic double bond of the α,*β*-unsaturated ketone in **23** is converted to a cyclopropane (**47**), the effect on VCAM-1 expression is eliminated, further confirming that the α,*β*-unsaturated ketone portion is essential for efficacy.



47

Since VCAM-1 is implicated in numerous inflammatory diseases, the chalcone compounds that potently inhibit the expression of VCAM-1 reported herein could work in disease models and potentially benefit patients with disorders such as asthma. A chronic inflammatory disease of the airways, asthma entails a complex interaction involving resident, recruited, and structural cells. These cells synthesize an array of cytokines and cell mediators that ultimately contribute to, or result in, bronchoconstriction, airway edema, mucus plug formation, and airway wall remodeling. Despite being a minority constituent of circulating leucocytes, eosinophils are a prominent cell type in, and their products make a major contribution to, allergic and asthmatic diseases. There is as much as a 100-fold increase in the accumulation of eosinophils versus neutrophils in the airways of patients with asthma.

Compound **19** was evaluated for its effects on eosinophil levels in bronchoalveolar lavage fluid (BALF) in a 14-day mouse model of allergic airway inflammation.[16] Dosed subcutaneously at 50, 100, and 150 mg/kg twice a day on days 11 through 13, compound **19** significantly and dose-dependently reduced eosinophil levels in BALF (Figure 2). Plasma drug levels taken roughly 3−4 h after the last dose were also dose-related and were 10, 14, and 19 μM, respectively. Compound **19** also exhibited activity when dosed at 100 mg/kg twice a day orally, reducing eosinophil levels in BALF by 43%. Compound **19** was well tolerated by the animals at all dose levels and in both subcutaneous and oral routes of dosing.

Compound **5** inhibited E-selectin and MCP-1 expression in cultured, TNF-α-induced human pulmonary arterial endothelial cells (HPAECs) besides inhibiting VCAM-1 expression. In

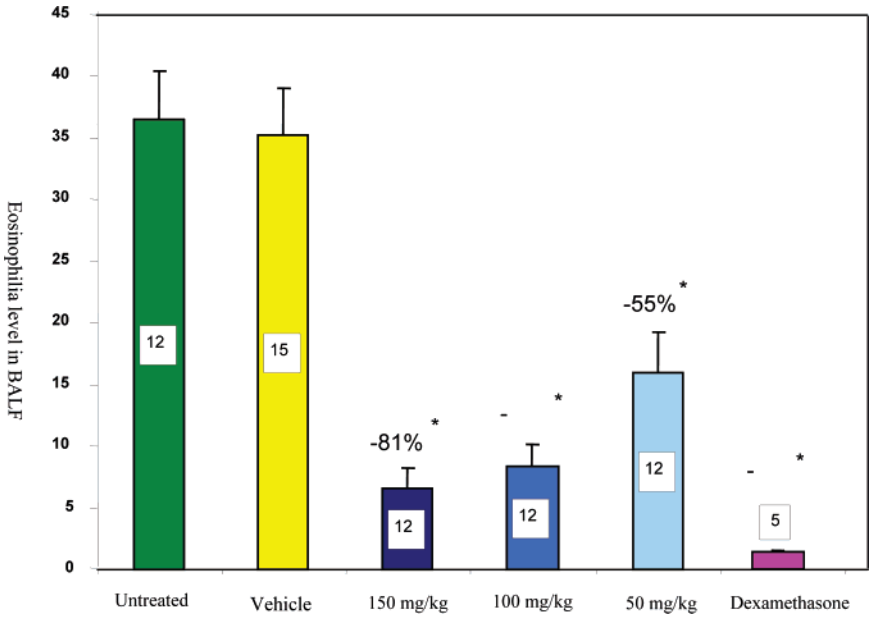


Figure 2. Inhibitory effects of compound **19** on airway eosinophilia in a mouse model. Animals were sensitized intraperitoneally (i.p.) with ovalbumin on days 0 and 5 and then challenged with aerosolized ovalbumin twice on day 12. Compound **19** was dosed on days 11 through 13 subcutaneously at 150, 100, and 50 mg/kg, twice a day. The animals were sacrificed on day 14, and BALF was collected. Cell differentials were conducted and data reported as percentage of eosinophilia in the BALF. Dexamethasone (3 mg/kg, given i.p. at the time of challenge) was used as positive control. Numbers of animals in each group are given in a square on or above each bar. Inhibition of eosinophilia in percentage is given above each bar and * indicates $p < 0.05$ as determined by ANOVA, followed by Fisher's PLSD post hoc test.

cultured, LPS-induced human peripheral blood mononuclear cells (HPBMCs), **5** completely inhibited IL-1β secretion at 5 μM. After prophylactic, subcutaneous dosing at 25 and 75 mg/kg, **5** dose-dependently inhibited both paw swelling and splenomegaly in a rat adjuvant arthritis model. It also improved histological bone resorption and inflammation scores. These data indicate that **5** has the potential to be a disease-modifying antirheumatic drug (DMARD). Compound **5** also inhibited paw swelling in a dose-dependent manner when dosed therapeutically and showed oral efficacy when dosed prophylactically in this model.[17]

In an ovalbumin-sensitized/challenged mouse model of allergic asthma, compound **5** dose-dependently inhibited airway and tissue eosinophilia, reduced serum IgE levels, and reduced elevated lung mRNA levels of T helper 2 (Th2) cytokines such as IL-4, IL-13, and IL-5 without affecting mRNA levels of Th1 cytokines such as IFN-γ and IL-2. Compound **5** also reduced airway hyperresposiveness in this model.[18]

In summary, a series of novel carboxylated, heteroaryl-substituted chalcone derivatives has been discovered as potent inhibitors of VCAM-1 expression. SAR studies have shown that a variety of substituents can be tolerated at several positions of the chalcone backbone. The α,β-unsaturated ketone moiety of the chalcone seems to be the pharmacophore of this series of compounds for inhibition of VCAM-1 expression. No other structural features are essential for potency though a correlation between lipophilicity and inhibitory efficacy has been observed among structurally similar compounds within the series. A representative compound (**19**) of the series showed significant antiinflammatory effects in a mouse model of allergic inflammation, indicating that this series of compounds might have therapeutic value for human asthma and other inflammatory disorders.

Experimental Section

Chemistry. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a QE300 spectrometer and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as internal standard. Mass spectra were obtained on a VG 70S (for EI) or Micromass Q-TOF (for ES) instrument. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Silica gel 60 (E. Merck, 230−400 mesh) was used for preparative column chromatography. Calculated logP was obtained by using ChemDraw Ultra 7.0. All compounds reported herein had 95% or higher purity according to ^{1}H NMR spectra and analytical HPLC.

5-(Benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (3). 5-Bromo-2,4-dimethoxybenzaldehyde (20 g), benzo[*b*]thiophene-2-boronic acid (16 g), and THF (200 mL) were sequentially charged into a clean reaction vessel fitted with a reflux condenser, mechanical stirrer, and nitrogen inlet adapter. Nitrogen was bubbled into the resulting solution for 20 min followed by the sequential addition of KF (10 g) and Pd(*t*-Bu$_3$P)$_2$ (0.417 g). The solution was immediately heated to 60 °C and aged for 1.5 h. Upon completion, as determined by HPLC, the reaction was diluted with H_2O (200 mL) and transferred to a separatory funnel containing EtOAc (200 mL) and H_2O (200 mL). The layers were cut, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic cuts were filtered through a prewashed pad of Solka-Floc (5 g). The pad of Solka-Floc and spent catalyst were washed with fresh EtOAc (200 mL), and this wash was combined with the batch. The resultant filtrate was batch concentrated and solvent switched to 33 wt % 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde in THF in preparation for crystallization. (Note: The internal temperature during batch concentration should be kept above 45 °C to prevent premature crystallization.) The resulting THF solution of 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde was then charged with heptane (20 mL) and slowly cooled to rt. Crystallization was then completed with the slow addition of heptane (175 mL) and cooling to 4 °C. After being aged for 1 h, the batch was filtered and then dried on a filter funnel under a stream of N_2. The semiwet cake was then transferred to clean trays and dried to a constant weight in a vacuum oven (40 °C, 20 in Hg), affording 23.74 g (97% yield) of the title compound as a light orange crystalline solid, mp 134−136 °C. ^{1}H NMR ($CDCl_3$): δ 10.36 (s, 1H), 8.20 (s, 1H), 7.83−7.78 (m, 2H), 7.68 (s, 1H), 7.36−7.27 (m, 2H), 6.54 (s, 1H), 4.06 (s, 3H), 4.00 (s, 3H).

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic Acid (5). To a solution of 4-acetylbenzoic acid (1.50 g, 9.1 mmol) and 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde

(3.27 g, 11.0 mmol) in DMF (76 mL) was added a solution of sodium hydroxide (5 M, 7.3 mL, 36.5 mmol). The reaction mixture was allowed to stir at rt for 2 h and was then diluted with water to a volume of 150 mL. The solution was washed with dichloromethane and acidified with concentrated sulfuric acid to pH = 3. The resulting solution was then extracted with dichloromethane. The dichloromethane extract was washed with brine, dried over sodium sulfate, and concentrated. The resulting oily product solidified in ethanol. The solid was further stirred in ethanol for 1 day and collected by filtration. The solid was washed with ethanol, then dried in vacuo to afford the title compound as a yellow solid (2.2 g, 54%), mp 223−224 °C (dec). ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 8.21 (d, 2H), 8.07 (m, 3H), 7.93 (m, 3H), 7.82 (d, 1H), 7.32 (m, 2H), 6.86 (s, 1H), 4.08 (s, 3H), 4.00 (s, 3H). Anal. ($C_{26}H_{20}O_5S$•1/6H_2O): C, H, S.

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-(2-morpholin-4-yl-ethyl)-benzamide (6). To a solution of 4-[3*E*-(5-benzo[*b*]thien-2-yl-2,4-dimethoxyphenyl)-acryloyl]-benzoic acid (0.44 g, 1 mmol) and 2-morpholin-4-yl-ethylamine (0.18 mL) in dichloromethane (20 mL) was added EDCI (0.38 g, 2 mmol), and the mixture was stirred at rt for four h. It was poured into brine (100 mL) and extracted with dichloromethane (2 × 50 mL). The organic phase was dried and evaporated. Chromatography (dichloromethane/methanol 50:1) gave the title compound as a yellow solid (0.43 g, 77%). ^{1}H NMR ($CDCl_3$): δ 8.12 (d, J = 16 Hz, 1H), 8.09 (d, J = 8 Hz, 2H), 7.95 (s, 1H), 7.90 (d, J = 8 Hz, 2H), 7.77−7.85 (m, 2H), 7.68 (s, 1H), 7.56 (d, J = 16 Hz, 1H), 7.29−7.40 (m, 2H), 6.80−6.85 (br s, 1H), 6.58 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.75 (t, J = 5 Hz, 4H), 3.59 (q, J = 5 Hz, 2H), 2.64 (t, J = 5 Hz, 2H), 2.53 (t, J = 5 Hz, 4H). Anal. ($C_{32}H_{32}N_2O_5S$•H_2O): C, H, N.

2-Hydroxy-4-methoxy-5-thien-2-yl-benzaldehyde (7). 2-Hydroxy-4-methoxybenzaldehyde (6.0 g, 39 mmol) was dissolved in dichloromethane (50 mL) and cooled with an ice/water bath. Bromine (6.8 g, 43 mmol) in dichloromethane (2 mL) was added dropwise to the cooled solution and stirred for 2 h at 0 °C. The mixture was warmed to rt and stirred for an additional 1 h, and the resulting yellow precipitate was collected. Recrystallization (ethyl acetate/hexanes) yielded 7.1 g (80%) of 5-bromo-2-hydroxy-4-methoxybenzaldehyde as white needles, mp 63−64 °C. ^{1}H NMR ($CDCl_3$): δ 11.43 (s, 1H), 9.69 (s, 1H), 7.68 (s, 1H), 6.48 (s, 1H), 3.95 (s, 3H). Anal. ($C_8H_7BrO_3$): calcd C 41.59, H 3.05; found C 41.86, H 3.05.

5-Bromo-2-hydroxy-4-methoxybenzaldehyde (1.5 g, 6.5 mmol) and thiophene-2-boronic acid (0.91 g, 7.1 mmol) were dissolved in tetrahydrofuran (15 mL). Nitrogen was bubbled into the solution for 10 min followed by the sequential addition of potassium fluoride (0.80 g, 14 mmol, spray-dried) and bis(tri-*t*-butylphosphine)-palladium (0) (0.033 g, 0.065 mmol). The solution was immediately heated to 60 °C and aged for 1.5 h. Upon completion, as determined by HPLC, the reaction was diluted with water (25 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over sodium sulfate and concentrated to a brown solid. Silica gel chromatography (ethyl acetate/hexanes, 1:3) gave 1.46 g (97%) of the title compound as a yellow solid, mp 118−119 °C. ^{1}H NMR ($CDCl_3$): δ 11.48 (s, 1H), 9.79 (s, 1H), 7.72 (s, 1H), 7.37 (dd, J = 3.6 Hz, 1H), 7.31 (dd, J = 5.1, 1.5 Hz, 1H), 7.08 (dd, J = 5.1, 3.6 Hz, 1H), 6.54 (s, 1H), 3.98 (s, 3 H). Anal. ($C_{12}H_{10}O_3S$): C, H, S.

Methanesulfonic Acid 3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propyl Ester (8). To a solution of 3-(*tert*-butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propan-1-ol [14] (25.0 g, 74.3 mmol) and triethylamine (22.6 g, 223 mmol) in dichloromethane (150 mL) at 0 °C was added mesyl chloride (12.8 g, 111 mmol), and the resulting slurry was stirred at 0 °C for 15 min and allowed to warm to rt. The solution was stirred for an additional 3 h at rt and diluted with water (130 mL) and ethyl acetate (350 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (1 × 150 mL). The combined organic extracts were washed with saturated sodium bicarbonate (1 × 200 mL) and 50% sodium chloride (2 × 200 mL), dried over sodium sulfate, and concentrated to afford 29.5 g (97%) of the title compound as a yellow oil (97% yield). ^{1}H NMR ($CDCl_3$): δ 4.29 (d, 2H, J = 5.7 Hz), 3.61−3.68 (m, 4H), 2.99 (s, 3H), 2.04−2.11 (m, 1H), 0.88 (s, 18H), 0.049 (s, 12H). HRMS (ESI) calcd for $C_{17}H_{40}O_5SSi_2$: 413.2213; found: 413.2226.

2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propoxy]-4-methoxy-5-thien-2-yl-benzaldehyde (9). To a solution of 2-hydroxy-4-methoxy-5-thien-2-yl-benzaldehyde (10.0 g, 42.7 mmol) in DMF (100 mL) was added potassium carbonate (11.8 g, 85.4 mmol), and the resulting yellow slurry was heated to 80 °C. Once at 80 °C, **8** (19.5 g, 46.9 mmol) was added dropwise and the reaction was stirred for an additional 24 h at 80 °C and cooled to rt. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were sequentially washed with saturated sodium bicarbonate (1 × 150 mL), water (1 × 150 mL), and brine (1 × 150 mL), dried over sodium sulfate, and concentrated to a brown oil. Silica gel chromatography (0−10% ethyl acetate in hexanes) gave 19.0 g (81%) of the title compound as an off-white solid, mp 91−92 °C. ^{1}H NMR ($CDCl_3$): δ 10.37 (s, 1H), 8.12 (s, 1H), 7.44 (dd, J = 3.6, 1.2 Hz, 1H), 7.29 (d, J = 5.1 Hz, 1H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 6.54 (s, 1H), 4.19 (d, J = 6.0 Hz, 2H), 3.99 (s, 3H), 3.72−3.82 (m, 4H), 2.28 (pentet, J = 6.0 Hz, 1H), 0.88 (s, 18H), 0.048 (s, 12H). MS (EI) m/z = 550 ([M]$^+$, 100%). Anal. ($C_{28}H_{46}O_5SSi_2$): C, H, S.

2-(5-Bromo-2,4-dimethoxy-phenyl)-[1,3]dioxolane (10). 5-Bromo-2,4-dimethoxybenzaldehyde (4.92 g, 20.1 mmol) was dissolved in benzene (41 mL). Ethylene glycol (3 mL, 54 mmol) and *p*-toluenesulfonic acid (25 mg, 0.13 mmol) were added, and the solution was refluxed with a Dean−Stark trap attached. After 6 h, the reaction was cooled and washed with water (1 × 20 mL), saturated $NaHCO_3$ (1 × 20 mL), and water (1 × 20 mL). The organic phase was dried over sodium sulfate, filtered, concentrated, and dried to provide 5.32 g of the title compound as a faint yellow oil which solidified upon standing (92% yield). ^{1}H NMR ($CDCl_3$): δ 7.67 (s, 1H), 6.47 (s, 1H), 6.06 (s, 1H), 4.11−4.13 (m, 2H), 3.98−4.03 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H).

2-(5-[1,3]Dioxolan-2-yl-2,4-dimethoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (11). 2-(5-Bromo-2,4-dimethoxyphenyl)-[1,3]dioxolane (4.78 g, 10.5 mmol) was dissolved in dioxane (75 mL), and the solution was purged with nitrogen for 15 min. $Pd(OAc)_2$ (188 mg, 0.84 mmol), Et_3N (6.91 mL, 49.6 mmol), and 2-(dicyclohexylphosphino)biphenyl (1.16 g, 3.31 mmol) were added. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (3.6 mL, 24.8 mmol) was then added slowly, accompanied by gas evolution and the darkening of the reaction solution. The solution was heated at reflux for 2.5 h and then cooled. Saturated NH_4Cl (60 mL) and water (20 mL) were added, and the solution was extracted with EtOAc (1 × 100 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography (1:1 EtOAc/hexanes in a column prewashed with 5% Et_3N in 1:1 EtOAc/hexanes) to provide 3.27 g of the title compound as a yellow solid (with some starting borolane present), 59% yield. ^{1}H NMR ($CDCl_3$): δ 7.85 (s, 1H), 6.39 (s, 1H), 6.07 (s, 1H), 4.13−4.18 (m, 2H), 3.98−4.02 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 1.33 (s, 9H).

2-(5-[1,3]Dioxolan-2-yl-2,4-dimethoxy-phenyl)-thiazole (12). 2-(5-Bromo-2,4-dimethoxy-phenyl)-[1,3]dioxolane (1.50 g, 5.19 mmol) was dissolved in dioxane (10 mL). $Pd(OAc)_2$ (59 mg, 0.26 mmol), Et_3N (2.9 mL, 21 mmol), and 2-(dicyclohexylphosphino)-biphenyl (363 mg, 1.04 mmol) were added, and the solution was purged with nitrogen for 15 min. 4,4,5,5-Tetramethyl-[1,3,2]-dioxaborolane (1.1 mL, 16.2 mmol) was then added slowly, accompanied by gas evolution and the darkening of the reaction solution. The solution was heated at reflux for 1.5 h and then cooled. Na_2CO_3 (2 M, 7.8 mL, 15.6 mmol) and then 2-bromothiazole (0.48 mL, 5.3 mmol) were added, and the solution was heated to 100 °C for 6 h. Water (30 mL) was added and the solution extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was washed with water (1 × 10 mL), then dried over sodium sulfate, filtered, and concentrated to a dark oil. The oil was purified *via* silica gel

chromatography (30−50% EtOAc/hexanes) to provide 286 mg of the title compound as a semi-pure yellow oil (19% yield). ^{1}H NMR ($CDCl_3$): δ 8.54 (s, 1H), 7.85 (d, J = 3 Hz, 1H), 7.29 (d, J = 4 Hz, 1H), 6.50 (s, 1H), 6.13 (s, 1H), 4.09−4.16 (m, 2H), 4.00 (s, 3H), 3.89 (s, 3H), 3.78−3.87 (m, 2H).

2,4-Dimethoxy-5-thiazol-2-yl-benzaldehyde (13). 2-(5-[1,3]-Dioxolan-2-yl-2,4-dimethoxy-phenyl)-thiazole (286 mg, 0.97 mmol) was dissolved in acetone (20 mL), and *p*-toluenesulfonic acid (13 mg, 0.068 mmol) and water (0.5 mL) were added. The solution was stirred overnight at rt, then diluted with water (25 mL) and extracted with EtOAc (3 × 25 mL). The organic phase was washed with saturated $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, filtered, and concentrated. Silica gel chromatography (2.5% MeOH/CH_2Cl_2) provided 202 mg of the title compound as an off-white solid (83% yield). ^{1}H NMR ($CDCl_3$): δ 10.34 (s, 1H), 8.86 (s, 1H), 7.89 (d, J = 3 Hz, 1H), 7.36 (d, J = 4 Hz, 1H), 6.56 (s, 1H), 4.12 (s, 3H), 4.02 (s, 3H).

5-Iodo-2,4-dimethoxybenzaldehyde (14). To a solution of 2.4-dimethoxybenzaldehye (20.0 g, 120.4 mmol) in methanol (550 mL) was added iodine monochloride (23.5 g in 60 mL methanol) dropwise over 20 min at ambient temperature. The solution was allowed to stir at this temperature. HPLC showed about 94% conversion after 3 h. The reaction mixture was then poured into a solution of HCl (0.5 M, 600 mL). The precipitate was collected by filtration, washed with water, and dried in vacuo (40 °C) to give a crude product. The crude product was further purified by recrystallization from THF/heptane (1:1) to give the title compound as an off-white solid (27.5 g, mp 170−172 °C). The mother liquid was concentrated to dryness. The residual material was dissolved in EtOH (100 mL) and acetone (20 mL) followed by addition of water (20 mL) to give additional product (3.12 g, mp 169−171 °C). Overall isolated yield of this reaction was 87.5%. ^{1}H NMR ($CDCl_3$): δ 10.20 (s, 1H), 8.22 (s, 1H), 6.39 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H). HRMS calcd for $C_9H_9IO_3$: 291.9596 (M^+), found: 291.9602. Anal. ($C_9H_9IO_3$): C, H; I: calcd 43.3, found 43.3.

5-(2-Aminophenylethynyl)-2,4-dimethoxybenzaldehyde (15). To a solution of 5-iodo-2,4-dimethoxybenzaldehyde (11.7 g, 40 mmol) in 250 mL of THF were added $PdCl_2(PPh_3)_2$ (0.56 g, 0.8 mmol), CuI (0.3 g, 1.6 mmol), Et_3N (6.06 g, 60 mmol), and 2-[(trimethylsilyl)ethynyl]aniline (7.92 g, 42 mmol). The mixture was stirred to a homogeneous solution, and then TBAF (10.4 g, 40 mmol) was added. The reaction mixture was aged at rt for 4 h and then filtered. The filtrate was concentrated to about 50 mL, and the precipitate was filtered to give a first portion of the title compound (8.5 g) as light yellow crystals. The filtrate was concentrated, and the residue was recrystallized from EtOAc/hexanes to give 1.85 g of additional product (total 10.35 g, 92%), mp 180−181 °C. ^{1}H NMR ($CDCl_3$): δ 10.30 (s, 1H), 7.99 (s, 1H), 7.36 (d, J = 8 Hz, 1H), 7.11−7.17 (m, 1H), 6.69−6.75 (m, 2H), 6.46 (s, 1H), 4.41 (brs, 2H), 4.02 (s, 3H), 4.00 (s, 3H). HRMS calcd for $C_{17}H_{15}NO_3$: 281.1052 (M^+), found: 281.1056. Anal. ($C_{17}H_{15}NO_3$): C, H, N.

***N*-[2-(5-Formyl-2,4-dimethoxyphenylethynyl)phenyl]-2,2-dimethylpropionamide (16).** Pyridine (12.6 mL, 156.24 mmol) was added to a suspension of 5-(2-aminophenylethynyl)-2,4-dimethoxybenzaldehyde (20.90 g, 74.4 mmol) in anhydrous methylene chloride (572 mL) and chilled to 0 °C. The reaction mixture was treated dropwise with pivaloyl chloride (9.25 mL, 75.1 mmol) and then aged at rt for 2 h. The reaction was quenched with 1 N HCl (200 mL), and the layers were cut. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness to afford 21.47 g (79%) of the title compound as a light brown solid. ^{1}H NMR (DMSO-d_6): δ 10.14 (s, 1H), 8.74 (br s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.80 (s, 1H), 7.50 (dd, J = 1.2, 7.8 Hz, 1H), 7.35 (dt, 1.8, 9.3 Hz, 1H), 7.12 (t, J = 9.0 Hz, 1H), 6.82 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 1.23 (s, 9H).

5-(1*H*-Indol-2-yl)-2,4-dimethoxybenzaldehyde (17). A solution of $PdCl_2$ (0.066 g, 0.373 mmol) in 200 mL of acetonitrile was heated to reflux. To this solution was added 5-(2-amino-phenylethynyl)-2,4-dimethoxybenzaldehyde (1.4 g, 5 mmol) portion by portion slowly so that no cloudiness of the solution occurred. After the addition, the reaction was kept at reflux for another 10 min. Then the mixture was cooled to rt and filtered. The filtrate was treated with 5 g of 3-mercaptopropyl functionalized silica gel with stirring for 30 min and filtered. The filtrate was concentrated, and the residue was recrystallized from EtOAc/hexane to give 0.84 g (60%) of the title compound. ^{1}H NMR (DMSO-d_6): δ 11.29 (br s, 1H), 10 24 (s, 1H), 8.10 (s, 1H), 7.47 (d, J = 8 Hz, 1H), 7.37 (d, J = 7 Hz, 1H), 7.01−7.05 (m, 1H), 6.91−6.95 (m, 1H), 6.85−6.86 (m, 2H), 4.06 (s, 3H), 3.99 (s, 3H).

5-[1-(2,2-Dimethylpropionyl)-1*H*-indol-2-yl]-2,4-dimethoxybenzaldehyde (18). *N*-[2-(5-Formyl-2,4-dimethoxy-phenylethynyl)-phenyl]-2,2-dimethylpropionamide (19.86 g, 54.4 mmol) was dissolved in nitrogen-purged DMF (189 mL) and heated to 80 °C, followed by the addition of palladium(II) chloride (754 mg). After 1 h, the reaction mixture was diluted with water (300 mL) and extracted with EtOAc (2 × 200 mL). The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to a brown oil. The oil was purified by silica gel chromatography (30−50% ethyl acetate/hexanes) to yield 14.31 g (72%) of the title compound as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 10.21 (s, 1H), 7.69 (s, 1H), 7.57 (d, J = 37.8 Hz, 1H), 7.30 (d, J = 8.10 Hz, 1H), 7.20 (t, J = 6.9 Hz, 1H), 7.12 (t, J = 6.9 Hz, 2H), 6.85 (s, 1H), 6.70 (s, 1H), 4.00 (s, 3H), 3.87 (s, 3H), 0.95 (s, 9H).

4-{3*E*-[5-(1*H*-Indol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic Acid (19). The title compound was prepared by condensing 5-(1*H*-indol-2-yl)-2,4-dimethoxy-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**. Red solid, mp 210−212 °C, 66% yield. ^{1}H NMR (Acetone-d_6): δ 10.53 (br, s, 1H), 8.32 (s, 1H), 8.14−8.21 (m, 5H), 7.89 (d, J = 15 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.38 (d, J = 7 Hz, 1H), 6.97−7.07(m, 3H), 6.87(s, 1H), 4.07 (s, 3H), 4.02(s, 3H). MS m/z = 427 ([M]$^+$). HMRS (EI) calcd for $C_{26}H_{21}NO_5$: 427.1420, found: 427.1435. Anal. ($C_{26}H_{21}NO_5 \cdot 1/4H_2O$): C, H, N.

4-[3*E*-(2,4-Dimethoxy-phenyl)-acryloyl]-benzoic Acid (21). 4-[3*E*-(5-Bromo-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid was prepared in a similar manner as described for compound **5**. ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 8.21 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 2H), 7.95 (d, J = 16 Hz, 1H), 7.84 (d, J = 16 Hz, 1H), 6.78(s, 1H), 3.93 (s, 6H).

4-[3*E*-(5-Bromo-2,4-dimethoxy-phenyl)-acryloyl]-benzoic acid (0.83 g, 2.0 mmol) was suspended in 20 mL of acetonitrile, and the mixture was bubbled with N_2 for 15 min. Pyrimidine-5-boronic acid (0.25 g, 2.0 mmol) and $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) were added, and the mixture was bubbled with N_2 for 10 min. Then, 5 mL of $NaCO_3$ (2M) was added. The mixture was stirred at reflux overnight under N_2. Upon cooling, the mixture was filtered and the filtrate was acidified to pH 1 with 3 N HCl. The yellow precipitate was filtered and purified by column chromatography (10% MeOH in dichloromethane) to give 100 mg of the title compound (instead of the expected Suzuki coupling product) as a yellow solid, mp 189−191 °C. ^{1}H NMR (DMSO-d_6): δ 8.13 (d, J = 8 Hz, 2H), 8.04 (d, J = 8 Hz, 2H), 7.98 (d, J = 15 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.73 (d, J = 15 Hz, 1H), 6.58−6.62(m, 2H), 3.87 (s, 3H), 3.81 (s, 3H). MS m/z: 312([M]$^+$, 45%), 281 (100%). HMRS calcd for $C_{18}H_{16}O_5$: 313.1076 (M + H), found: 313.1067. Anal. ($C_{18}H_{16}O_5 \cdot 1/5H_2O$): C, H.

4-[3*E*-(5-Ethyl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic Acid (22). To a solution of *N*-methylpyrrole (0.81 g, 10 mmol) in 50 mL of THF was added *t*-BuLi (1.7 M in pentane, 7.1 mL, 12 mmol) at 0 °C and the mixture stirred at rt for 1 h. BEt_3 (1.0 M in THF, 12 mL, 12 mmol) was added, and the mixture was stirred for another 1 h. 5-Bromo-2,4-dimethoxybenzaldehyde (3.7 g, 15 mmol) and $PdCl_2(PPh_3)_2$ (0.35 g, 0.5 mmol) were added to the mixture, and the mixture was stirred at 60 °C for 30 min. Upon cooling, 50 mL of NaOH (10%) and 5 mL of H_2O_2 (30%) were added at 0 °C and the mixture was stirred for 10 min. The mixture was extracted with EtOAc, and the combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to give 5-ethyl-2,4-dimethoxy-benzaldehyde (instead of the expected Suzuki coupling product). ^{1}H NMR ($CDCl_3$): δ 10.30 (s, 1H), 7.64 (s, 1H), 6.40 (s,

1H), 3.92 (s, 3H), 3.93 (s, 3H), 2.56 (q, $J = 7$ Hz, 2H), 1.16 (t, $J = 7$ Hz, 3H).

The title compound was prepared in a similar manner as described for compound **5** from 5-ethyl-2,4-dimethoxy-benzaldehyde. Yellow solid, mp 192−194 °C. ^{1}H NMR (acetone-d_6): δ 8.11−8.15 (m, 5H), 7.73 (d, $J = 16$ Hz, 1H), 7.67 (s, 1H), 6.71 (s, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 2.56 (q, $J = 7$ Hz, 2H), 1.14 (t, $J = 7$ Hz, 3H). HMRS (EI) calcd for $C_{20}H_{20}O_5$: 340.1311, found: 340.1305. Anal. ($C_{20}H_{20}O_5 \cdot 1/3H_2O$): C, H.

4-[3*E*-(2,4-Dimethoxy-5-thien-2-yl-phenyl)-acryloyl]-benzoic Acid (23). 5-Bromo-2,4-dimethoxybenzaldehyde (20.3 g), thiophene-2-boronic acid (11.6 g) and THF (200 mL) were sequentially charged into a clean reaction vessel fitted with a reflux condenser, mechanical stirrer, and nitrogen inlet adapter. Nitrogen was bubbled into the resulting solution for 20 min followed by the sequential addition of KF (10.1 g), and Pd(*t*-$Bu_3P)_2$ (0.424 g). The solution was immediately heated to 60 °C and aged for 1.5 h. The reaction was diluted with H_2O (200 mL) and transferred to a separatory funnel containing EtOAc (200 mL) and H_2O (200 mL). The layers were cut, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic cuts were filtered through a prewashed pad of Solka-Floc (5 g). The pad of Solka-Floc and spent catalyst were washed with fresh EtOAc (200 mL), and this wash was combined with the batch. The resultant filtrate was concentrated to dryness. The crude product was dissolved in THF (38 mL) and crystallized upon heptane (152 mL) addition. The product was filtered and then dried to a constant weight in the vacuum oven (38 °C, 20 in Hg), affording 19.32 g (94% yield) of the desired 2,4-dimethoxy-5-thien-2-yl-benzaldehyde as a light off-white solid, mp 125−126 °C. ^{1}H NMR ($CDCl_3$): δ 10.34 (s, 1H), 8.12 (s, 1H), 7.44 (dd, $J = 3.5$ and 1.5 Hz, 1H), 7.31 (dd, $J = 5.2$ and 1.5 Hz, 1H), 7.07 (dd, $J = 5.2$ and 3.5 Hz, 1H), 6.51 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H).

2,4-Dimethoxy-5-thien-2-yl-benzaldehyde (7.81 g), 4-acetylbenzoic acid (4.9 g), MeOH (60 mL), and DMF (150 mL) were sequentially charged into a clean reaction vessel fitted with a stir bar and nitrogen inlet adapter. After complete dissolution, LiOMe (4.60 g) was added and the resulting solution was aged for 5 h. The reaction was diluted with H_2O (200 mL) and transferred to a separatory funnel containing *i*-PrOAc (100 mL). The layers were cut, and the aqueous layer was acidified to pH 1 with 3 N HCl. The resulting precipitate was filtered and then dried on the filter funnel under a stream of N_2. The crude product was then dissolved in THF (60 mL) and crystallized with the addition of heptane (60 mL). The product was filtered and then dried to a constant weight in the vacuum oven affording 8.9 g (75%) of the title compound as a yellow solid, mp 213−216 °C. ^{1}H NMR ($CDCl_3$): δ 8.20 (d, $J = 8.5$ Hz, 2H), 8.09 (d, $J = 16.1$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 2H), 7.85 (s, 1H), 7.52 (d, $J = 16.1$ Hz, 1H), 7.40 (m, 1H), 7.30 (dd, $J = 5.2$ and 1.7 Hz, 1H), 7.08 (dd, $J = 5.2$ and 3.6 Hz, 1H), 6.53 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H). EIMS $m/z = 394$ (M^+). Anal. ($C_{22}H_{18}O_5S$): C, H, S.

4-(3*E*-{4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thien-2-yl-phenyl}-acryloyl)-benzoic Acid (24). To a solution of 2-hydroxy-4-methoxy-5-thien-2-yl-benzaldehyde (**7**, 0.10 g, 0.43 mmol) in *N*,*N*-dimethylformamide (3 mL) was added potassium carbonate (0.18 g, 1.3 mmol), and the resulting yellow slurry was heated to 80 °C. Once at 80 °C, 1-bromo-2-(2-methoxyethoxy)ethane (0.24 g, 1.3 mmol) was added dropwise in three equal portions with stirring at 1 h intervals. After the last addition, the reaction was stirred for an additional 1 h at 80 °C and cooled to rt. The mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were sequentially washed with a saturated ammonium chloride solution (1 × 15 mL), water (1 × 15 mL), and brine (1 × 15 mL), dried over sodium sulfate, and concentrated to a brown oil. Silica gel chromatography (ethyl acetate/hexanes, 4:1) afforded 0.13 g (87%) of 4-methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thien-2-yl-benzaldehyde as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.12 (s, 1H), 7.44 (dd, $J = 3.6$, 1.5 Hz, 1H), 7.30 (d, $J = 1.5$ Hz, 1H), 7.07 (dd, $J = 5.1$, 3.6 Hz, 1H), 6.57 (s, 1H), 4.33 (t, $J = 4.2$ Hz, 2H), 4.00 (s, 3H), 3.94 (t, $J = 4.2$ Hz, 2H), 3.74 (m, 2H), 3.59 (m, 2H), 3.40 (s, 3H). HRMS (EI) calcd for $C_{17}H_{20}O_5S$: 336.1031, found: 336.1027.

4-Methoxy-2-[2-(2-methoxyethoxy)ethoxy]-5-thien-2-yl-benzaldehyde (0.13 g, 0.37 mmol) and 4-acetylbenzoic acid (0.061 g, 0.37 mmol) were dissolved in a tetrahydrofuran−methanol solution (2 mL, 7:3). After complete dissolution, lithium methoxide (0.057 g, 1.5 mmol) was added, and the resulting bright orange slurry was stirred in the dark at rt for 4 h. Upon completion, as determined by HPLC, the mixture was diluted with water (10 mL), acidified with a 1 N hydrochloric acid, and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude oil was taken up in ethyl alcohol (3 mL) and warmed to 60 °C to obtain complete dissolution and allowed to cool to rt. The resulting precipitate was collected and dried *in vacuo* to yield 0.14 g (85%) of the title compound as a yellow solid, mp 145−146 °C. ^{1}H NMR (DMSO-d_6) δ 8.19−8.22 (m, 3H), 8.09 (d, $J = 8.4$ Hz, 2H), 7.91−8.03 (m, 3H), 7.66 (dd, $J = 3.6$, 1.5 Hz, 1H), 7.52 (d, $J = 5.1$ Hz, 1H), 7.13 (dd, $J = 5.1$, 3.9 Hz, 1H), 6.88 (s, 1H), 4.36 (t, $J = 4.2$ Hz, 2H), 4.00 (s, 3H), 3.88 (t, $J = 4.2$ Hz, 2H), 3.63−3.67 (m, 2H), 3.45−3.48 (m, 2H), 3.22 (s, 3H). Anal. calcd for $C_{26}H_{26}O_7S$: C, H, S.

4-[3*E*-(4-Methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thien-2-yl-phenyl)-acryloyl]-benzoic Acid (25). Methanesulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester was prepared in an analogous fashion as described for compound **8** using 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethanol. The crude orange oil was dried in vacuo to give the expected product (oil) and was used without any further purification (99%). ^{1}H NMR ($CDCl_3$): δ 4.37−4.40 (m, 2H), 3.76−3.78 (m, 2H), 3.61−3.70 (m, 6H), 3.53−3.57 (m, 2H), 3.38 (s, 3H), 3.08 (s, 3H). MS (ESI) $m/z = 243$ ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_8H_{18}O_6S$: 243.0902, found: 243.0914.

4-Methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thien-2-yl-benzaldehyde was prepared in an analogous fashion as described for compound **9** using methanesulfonic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester and 2-hydroxy-4-methoxy-5-thien-2-yl-benzaldehyde. Silica gel chromatography (ethyl acetate/hexanes, 8:1) gave the expected product as a pale yellow oil (70%). ^{1}H NMR ($CDCl_3$): δ 10.38 (s, 1H), 8.12 (s, 1H), 7.44 (d, $J = 3.6$ Hz, 1H), 7.30 (d, $J = 5.4$ Hz, 1H), 7.07 (dd, $J = 5.4$, 3.6 Hz, 1H), 6.57 (s, 1H), 4.31 (t, $J = 4.8$ Hz, 2H), 3.99 (s, 3H), 3.94 (t, $J = 4.8$ Hz, 2H), 3.74−3.78 (m, 2H), 3.62−3.69 (m, 4H), 3.53−3.56 (m, 2H), 3.37 (s, 3H). MS (EI) $m/z = 380$ ([M]$^+$, 100%).

The title compound was prepared by condensing 4-methoxy-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-5-thien-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**. Yellow solid, mp 137−138 °C, 82% yield. ^{1}H NMR (DMSO-d_6): δ 8.20−8.23 (m, 3H), 8.09 (d, $J = 8.3$ Hz, 2H), 8.01 (m, 2H), 7.66 (d, $J = 3.6$ Hz, 1H), 7.52 (d, $J = 5.1$ Hz, 1H), 7.13 (dd, $J = 5.1$, 3.6 Hz, 1H), 6.88 (s, 1H), 4.37 (t, $J = 3.6$ Hz, 2H), 4.01 (s, 3H), 3.89 (t, $J = 3.6$ Hz, 2H), 3.64−3.67 (m, 2H), 3.53−3.56 (m, 2H), 3.47−3.50 (m, 2H), 3.36−3.95 (m, 2H), 3.19 (s, 3H). MS (ESI) $m/z = 527$ ([M + H]$^+$, 100%). Anal. ($C_{28}H_{30}O_8S$): C, H, S.

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thien-2-yl-phenyl]-acryloyl}-benzoic Acid Hydrochloride (26). 4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thien-2-yl-benzaldehyde was prepared in an analogous fashion as described for compound **24** using 4-(2-chloroethyl)morpholine and 2-hydroxy-4-methoxy-5-thien-2-yl-benzaldehyde. Silica gel chromatography (80−100% ethyl acetate in hexanes and then 5% methanol in methylene chloride) gave the expected product as an off-white solid (81%). ^{1}H NMR ($CDCl_3$): δ 10.36 (s, 1H), 8.12 (s, 1H), 7.44 (dd, $J = 3.6$, 1.5 Hz, 1H), 7.30 (dd, $J = 5.1$, 1.5 Hz, 1H), 7.07 (dd, $J = 5.1$, 3.6 Hz, 1H), 6.53 (s, 1H), 4.27 (t, $J = 6.3$ Hz, 2H), 4.00 (s, 3H), 3.72−3.76 (m, 4H), 2.89 (t, $J = 6.3$ Hz, 2H), 2.60−2.63 (m, 4H). MS (ESI) $m/z = 348$ ([M + H]$^+$, 100%). HRMS (EI) calcd for $C_{18}H_{21}NO_4S$: 347.1191, found: 347.1188.

4-Methoxy-2-(2-morpholin-4-yl-ethoxy)-5-thien-2-yl-benzaldehyde (0.15 g, 0.43 mmol) and 4-acetylbenzoic acid (0.071 g, 0.43 mmol) were dissolved in a DMF/methanol solution (3.0 mL, 7:3).

After complete dissolution, lithium methoxide (0.065 g, 1.7 mmol) was added and the resulting bright orange slurry was stirred in the dark at rt for 2 h. Upon completion, as determined by HPLC, the mixture was diluted with water (10 mL), acidified with a 1 N hydrochloric acid solution, and extracted with an ethyl acetate/tetrahydrofuran mixture (1:1, 6 × 20 mL). The combined organic extracts were dried over sodium sulfate and evaporated to dryness. The crude solid was slurried in ethyl alcohol (5 mL) to remove residual impurities, and the resulting solid was collected on filter paper and dried in vacuo to yield 0.21 g (98%) of the title compound as a dark yellow solid, mp: 255 °C (dec). ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1H), 8.26 (d, J = 8.7 Hz, 2H), 8.11 (d, J = 8.7 Hz, 2H), 8.08 (s, 1H), 7.95 (d, J = 15.9 Hz, 1H), 7.71 (d, J = 3.3 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H), 7.15 (dd, J = 4.5, 3.3 Hz, 1H), 6.94 (s, 1H), 4.68 (br s, 2H), 4.04 (s, 3H), 3.98 (br s, 2H), 3.81−3.88 (br m, 2H), 3.70 (brs, 2H), 3.54−3.58 (br m, 2H), 3.29 (br s, 2H). MS (ESI) m/z = 494 ([M + H]$^+$, 100%). Anal. ($C_{27}H_{27}NO_6S$·HCl): C, H, N, S; Cl: calcd 6.69, found 6.16.

4-{3*E*-[4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thien-2-yl-phenyl]-acryloyl}-benzoic Acid Hydrochloride (27). 4-Methoxy-2-(3-morpholin-4-yl-propoxy)-5-thien-2-yl-benzaldehyde was prepared in a similar manner as described for **24**, 78% yield. ^{1}H NMR (DMSO-d_6): δ 10.21 (s, 1 H), 7.88 (s, 1H), 7.48 (d, J = 5.4 Hz, 1H), 7.45 (d, J = 3.9 Hz, 1H), 7.06 (dd, J = 5.1, 3.9 Hz, 1H), 6.82 (s, 1H), 4.24 (t, J = 6.3 Hz, 2H), 4.00 (s, 3H), 3.53 (t, J = 5.1 Hz, 4H), 2.34 (t, J = 4.5 Hz, 4H), 1.93 (pentet, J = 6.6 Hz, 2H).

The title compound was prepared by condensing 4-methoxy-2-(3-morpholin-4-yl-propoxy)-5-thiophen-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, 72% yield, mp 188−191 °C (dec). ^{1}H NMR (DMSO-d_6): δ 12.72 (br s, 1 H), 11.08 (br s, 1H), 8.33 (s, 1H), 8.19 (d, J = 8.1 Hz, 2H), 8.02−8.08 (m, 3H), 7.89 (d, J = 15.6 Hz. 1H), 7.65 (d, J = 3.3 Hz, 1H), 7.49 (d, J = 4.5 Hz, 1H), 7.10 (t, J = 5.1 Hz, 1H), 6.84 (s, 1H), 4.30 (t, J = 6.0 Hz, 2H), 3.98 (s, 3H), 3.84 (br s, 4H), 3.21−3.51 (m, 6H), 2.08−2.16 (m, 2H). MS m/z = 508 ([M + H]$^+$, 100%). Anal. ($C_{28}H_{29}NO_6S$·HCl·H_2O): C, H, S.

4-{3*E*-[4-Methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thien-2-yl-phenyl]-acryloyl}-benzoic Acid (28). 4-Methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thien-2-yl-benzaldehyde was prepared in an analogous fashion as described for **24** using 4-(2-chloroacetyl)-morpholine. Silica gel chromatography (80% ethyl acetate/hexanes to 100% ethyl acetate) gave the expected product as a pale yellow solid, mp 200−201 °C. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 8.12 (s, 1H), 7.44 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 5.1 Hz, 1H), 7.08 (dd, J = 5.1, 3.6 Hz, 1H), 6.74 (s, 1H), 4.89 (s, 2H), 4.00 (s, 3H), 3.67 (brs, 8H). MS (ESI) m/z = 362 ([M + H]$^+$, 100%). Anal. ($C_{18}H_{19}NO_5S$): C, H, N, S.

The title compound was prepared by condensing 4-methoxy-2-(2-morpholin-4-yl-2-oxo-ethoxy)-5-thien-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; orange solid, mp 231−233 °C, 70% yield. ^{1}H NMR (DMSO-d_6): δ 8.28−8.35 (m, 3H), 8.21 (s, 1H), 8.07−8.11 (m, 3H), 7.66 (d, J = 3.3 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 7.13 (dd, J = 5.1, 3.3 Hz, 1H), 6.87 (s, 1H), 5.13 (s, 2H), 4.00 (s, 3H), 3.65 (brm, 4H), 3.54−3.55 (m, 4H). MS (EI) m/z = 507 ([M]$^+$, 100%). Anal. ($C_{27}H_{25}NO_7S$·1/2EtOH): C, H, N, S.

4-{3*E*-[2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thien-2-yl-phenyl]-acryloyl}-benzoic Acid (29). 2-(3-Hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thien-2-yl-benzaldehyde was prepared by treating compound **9** with tetrabutylammonium fluoride in THF. Silica gel chromatography (ethyl acetate/hexanes, 1:9) gave the expected product as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 10.17 (s, 1H), 8.03 (s, 1H), 7.43 (dd, J = 3.6, 1.2 Hz, 1H), 7.31 (d, J = 5.1 Hz, 1H), 7.08 (dd, J = 5.1, 3.6 Hz, 1H), 6.58 (s, 1H), 4.32 (d, J = 6.0 Hz, 2H), 4.01 (s, 3H), 3.95−3.99 (m, 4H), 2.51 (t, J = 5.1 Hz, 2H), 2.33 (pentet, J = 5.4 Hz, 1H). MS (EI) m/z = 322 ([M]$^+$, 100%). HRMS (EI) calcd for $C_{16}H_{18}O_5S$: 322.0875, found: 322.0873.

The title compound was prepared by condensing 2-(3-hydroxy-2-hydroxymethyl-propoxy)-4-methoxy-5-thien-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; light orange solid, mp 219−220 °C, 61% yield. ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 8.20 (d, J = 7.5 Hz, 2H), 8.05−8.11 (m, 3H), 7.93 (d, J = 16.2 Hz, 1H), 7.67 (d, J = 3.0 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 7.13 (dd, J = 5.1, 3.0 Hz, 1H), 6.88 (s, 1H), 4.66 (brs, 2H), 4.23 (d, J = 6.3 Hz, 2H), 4.01 (s, 3H), 3.55−3.66 (m, 4H), 2.09−2.14 (m, 1H). MS (ESI) m/z = 469 ([M + H]$^+$, 100%). Anal. ($C_{25}H_{24}O_7S$·H_2O): C, H, S.

4-[3*E*-(2-Methoxy-5-thien-2-yl-phenyl)-acryloyl]-benzoic Acid (30). 2-Methoxy-5-(thien-2-yl)-benzaldehyde was prepared from 5-bromo-2-methoxybenzaldehyde and thiophene-2-boronic acid in a similar manner as described for compound **3**. ^{1}H NMR ($CDCl_3$): δ 10.49 (s, 1H), 8.07 (d, J = 3 Hz, 1H), 7.79 (dd, J = 3, 9.0 Hz, 1H), 7.28−7.26 (m, 2H), 7.09−7.06 (m, 1H), 7.02 (d, J = 9 Hz, 1H), 3.97 (s, 3H).

The title compound was prepared by condensing 2-methoxy-5-(thien-2-yl)-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp 195−196 °C. ^{1}H NMR (DMSO-d_6): δ 8.23−8.20 (m, 3H), 8.08−7.96 (m, 4H), 7.67 (dd, J = 2.1, 6.8 Hz, 1H), 7.55 (d, J = 3.8 Hz, 1H), 7.49 (d, J = 5.1 Hz, 1H), 7.16−7.11 (m, 2H), 3.90 (s, 3H). MS m/z = 364 (M$^+$, 100%). Anal. ($C_{21}H_{16}O_4S$): C, H, S.

4-[3*E*-(4-Ethoxy-2-methoxy-5-thien-2-yl-phenyl)-acryloyl]-benzoic Acid (31). 5-Bromo-4-hydroxy-2-methoxy-benzaldehyde was prepared in an analogous fashion as described in section for compound **7** using 4-hydroxy-2-methoxybenzaldehyde. The crude solid was slurried in water to remove residual HBr and dried in vacuo to give the bromide as an off-white solid (98%), mp 199−201 °C. ^{1}H NMR (DMSO-d_6): δ 11.58 (s, 1H), 10.07 (s, 1H), 7.75 (s, 1H), 6.69 (s, 1H), 3.87 (s, 3H). MS (EI) m/z = 230 ([M]$^+$, 100%). Anal. ($C_8H_7BrO_3$·1/4H_2O): calcd C 40.79, H 3.21, found C 40.66, H 3.01.

4-Hydroxy-2-methoxy-5-thien-2-yl-benzaldehyde was prepared in an analogous fashion as described for compound **7**. Silica gel chromatography (ethyl acetate/hexanes, 2:1) gave the expected product as a solid (85%), mp 200 °C (dec). ^{1}H NMR ($CDCl_3$): δ 10.31 (s, 1H), 7.89 (s, 1H), 7.42 (dd, J = 4.8, 1.2 Hz, 1H), 7.14−7.19 (m, 2H), 6.59 (s, 1H), 6.14 (brs, 1H), 3.94 (s, 3H). MS (EI) m/z: 234 ([M]$^+$, 100%). Anal. ($C_{12}H_{10}O_3S$·H_2O): calcd C 57.13, H 4.79, S 12.71, found C 57.16, H 4.47, S 12.48.

Reaction of 4-hydroxy-2-methoxy-5-thien-2-yl-benzaldehyde and (2-ethoxy-5-hydroxymethyl-[1,3]dioxolan-4-yl)methanol was preformed under Mitsunobu conditions using triphenylphosphine and diethyl azodicarboxylate in THF. However, the expected product, 4-(2-ethoxy-5-hydroxymethyl-[1,3]dioxolan-4-ylmethoxy)-2-methoxy-5-thien-2-yl-benzaldehyde, was not obtained. Instead, 4-ethoxy-2-methoxy-5-thien-2-yl-benzaldehyde was formed *via* cleavage of the cyclic ethyl orthoformate group under the reaction conditions. Silica gel chromatography (ethyl acetate/hexanes, 1:2) gave 0.16 g (90%) of 4-ethoxy-2-methoxy-5-thien-2-yl-benzaldehyde, mp 101−103 °C. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 8.15 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H), 7.07 (dd, J = 5.2, 3.6 Hz, 1H), 6.50 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 1.59 (t, J = 7.2 Hz, 3H). MS (EI) m/z = 262 ([M]$^+$, 100%). HMRS (EI) calcd for $C_{14}H_{14}O_3S$: 262.0664, found: 262.0667.

The title compound was prepared by condensing 4-ethoxy-2-methoxy-5-thien-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp 210−212 °C, 76% yield. ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 1H), 8.23 (d, J = 9.0 Hz, 2H), 8.06−8.11 (m, 3H), 7.92 (d, J = 16.2 Hz, 1H), 7.71 (d, J = 3.9 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 7.13 (dd, J = 5.1, 3.9 Hz, 1H), 6.82 (s, 1H), 4.33 (q, J = 6.1 Hz, 2H), 3.99 (s, 3H), 1.48 (t, J = 6.1 Hz, 3H). MS (ESI) m/z = 409 ([M + H]$^+$, 100%). Anal. ($C_{23}H_{20}O_5S$·1/6H_2O): C, H, S.

4-(3*E*-{2-Methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thien-2-yl-phenyl}-acryloyl)-benzoic Acid (32). To a solution of 4-hydroxy-2-methoxy-5-thien-2-yl-benzaldehyde and tri(ethylene glycol) monomethyl ether (0.38 g, 3.2 mmol) in tetrahydrofuran (20 mL) was added triphenylphosphine (0.84 g, 3.2 mmol), and the resulting

mixture was cooled to 0 °C. Diethyl azodicarboxylate (0.55 g, 3.2 mmol) was then added dropwise, stirred at 0 °C for 30 min, and allowed to warm to rt. The solution was stirred for an additional 24 h and concentrated under reduced pressure to a brown oil. Silica gel chromatography (ethyl acetate/hexanes, 8:1) afforded 0.31 g (45%) of the expected 2-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thien-2-yl-benzaldehyde as a viscous clear oil. ^{1}H NMR ($CDCl_3$): δ 10.34 (s, 1H), 8.13 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.30 (t, J = 5.1 Hz, 1H), 7.06 (dd, J = 5.1, 3.6 Hz, 1H), 6.56 (s, 1H), 4.34 (t, J = 5.1 Hz, 2H), 3.94 (t, J = 5.1 Hz, 2H), 3.96 (s, 3H), 3.72−3.75 (m, 2H), 3.56−3.59 (m, 2H), 3.39 (s, 3H). MS (ESI) m/z = 337 ([M + H]$^+$, 100%). HRMS (EI) calcd for $C_{17}H_{20}O_5S$: 336.1031, found: 336.1028.

The title compound was prepared by condensing 2-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-5-thien-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp 174−175 °C, 61% yield. ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 8.23 (d, J = 8.1 Hz, 2H), 8.05−8.11 (m, 3H), 7.91 (d, J = 15.3 Hz, 1H), 7.72 (d, J = 2.7 Hz, 1H), 7.52 (d, J = 4.2 Hz, 1H), 7.11−7.15 (m, 1H), 6.86 (s, 1H), 4.39 (t, J = 3.9 Hz, 2H), 3.99 (s, 3H), 3.89 (t, J = 3.9 Hz, 2H), 3.64 (t, J = 3.9 Hz, 2H), 3.48 (t, J = 3.9 Hz, 2H), 3.25 (s, 3H). MS (ESI) m/z = 483 ([M + H]$^+$, 100%). Anal. ($C_{26}H_{26}O_7S$): C, H, S.

4-{3*E*-[4-(3-Hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thien-2-yl-phenyl]-acryloyl}-benzoic Acid (33). 4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propoxy]-2-methoxy-5-thien-2-yl-benzaldehyde was prepared in an analogous fashion as described for compound **9** using methanesulfonic acid 3-(*tert*-butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propyl ester. Silica gel chromatography (ethyl acetate/hexanes, 1:6) gave the expected product as a pale green solid, 90% yield. ^{1}H NMR ($CDCl_3$): δ 10.34 (s, 1H), 8.13 (s, 1H), 7.41 (dd, J = 3.6, 1.2 Hz, 1H), 7.28 (dd, J = 5.1, 1.2 Hz, 1H), 7.05 (dd, J = 5.1, 3.6 Hz, 1H), 6.54 (s, 1H), 4.22 (d, J = 5.7 Hz, 2H), 3.96 (s, 3H), 3.80 (d, J = 5.7 Hz, 4H), 2.33 (pentet, J = 5.7 Hz, 1H), 0.88 (s, 18H), 0.012 (s, 12H). MS (ESI) m/z = 551 ([M + H]$^+$, 100%). HRMS (EI) calcd for $C_{28}H_{46}O_5SSi_2$: 550.2604, found: 550.2593.

To a solution of 4-[3-(*tert*-butyl-dimethyl-silanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-propoxy]-2-methoxy-5-thien-2-yl-benzaldehyde (0.78 g, 1.41 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 3.0 mL, 2.9 mmol), and the mixture was stirred at rt for 30 min. The reaction was diluted with ethyl acetate (50 mL) and washed with a 50% ammonium chloride solution (1 × 30 mL), water (2 × 30 mL), and brine (1 × 30 mL), dried over sodium sulfate, and concentrated to a crude yellow solid. Silica gel chromatography afforded 0.37 g (99%) of the expected 4-(3-hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thiophen-2-yl-benzaldehyde as a pale yellow solid, 90% yield, mp 144−145 °C. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 8.10 (s, 1H), 7.38 (dd, J = 3.6, 1.5 Hz, 1H), 7.30 (dd, J = 5.1, 1.5 Hz, 1H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 6.59 (s, 1H), 4.35 (d, J = 6.0 Hz, 2H), 4.02 (t, J = 4.8 Hz, 4H), 3.96 (s, 3H), 2.33 (pentet, J = 6.0 Hz, 1H), 1.89 (t, J = 4.8 Hz, 2H). MS (ESI) m/z = 323 ([M + H]$^+$, 100%).

The title compound was prepared by condensing 4-(3-hydroxy-2-hydroxymethyl-propoxy)-2-methoxy-5-thien-2-yl-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp 199−201 °C, 60% yield. ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 1H), 8.23 (d, J = 8.7 Hz, 2H), 8.06−8.11 (m, 3H), 7.93 (d, J = 15.0 Hz, 1H), 7.71 (d, J = 3.3 Hz, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.13−7.16 (m, 1H), 6.87 (s, 1H), 4.62 (brs, 2H), 4.27 (d, J = 5.1 Hz, 2H), 4.00 (s, 3H), 3.62 (brs, 4H), 2.11−2.15 (m, 1H). MS (ESI) m/z = 469 ([M + H]$^+$, 100%). Anal. ($C_{25}H_{24}O_7S\cdot 1/4H_2O$): C, H, S.

4-[3*E*-(2,4-Dimethoxy-5-thien-3-yl-phenyl)-acryloyl]-benzoic Acid (34). 2,4-Dimethoxy-5-thien-3-yl-benzaldehyde was prepared in a similar manner as described for compound **23**. ^{1}H NMR ($CDCl_3$): δ 10.35 (s, 1 H), 7.99 (s, 1 H), 7.55 (dd, 1 H, J = 3 and 1 Hz), 7.40 (dd, 1 H, J = 6 and 1 Hz), 7.33 (dd, 1 H, J = 3 and 6 Hz), 6.52 (s, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H).

The title compound was prepared in a similar manner as described for compound **23**; yellow solid, mp 217−219 °C. ^{1}H NMR ($CDCl_3$): δ 8.19 (d, J = 9 Hz, 2H), 8.10 (s, 1H), 8.06 (d, J = 17 Hz, 1H), 8.05 (d, J = 9 Hz, 2H), 7.85 (d, J = 17 Hz, 1H), 7.76 (m, 1H), 7.545 (s, 1H), 7.541 (s, 1H), 6.77 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H). Anal. ($C_{22}H_{18}O_5S\cdot 1/4H_2O$): C, H, S.

4-{3*E*-[2,4-Dimethoxy-5-(5-methyl-thien-2-yl)-phenyl]-acryloyl}-benzoic Acid (35). 2,4-Dimethoxy-5-(5-methyl-thien-2-yl)-benzaldehyde was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and 5-methyl-thiophene-2-boronic acid in a similar manner as described for compound **3**; 100% yield. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 8.05 (s, 1H), 7.22 (d, J = 4 Hz, 1H), 6.72 (d, J = 4 Hz, 1H), 6.49 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 2.50 (s, 3H). HMRS (EI) calcd for $C_{14}H_{14}O_3S$: 262.0664, found: 262.0665.

The title compound was prepared by condensing 2,4-dimethoxy-5-(5-methyl-thien-2-yl)-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp 213−215 °C, 27% yield. ^{1}H NMR (DMSO-d$_6$): δ 8.18 (d, J = 7 Hz, 2H), 8.17 (s, 1H), 8.00−8.06 (m, 3H), 7.85 (d, J = 15 Hz, 1H), 7.42(d, J = 4 Hz, 1H), 6.78(m, 2H), 3.96 (s, 3H), 3.95(s, 3H), 2.42 (s, 3H). MS m/z = 408 ([M]$^+$, 100%). HMRS (EI) calcd for $C_{23}H_{20}O_5S$: 408.1031, found: 408.1023. Anal. ($C_{23}H_{20}O_5S$): C, H, S.

4-{3*E*-[2,4-Dimethoxy-5-(2-methyl-thiazol-4-yl)-phenyl]-acryloyl}-benzoic Acid (36). A solution of 2-bromo-1-(3,4-dimethoxy-phenyl)-ethanone (0.62 g, 2.39 mmol) and thioacetamide (0.18 g, 2.39 mmol) in ethanol (30 mL) was refluxed for 2 h, and the solvent was removed under reduced pressure. The product, 4-(3,4-dimethoxy-phenyl)-2-methyl-thiazole (0.56 g, 100%) was obtained as a white solid and used without further purification. To a suspension of 4-(3,4-dimethoxy-phenyl)-2-methyl-thiazole obtained above (0.70 g, 2.97 mmol) in dichloromethane (60 mL) at 0 °C was added dichloromethyl methyl ether (0.40 mL, 4.46 mmol) followed by addition of titanium tetrachloride (1.0 M solution in dichloromethane, 8.9 mL, 8.9 mmol) dropwise. The reaction mixture was allowed to stir overnight at ambient temperature and then poured into ice. The aqueous solution was extracted with dichloromethane. The solution of dichloromethane was washed with hydrochloric acid (0.5 M), saturated solution of sodium bicarbonate and brine, dried over sodium sulfate, and concentrated. The product, 2,4-dimethoxy-5-(2-methyl-thiazol-4-yl)-benzaldehyde, was obtained as a white solid. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 8.67 (s, 1H), 7.56 (s, 1H), 6.52 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 2.75 (s, 3H).

The title compound was prepared by condensing 2,4-dimethoxy-5-(2-methyl-thiazol-4-yl)-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp 201−202 °C (dec). ^{1}H NMR (DMSO-d_6): δ 8.47 (s, 1H), 8.14−7.97 (m, 5H), 7.76 (s, 1H), 7.65 (d, J = 15.8 Hz, 1H), 6.81 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 2.69 (s, 3H). MS m/z = 409 (M$^+$, 70%), 378 ([M − OCH$_3$]$^+$, 100%). Anal. ($C_{22}H_{19}NO_5S\cdot 5/4H_2O$): C, H, N, S.

4-[3*E*-(5-Benzofuran-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic Acid (37). 5-Benzofuran-2-yl-2,4-dimethoxy-benzaldehyde was prepared in a similar manner as described for compound **3**. ^{1}H NMR ($CDCl_3$): δ 10.36(s, 1H), 8.55(s, 1H), 7.50−7.58 (m, 2H), 7.19−7.28 (m, 3H), 6.52 (s, 1H), 4.08 (s, 3H), 3.99 (s, 3H).

The title compound was prepared in a similar manner as described for compound **5**; yellow solid, mp 227−229 °C. ^{1}H NMR (DMSO-d_6): δ 8.42 (s, 1H), 8.13−8.22 (m, 5H), 7.85 (d, J = 15 Hz, 1H), 7.51−7.61 (m, 2H), 7.18−7.30 (m, 3H), 6.93 (s, 1H), 4.14 (s, 3H), 4.06 (s, 3H). MS m/z: 428 ([M]$^+$, 100%). HMRS calcd for $C_{26}H_{20}O_6$: 429.1338 (M + H); found: 429.1331. Anal. ($C_{26}H_{20}O_6$): C, H.

2-{5-[3-(4-Carboxy-phenyl)-3-oxo-*E*-propenyl]-2,4-dimethoxy-phenyl}-indole-1-carboxylic Acid *tert*-Butyl Ester (38). 2-(5-Formyl-2,4-dimethoxy-phenyl)-indole-1-carboxylic acid *tert*-butyl ester was prepared from 5-bromo-2,4-dimethoxybenzaldehyde and *N*-Boc-indole-2-boronic acid in a similar manner as described for compound **3**; yellow oil, 79% yield. ^{1}H NMR ($CDCl_3$): δ 10.36 (s, 1H), 8.15 (d, J = 8 Hz, 1H), 7.88 (s, 1H), 7.45 (d, J = 8 Hz,

3H), 7.27−7.35 (m, 1H), 7.19−7.27 (m, 1H), 6.52 (s, 1H), 6.47 (s, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 1.42 (s, 9H).

The title compound was prepared by condensing 2-(5-formyl-2,4-dimethoxy-phenyl)-indole-1-carboxylic acid *tert*-butyl ester and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, 8% yield, mp 182−183 °C. ^{1}H NMR ($CDCl_3$): δ 8.21 (d, J = 8 Hz, 2H), 8.19 (d, J = 13 Hz, 1H), 8.16 (d, J = 7 Hz, 1H), 8.07 (d, J = 8 Hz, 2H), 7.69 (s, 1H), 7.54 (d, J = 7 Hz, 1H), 7.52 (d, J = 13 Hz, 1H), 7.29−7.35 (m, 1H), 7.23 (d, J = 7 Hz, 1H), 6.55 (s, 1H), 6.50 (s, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 1.42 (s, 9H). MS m/z = 528 ([M + H]$^+$, 100%). Anal. ($C_{31}H_{29}NO_7\cdot H_2O$): C, H, N.

4-{3*E*-[5-(1*H*-Benzimidazol-2-yl)-2,4-dimethoxy-phenyl]-acryloyl}-benzoic Acid (39). A solution of benzene-1,2-diamine (2.60 g, 24.1 mmol) and 2,4-dimethoxy-benzaldehyde (4.0 g, 24.1 mmol) in ethanol (60 mL) containing a catalytic amount of acetic acid was refluxed overnight. The solvent was then evaporated under reduced pressure, and the residual oil was triturated in ethyl acetate to give 2-(2,4-dimethoxy-phenyl)-1*H*-benzimidazole (0.76 g, 12%). The crude product was used without further purification. To a solution of 2-(2,4-dimethoxy-phenyl)-1*H*-benzimidazole obtained above (0.76 g, 2.99 mmol) in dichloromethane (20 mL) was added dichloromethyl methyl ether (0.41 mL, 4.48 mmol) followed by the addition of titanium tetrachloride (1.0 M in dichloromethane, 9.0 mL, 9.0 mmol) at 0 °C. The reaction mixture was allowed to stir overnight at ambient temperature and then poured into ice. A solution of sodium hydroxide (5 M) was added dropwise until the pH of the solution was about 12. The basic solution was extracted with dichloromethane. The combined solution of dichloromethane was subsequently washed with brine, dried over sodium carbonate, and concentrated. The product, 5-(1*H*-benzimidazol-2-yl)-2,4-dimethoxy-benzaldehyde (0.40 g, 47%), was obtained and used without further purification. ^{1}H NMR ($CDCl_3$): δ 10.32 (s, 1H), 10.27 (bs, 1H), 9.03 (s, 1H), 7.83 (d, J = 9 Hz, 1H), 7.48−7.45 (m, 1H), 7.31−7.22 (m, 1H), 6.58 (s, 1H), 4.18 (s, 3H), 4.01 (s, 3H). MS m/z = 282 (M$^+$, 100%).

The title compound was prepared by condensing 5-(1*H*-benzimidazol-2-yl)-2,4-dimethoxy-benzaldehyde and 4-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, mp >240 °C (dec); ^{1}H NMR (DMSO-d_6): δ 8.72 (s, 1H), 12.10 (s, 1H), 8.18 (d, J = 8.4 Hz, 2H), 8.08−8.02 (m, 3H), 7.80 (d, J = 15.4 Hz, 1H), 7.59 (s, 2H), 7.17−7.13 (m, 2H), 6.89 (s, 1H), 4.10 (s, 3H), 4.03 (s, 3H). MS m/z = 429 ([M + H]$^+$, 100%). Anal. ($C_{25}H_{20}N_2O_5\cdot H_2O$): C, H, N.

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzoic Acid Ethyl Ester (40). The title compound was prepared starting from compound **5** and ethanol in an ester formation reaction using EDCI in a similar manner as described for compound **6**; orange solid, mp 167−169 °C, 44% yield. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 15.9 Hz, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.95 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.67 (s, 1H), 7.57 (d, J = 16.5 Hz, 1H), 7.28−7.37 (m, 2H), 6.57 (s, 1H), 4.42 (q, J = 7.5 Hz, 2H), 4.03 (s, 3H), 4.00 (s, 3H), 1.43 (t, J = 6.6 Hz, 3H). HRMS (EI) calcd for $C_{28}H_{25}O_5S$: 473.1422, found: 473.1429. Anal. ($C_{28}H_{24}O_5S$): C, H, S.

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide (41). To a solution of 4-acetyl-benzamide (0.3 g, 1.84 mmol) and 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (0.55 g, 1.84 mmol) in a mixture of DMF (7 mL) and methanol (3 mL) was added lithium methoxide (0.14 g, 3.68 mmol). The reaction mixture was allowed to stir at ambient temperature for 9 h. The resulting precipitate was collected by filtration, washed with methanol, and dried in vacuo to give the title compound as a yellow solid (5.56 g, 68%), mp 240−241 °C. ^{1}H NMR (DMSO-d_6): δ 8.37 (s, 1H), 8.19 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 15.3 Hz, 1H), 8.04−7.91 (m, 6H), 7.83 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.36−7.30 (m, 2H), 6.87 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H). MS m/z = 444 ([M + H]$^+$, 100%). Anal. ($C_{26}H_{21}NO_4S\cdot 1/6H_2O$): C, H, N, S.

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-methoxy-benzamide (42). This compound was synthesized by treating compound **5** with *O*-methyl-hydroxylamine and EDCI in a similar manner as described for compound **6**; yellow solid, mp 174−176 °C, 66% yield. ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 15.0 Hz, 1H), 7.94−7.87 (m, 5H), 7.82 (d, J = 7.5 Hz, 1H), 7.37−7.27 (m, 2H), 6.85 (s, 1H), 4.28 (s, 3H), 3.99 (s, 4H), 3.71 (s, 3H). MS (EI): 474 (M + H). Anal. ($C_{27}H_{23}NO_5S$): C, H, N, S.

***N*-Acetyl-4-[3*E*-(5-benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide (43).** A suspension of 4-[3*E*-(5-benzo[*b*]-thiophen-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide (0.5 g, 1.13 mmol) in THF (15 mL) was cooled to −78 °C followed by the addition of lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.3 mL, 2.3 mmol). The mixture was stirred at this temperature for 1 h and warmed up to 0 °C. Acetic anhydride (0.48 mL, 6.8 mmol) was then added dropwise. After the addition was complete the reaction mixture was warmed up to ambient temperature and stirred for 2 h. The reaction was quenched with water. The aqueous solution was extracted with ethyl acetate. The combined extract was washed with NH_4Cl solution, brine, dried, and concentrated. Flash chromatography (50% EtOAc/hexanes) gave the title compound as yellow solid (0.16 g, 29%), mp 228−229 °C. ^{1}H NMR ($CCDl_3$): δ 8.52 (s, 1H), 8.15−8.10 (m, 3H), 7.96 (d, J = 7.6 Hz, 2H), 7.85−7.77 (m, 2H), 7.67 (s, 1H), 7.55 (d, J = 16.7 Hz, 1H), 7.34−7.29 (m, 3H), 6.58 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 2.65 (s, 3H). MS m/z = 485 (M$^+$, 100%). Anal. ($C_{28}H_{23}NO_5S$): C, H, N, S.

4-[3*E*-(5-Benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-*N*-isobutyryl-benzamide (44). The title compound was prepared in a similar manner as described for compound **43** from 4-[3*E*-(5-benzo[*b*]thien-2-yl-2,4-dimethoxy-phenyl)-acryloyl]-benzamide and isobutyric anhydride; yellow solid, mp 208−209 °C. ^{1}H NMR ($CCDl_3$): δ 8.14 (s, 1H), 8.15−8.10 (m, 3H), 7.96 (d, J = 7.2 Hz, 2H), 7.85−7.77 (m, 2H), 7.67 (s, 1H), 7.56 (d, J = 16.2 Hz, 1H), 7.38−7.29 (m, 3H), 6.59 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.68−3.59 (m, 1H), 1.28 (d, J = 6.2 Hz, 6H). MS m/z = 513 (M$^+$, 93%), 425 (100%). Anal. ($C_{30}H_{27}NO_5S\cdot 1/2H_2O$): C, H, N, S.

3-[3*E*-(2,4-Dimethoxy-5-thien-2-yl-phenyl)-acryloyl]-benzoic Acid (45). The title compound was prepared by condensing 2,4-dimethoxy-5-(thien-2-yl)-benzaldehyde and 3-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, 65% yield, mp 179−182 °C. ^{1}H NMR (DMSO-d_6): δ 13.24 (s, 1H), 8.54 (s, 1 H), 8.39 (d, J = 7.5 Hz, 1H), 8.25 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 15.9 Hz, 1H), 7.89 (d, J = 15.0 Hz, 1H), 7.63−7.70 (m, 2H), 7.48 (d, J = 5.1 Hz, 1H), 7.09(dd, J = 3.9, 5.4 Hz, 1H), 6.81 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H). MS m/z = 394 ([M]$^+$, 72%), 363 (100%). Anal. ($C_{22}H_{18}O_5S$): C, H, S.

2-[3*E*-(2,4-Dimethoxy-5-thien-2-yl-phenyl)-acryloyl]-benzoic Acid (46). The title compound was prepared by condensing 2,4-dimethoxy-5-(thien-2-yl)-benzaldehyde and 2-acetylbenzoic acid in a similar manner as described for compound **5**; yellow solid, 47% yield, mp 196−198 °C. ^{1}H NMR (DMSO-d_6): δ 8.00 (s, 1H), 7.91 (s, 1H), 7.85 (dd, J = 7.5, 1.5 Hz, 1H), 7.67−7.55 (m, 3H), 7.48−7.43 (m, 3H), 7.20 (d, J = 15.9 Hz, 1H), 7.05 (dd, J = 3.9, 5.1 Hz, 1H), 6.76 (s, 1H), 3.95 (s, 3H), 3.86 (s, 3H). MS m/z = 394 ([M]$^+$, 100%). Anal. ($C_{22}H_{18}O_5S$): C, H, S.

4-[2-(2,4-Dimethoxy-5-thiophen-2-yl-phenyl)-cyclopropane-carbonyl]-benzoic Acid (47). To a clean reaction vessel fitted with a stir bar and nitrogen inlet adapter was sequentially charged 60 wt % NaH (42 mg, 1.05 mmol), trimethylsulfoxonium iodide (231 mg, 1.05 mmol), and DMSO (3 mL). After aging for 1 h at rt, 4-[3*E*-(2,4-dimethoxy-5-thiophen-2-yl-phenyl)-acryloyl]-benzoic acid (100 mg, 0.25 mmol) was added dropwise over 5 min as a DMSO (2 mL) solution. The reaction was aged overnight at rt, diluted with 1 N HCl (11 mL), and transferred to a separatory funnel containing EtOAc (11 mL). The layers were cut, and the aqueous layer was extracted with additional EtOAc (15 mL). The organic cuts were combined and washed with brine (30 mL). The resulting organic phase was concentrated to a crude solid and purified by silica gel chromatography ($MeOH/CH_2Cl_2$/AcOH, 49:49:2) to afford 54 mg (52% yield) of the title compound, mp 92−96 °C. ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 8.3 Hz, 2H), 8.09 (d, J = 8.3 Hz, 2H), 7.44 (m, 1H), 7.37 (dd, J = 3.6 and 1.4 Hz, 1H), 7.28 (s, 1H), 7.07 (dd, J

= 5.2 and 3.6 Hz, 1H), 6.53 (s, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 2.77 (m, 2H), 1.95 (m, 1H), 1.65 (m, 1H). Anal. ($C_{23}H_{20}O_5S \cdot 1/3H_2O$): C, H, S.

In Vitro VCAM-1 Assay. Cultured primary human aortic (HAEC) or pulmonary artery (HPAEC) endothelial cells were obtained from Clonetics and were used below passage 9. Cells were seeded in 96-well plates such that they reach 90−95% confluency by the following day. On the following day cells were stimulated with TNF-α (1 ng/mL) in the presence or absence of compounds dissolved in DMSO such that the final concentration of DMSO was 0.25%. Cells were exposed to TNF-α and compounds for approximately 16 h. Then cells were examined under microscope to score for visual sign of toxicity or cell stress. The media was discarded and cells washed once with Hanks Balanced Salt Solution (HBSS)/phosphate-buffered saline (PBS) (1:1). Primary antibody against VCAM-1 (0.25 μg/mL in HBSS/PBS + 5% FBS) was added, and cells were incubated for 30 min at 37 °C. Cells were washed with HBSS/PBS three times and then secondary antibody horse radish peroxidase (HRP)-conjugated goat anti-mouse IgG (1:500 in HBSS/PBS + 5% FBS) was added, and cells were incubated for 30 min at 37 °C. Cells were then washed with HBSS/PBS four times, 3,3′,5,5′-tetramethylbenzidine (TMB) was added, and cells were incubated at rt in the dark until there was adequate development of blue color. The length of time of incubation was typically 5−15 min. Sulfuric acid (2 N) was added to stop the color development, and the data were collected by reading the absorbance on a BioRad ELISA plate reader at OD 450 nm. The results were expressed as IC_{50} values (the concentration of test compound required to inhibit 50% of the maximal response of the control sample stimulated by TNF-α only). IC_{50} numbers reflect an average of at least three determinations.

In Vivo Pharmacology in Asthma Model. Five to 6-week-old, male Balb/C mice (Jackson Laboratories, Bar Harbor, ME) were sensitized by means of intraperitoneal (i.p.) injection with a mixture of ovalbumin (Calbiochem, La Jolla, CA) emulsified in aluminum hydroxide (AlumImject, Pierce, Rockford, IL) at a dose of 8 μg and 1 mg per mouse, respectively. On day 12, Animals were challenged twice with ovalbumin by the inhalation route in the AM and PM for 1 h each. For the inhalation challenge, a 0.5% solution of ovalbumin in sterile saline was nebulized (UltraNeb 99 nebulizer, Sunrise Medical, Somerset, PA) at a flow rate of 2 L/min with the sonication intensity at the $^1/_2$ maximal setting. On day 14, the mice were euthanized by an i.p. injection of ketamine, xylazine, and acepromazine mixture (J.A. Webster, Sterling, MA) at a dose of 24 mL/kg, and their lungs were lavaged through an intratracheal tube (3 × 0.9 mL) with DMEM/F-12 cell media (Gibco BRL, Carlsbad, CA) containing 5% fetal bovine serum (MediaTech, Herndon, VA). Total leukocyte numbers were measured (Coulter Counter, Coulter Corporation, Hialeah, FL), and differential cell counts were performed by counting at least 300 cells on cytocentrifuged cell preparations (Cytospin centrifuge, Shandon-Lipshaw, Pittsburgh, PA) that were stained with Diff Quik (VWR). Test compound was formulated in 2% Cremophor (BASF, Mount Olive, NJ) and administered to animals by the subcutaneous route at doses of 150, 100, and 50 mg/kg, bid from day 11 to 13 and once on day 14. On day 14, the animals were dosed 2−3 h prior to euthanization, and blood was collected for plasma drug level evaluation. Dexamethasone (Sigma, Saint Louis, MO) was used as a positive control and was administered intraperitoneally at a dose of 3 mg/kg in saline at 24 and 2 h before and 6 and 24 h after the first challenge.

Supporting Information Available: Elemental analysis data. This material is available via the Internet at http://pubs.acs.org.

References

(1) McMurray, R. W. Adhesion Molecules in Autoimmune Disease. *Semin. Arthritis Rheum.* **1996**, *25*, 215−234.

(2) Smith, C. H.; Barker, J. N.; Lee, T. H. Adhesion Molecules in Allergic Inflammation. *Am. Rev. Respir. Dis.* **1993**, *148*, S75−78.

(3) Bevilacqua, M. P.; Nelson, R. M.; Mannori, G.; Cecconi, O. Endothelial-Leukocyte Adhesion Molecules in Human Disease. *Annu. Rev. Med.* **1994**, *45*, 361−378.

(4) Peter, K.; Weirich, U.; Nordt, T. K.; Ruef, J.; Bode, C. Soluble Vascular Cell Adhesion Molecule-1 (VCAM-1) as Potential Marker of Atherosclerosis. *Thromb. Haemost.* **1999**, *82* (Suppl. 1), 38−43.

(5) Yusuf-Makagiansar, H.; Anderson, M. E.; Yakovleva, T. V.; Murray, J. S.; Siahaan, T. J. Inhibition of LFA-1/ICAM-1 and VLA-4/VCAM-1 as a Therapeutic Approach to Inflammation and Autoimmune Diseases. *Med. Res. Rev.* **2002**, *22*, 146−67.

(6) Schreiner, E. P.; Oberhauser, B.; Foster, C. A. Inhibitors of Vascular Cell Adhesion Molecule-1 Expression. *Expert Opin. Ther. Pat.* **2003**, *13*, 149−166.

(7) Miller, D. H.; Khan, O. A.; Sheremata, W. A.; Blumhardt, L. D.; Rice, G. P. A.; Libonati, M. A.; Willmer-Hulme, A. J.; Dalton, C. M.; Miszkiel, K. A.; O'Connor, P. W. A Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N. Engl. J. Med.* **2003**, *348*, 15−23.

(8) Sandborn, W. J.; Colombel, J. F.; Enns, R.; Feagan, B. G.; Hanauer, S. B.; Lawrance, I. C.; Panaccione, R.; Sanders, M.; Schreiber, S.; Targan, S.; van Deventer, S.; Goldblum, R.; Despain, D.; Hogge, G. S.; Rutgeerts, P. Natalizumab Induction and Maintenance Therapy for Crohn's Disease. *N. Engl. J. Med.* **2005**, *353*, 1912−25.

(9) Ghosh, S.; Goldin, E.; Gordon, F. H.; Malchow, H. A.; Rask-Madsen, J.; Rutgeerts, P.; Vyhnalek, P.; Zadorova, Z.; Palmer, T.; Donoghue, S. Natalizumab for Active Crohn's Disease. *N. Engl. J. Med.* **2003**, *348*, 24−32.

(10) Steinman, L. Blocking Adhesion Molecules as Therapy for Multiple Sclerosis: Natalizumab. *Nat. Rev. Drug Discovery* **2005**, *4*, 510−518.

(11) Ni, L.; Meng, C. Q.; Sikorski, J. A. Recent Advances in Therapeutic Chalcones. *Expert Opin. Ther. Pat.* **2004**, *14*, 1669−1691.

(12) Meng, C. Q.; Zheng, X. S; Ni, L.; Ye, Z.; Simpson, J. E.; Worsencroft, K. J.; Hotema, M. R.; Weingarten, M. D.; Skudlarek, J. W.; Gilmore, J. M.; Hoong, L. K.; Hill, R. R.; Marino, E. M.; Suen, K. L.; Kunsch, C.; Wasserman, M. A.; Sikorski, J. A. Discovery of Novel Heteroaryl-substituted Chalcones as Inhibitors of TNF-α-induced VCAM-1 Expression. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1513−1517.

(13) Weingarten, M. D.; Ni, L.; Meng, C. Q.; Worsencroft, K. J.; Sikorski, J. A. US Patent Application 20040181075, 2004.

(14) Kim, H. S.; Barak, D.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. Acyclic and Cyclopropyl Analogues of Adenosine Bisphosphate Antagonists of the $P2Y_1$ Receptor: Structure-Activity Relationship and Receptor Docking. *J. Med. Chem.* **2001**, *44*, 3092−3108.

(15) Ghaffari, M. A.; Ali, H.; Van Lier, J. E. The Oxidative Cleavage of Amines by Iodine Monochloride. *J. Labelled Compd. Radiat.* **1989**, *27*, 117−22.

(16) Walsh, G. M. Eosinophil Apoptosis: Mechanism and Clinical Relevance in Asthmatic and Allergic Inflammation. *Br. J. Haematol.* **2000**, *111*, 61−67.

(17) Howard, R. B.; McDonough, A. M.; Stefanopoulos, D.; Luchoomun, J.; Meng, C. Q.; Sikorski, J. A.; Wasserman, M. A.; Kunsch, C.; Sundell, C. L. The Synthetic Chalcone, AGI-2048, Inhibits Several Indices of Disease in Rat Adjuvant Arthritis. *FASEB J.* **2003**, *17*, A666.

(18) Sundell, C. L.; Landers, L. K.; Qui, F. H.; Ni, L.; Souder, A.; Karu, K.; McDonald, M.; Howard, R.; Meng, C. Q.; Sikorski, J.; Kunsch, C.; Wasserman, M. A. AGI-2048, a Novel Chalcone, Inhibits Inflammatory Gene Expression, Airway Eosinophilia and Hyperresponsiveness in Ovalbumin-sensitized and challenged Mice. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, A357.

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