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ARTICLE

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Discovery of a Clinical Stage Multi-Kinase Inhibitor Sodium (*E*)-2-{2-Methoxy-5-[(2′,4′,6′-trimethoxystyrylsulfonyl)methyl]phenylamino}-acetate (ON 01910.Na): Synthesis, Structure−Activity Relationship, and Biological Activity

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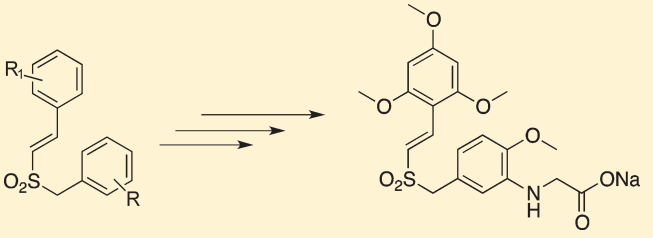
Supporting Information

ABSTRACT: Cyclin D proteins are elevated in many cancer cells, and targeted deletion of cyclin D1 gene in the mammary tissues protects mice from breast cancer. Accordingly, there is an increasing awareness of this novel nonenzymatic target for cancer therapeutics. We have developed novel, nonalkylating styrylbenzylsulfones that induce cell death in wide variety of cancer cells without affecting the proliferation and survival of normal cells. The development of derivatized styrylbenzylsulfones followed logically from a tumor cell cytotoxicity screen performed in our laboratory that did not have an a priori target profile. Modifications of some of the precursor molecules led to lead optimization with regard to tumor cell cytotoxicity. In this report we describe the synthesis and structure−activity relationships of novel, nonalkylating (*E*)-styrylbenzylsulfones and the development of the novel anticancer agent sodium (*E*)-2-{2-methoxy-5-[(2′,4′,6′-trimethoxystyrylsulfonyl)methyl]phenylamino}acetate (ON 01910.Na), which is in phase III trials for myelodysplastic syndromes (MDS) associated with aberrant expression of cyclin D proteins.



INTRODUCTION

In a recent paper,[1] we described the synthesis of a group of styrylbenzylsulfones that induce apoptotic death of a wide variety of human tumor cell lines at nanomolar concentrations while exhibiting relatively low toxicity to normal human cells. Our studies showed that the cytotoxic activity of styrylbenzylsulfones is completely dependent on the nature and position of the substituents on the two aromatic rings. Structure−function studies showed that positions of functional groups on the styryl aromatic ring play a critical role in determining the biochemical and biological activity of these molecules. Biological evaluation of the activity of these compounds showed that these compounds are highly active against a wide variety of human tumor cell lines including those that are resistant to the activity of many of the currently used chemotherapeutic agents. The low toxicity profile, both in vitro and in vivo, and their potent tumor inhibitory activity as seen in soft agar and nude mouse xenograft assays pointed to the potential value of these compounds as safe therapies for cancer, lacking many of the side effects normally associated with current chemotherapeutic agents. Many of the compounds described in this study were found to act as allosteric inhibitors of serine/theronine and tyrosine kinases, providing a rationale for further expansion of this chemotype for applications related to cancer therapy.

The present report describes the synthesis and structure−activity relationships of novel, nonalkylating (*E*)-styrylbenzylsulfones and the development of the novel anticancer agent sodium (*E*)-2-{2-methoxy-5-[(2′,4′,6′-trimethoxystyrylsulfonyl)methyl]phenylamino}acetate (ON 01910.Na, **28**).[2] The development of derivatized styrylbenzylsulfones followed logically from a tumor cell cytotoxicity screen performed in our laboratory. Precursors of **28** were identified specifically based upon their ability to target cancer cells while leaving nonmalignant cell cultures virtually unaffected. Modifications of some of the precursor molecules led to lead optimization with regard to tumor cell cytotoxicity. Structure−activity studies confirmed that the nature, number, and position of substituents on the two aromatic rings of the parent molecule are the determining factor in the tumor cell cytotoxicity of these compounds.

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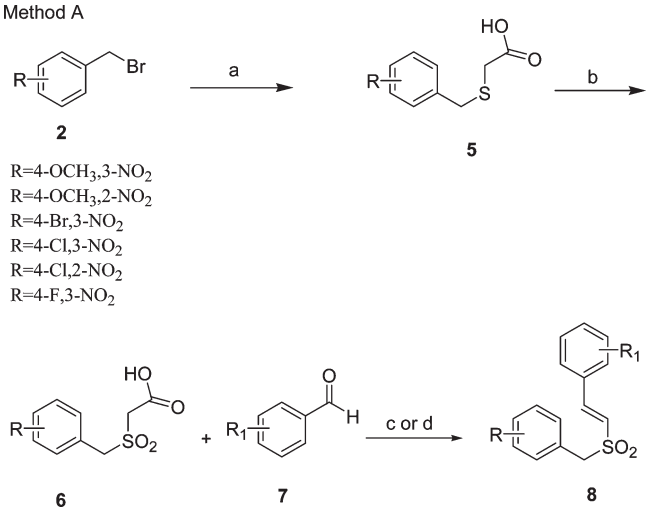
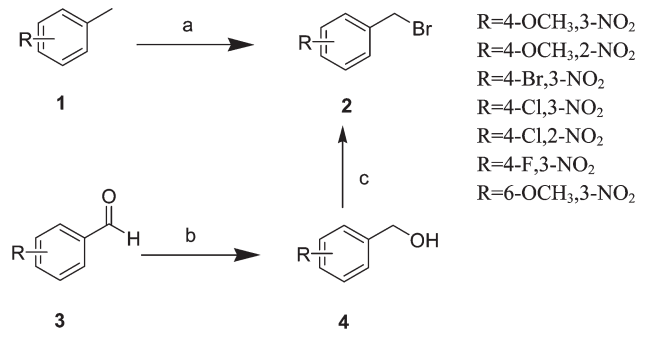
Scheme 1. Synthesis of (*E*)-Styrylbenzylsulfones from Benzylsulfonylacetic Acids[a]



[a] Reagents and conditions: (a) $HSCH_2COOH$, MeOH, NaOH, room temp, 3 h; (b) 30% H_2O_2, ACOH, room temp, 24 h; (c) benzylamine, AcOH, reflux, 2−8 h; (d) piperidine, benzoic acid, toluene, 2−4 h.

Scheme 2. Synthesis of Benzyl Bromides[a]



[a] Reagents and conditions: (a) NBS, benzoyl peroxide, CCl_4, 18 h; (b) $NaBH_4$, MeOH, 0−5 °C, 1 h; (c) PBr_3, toluene, 100 °C, 30 min.

In previous studies in our laboratory, **28** displayed desirable pharmacokinetic and pharmacodynamic properties and was able to reduce tumor size and increase survival in mice carrying tumor cell xenografts.[2] **28** received orphan drug status for the myelodysplastic syndrome, a heterogeneous hematopoietic stem cell disorder that affects cell proliferation, differentiation, and function. MDS is characterized by dyspoiesis, hyperproliferative bone marrow, and peripheral blood cytopenias involving one or more lineages.[3−5] Most of the untreated patients with high risk MDS die from progressive bone marrow failure within 1 year because of hemorrhage and/or infection. In vitro studies with **28** showed that incubation of human leukemic cells with this compound results in the inhibition of the PI3K/AKT pathway, down-regulation of cyclin D1, induction of NOXA and BIM, and activation of the JNK pathway.[6] Treatment of MDS patients with **28** results in a dramatic reduction of cytogenetically abnormal cells with a minimal inhibition of normal hematopoiesis. This drug is currently in phase III clinical trials.

CHEMISTRY

Multiple synthetic routes for synthesis of the (*E*)-styrylbenzylsulfone scaffold were explored. The initial method (method A) involved the synthesis of substituted (*E*)-styrylbenzylsulfones by the reaction of benzyl bromides (**2**) with mercaptoacetic acid in the presence of a strong base, sodium hydroxide in methanol, to obtain benzylthioacetic acids (**5**) in quantitative yields (Scheme 1). Oxidation of **5** with 30% hydrogen peroxide (H_2O_2) in glacial acetic acid afforded benzylsulfonylacetic acids **6**.[7] Knovenagel condensation of **6** with aromatic aldehydes **7** in either benzylamine/acetic acid[7] or piperidine/benzoic acid[8] in toluene afforded (*E*)-styrylbenzylsulfones **8** in good yields.

Some of the substituted benzyl bromides **2** that are not commercially available were synthesized as shown in the Scheme 2. Substituted toluenes **1** were brominated with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of benzoyl peroxide in carbon tetrachloride (CCl_4) to obtain **2**.[9] Some of these nitro substituted benzyl bromides **2** were also made starting from substituted nitrobenzaldehydes **3** which were reduced with sodium borohydride ($NaBH_4$)[10] and on subsequent bromination of the resulting alcohol **4** with phosphorus tribromide (PBr_3) (Scheme 2).[11]

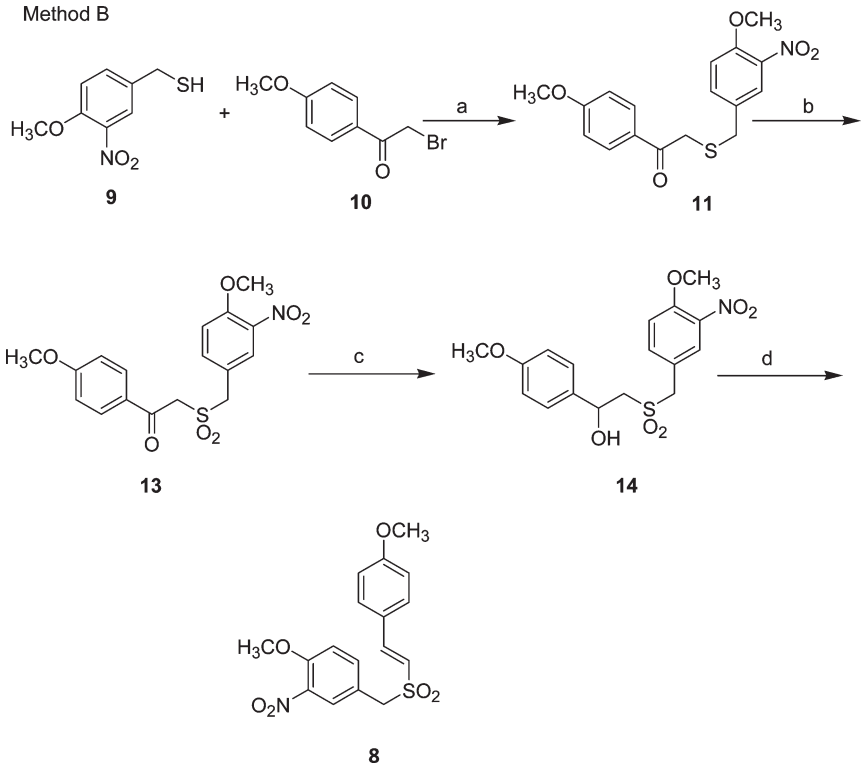
In method B, 3-nitro-4-methoxybenzylmercaptan (**9**) was treated with 4-methoxyphenacyl bromide (**10**) to obtain 4-methoxyphenacyl-3-nitro-4-methoxybenzyl sulfide **11**, which on oxidation with 30% H_2O_2 gave 4-methoxyphenacyl-3-nitro-4-methoxybenzylsulfone **13**.[7]

Sequential reduction of **13** with sodium borohydride[1] and subsequent dehydration with *p*-toluenesulfonic acid (*p*-TSA) afforded the desired **8** in moderate yields (Scheme 3).[12] Method A is superior to method B for the synthesis of **8**, as it involves steps with relatively higher yields. The 3-nitro-4-methoxybenzylmercaptan **9** was in turn synthesized from **2a** as outlined in Scheme 4. **2a** on treatment with thiourea in water gave an intermediate isothiouronium salt (**12**) which on reduction with ammonia yielded **9** in low to moderate yields.[13]

To see the effect of trans sulfide and sulfoxide on the biological activity of these (*E*)-styrylbenzylsulfones, we made (*Z*) (**16**) and (*E*) (**17**) 4-methoxy-3-nitrobenzyl- 2′,4′,6′-trimethoxystyryl sulfides by the reaction of 3-nitro-4-methoxybenzylmercaptan (**9**) and 2,4,6-trimethoxyphenylacetylene (**15**) in the presence of triethylborane−hexane (Et_3B) in benzene (Scheme 5).[14] In this reaction, (*Z*) to (*E*) ratio of 40:60 resulted in mainly trans isomers. **17** on controlled oxidation with 1,1,1,3,3,3-hexafluoro-2-propanol and 30% H_2O_2 at room temperature resulted in sulfoxide **20**,[15] which on reduction with sodium hydrosulfite in acetone−water mixture at 50 °C afforded the corresponding amine **21**.[9]

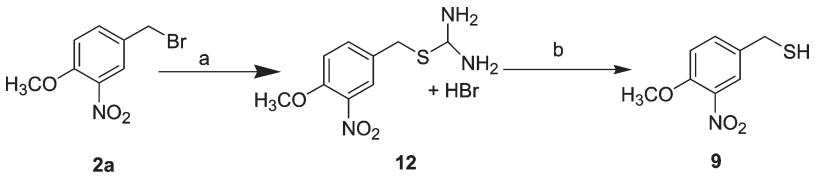
The sulfoxide **20** was oxidized to sulfone **22** with 30% hydrogen peroxide in glacial acetic acid[7] which was later reduced with sodium hydrosulfite to the corresponding sulfone **23**.[9] The nitro sulfide **17** was also converted to the corresponding amino sulfide **24** which on further oxidation with *m*-chloroperoxybenzoic acid (m-CPBA) afforded sulfone **23**. The acetylene **15** was synthesized starting from 2,4,6-trimethoxybenzaldehyde **18** and tetrabromomethane (CBr_4) in the presence of triphenyphosphine (Ph_3P) in dichloromethane.[16] The resulting 2′,2′-dibromovinyl-1,3,5-trimethoxybenzene **19** on treatment with *n*-BuLi in THF at −78 °C gave **15**[16] in high yields. The synthesis of nitro-(*E*)-styrylbenzyl sulfoxide **20** and amino-(*E*)-styrylbenzyl sulfoxide **21** was also achieved from 4-methoxy-3-nitrobenzylthioacetic

Scheme 3. Synthesis of (*E*)-Styrylbenzylsulfones from Phenacylbenzylsulfones[a]



[a] Reagents and conditions: (a) NaOH, MeOH, room temp, 2 h; (b) 30% H_2O_2, ACOH, room temp, 24 h; (c) $NaBH_4$, tetrahydrofuran, 0 °C, 1 h; (d) *p*-toluenesulfonic acid, toluene, 2−4 h.

Scheme 4. Synthesis of 4-Methoxy-3-nitrobenzylmercaptan[a]



[a] Reagents and conditions: (a) thiourea, H_2O, reflux, 2 h; (b) ammonia, hexane, reflux, 30 min.

acid **5a** by oxidation to sulfoxide **25**[17] and then condensation with 2,4,6-trimethoxybenzaldehyde **18** in the presence of benzylamine and acetic acid (Scheme 7).[7] The resulting **20** was reduced to **21** as described in Scheme 5.

To enhance the solubility and bioavailability of these (*E*)-styrylbenzylsulfones, several 3-amino substituted esters and acids were made from (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (**8p**) and (*E*)-3′,4′,5′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (**8q**) (Scheme 8). **8p** and **8q** were treated with different α-bromo esters in the presence of mild base sodium acetate in ethanol for 48 h to give amine esters (**26**) which on subsequent hydrolysis with sodium hydroxide in ethanol afforded the corresponding acids **27**.

The lead compound of our investigation, **28**, was synthesized from **8p** by its reaction with methyl 2-bromoacetate in the presence of a mild base sodium acetate in methanol for 4−6 h to give amino substituted methyl ester **26a** which on subsequent hydrolysis with sodium hydroxide in aqueous ethanol and dichloromethane followed by methyl ethyl ketone washing afforded crystalline **28** in high yields with two molecules of water of hydration as determined by Karl Fischer analysis (Scheme 9).

STRUCTURE−ACTIVITY RELATIONSHIPS (SAR)

After the synthesis of these compounds, their in vitro cytotoxicity was assessed using two different human tumor cell lines derived from human prostate (DU145) and leukemic (K562) cancers. The results of the study are presented in Table 1. These studies reveal that the cytotoxicity of the (*E*)-styrylbenzylsulfones is totally dependent on the nature and position of the substituents present on the two aromatic rings. For the purpose of structure−activity relationship, we have selected a few compounds from a library of 2000 (*E*)-styrylbenzylsulfones synthesized from our laboratory. In most of the selected compounds described here, we have kept a methoxy group at the fourth position and an amino group at the third position of benzylsulfonyl aromatic ring and one or more methoxy groups on styryl

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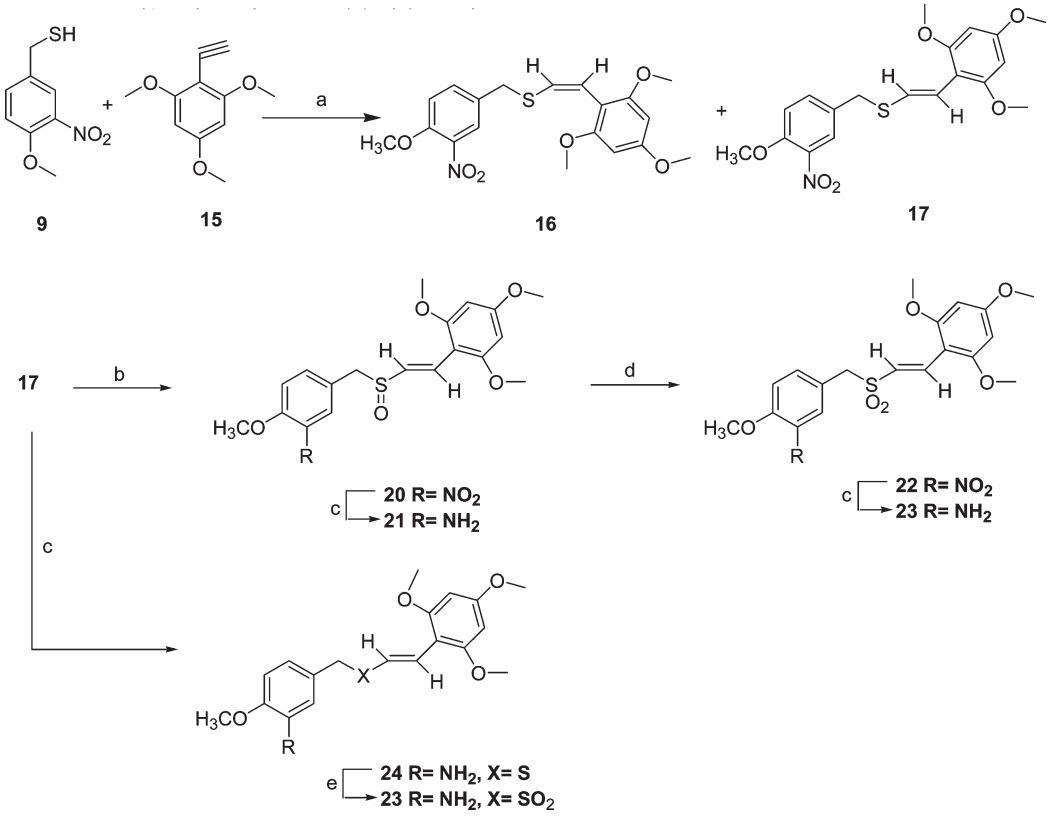
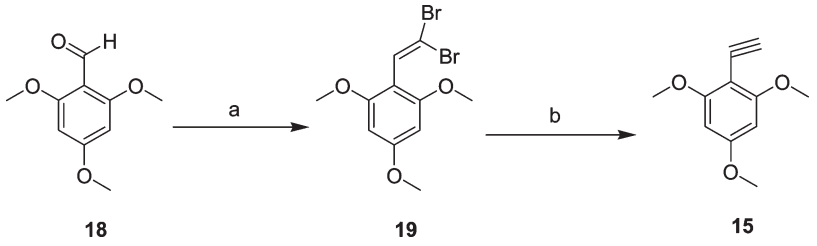
Scheme 5. Synthesis of (*Z*)- and (*E*)-Styrylbenzyl Sulfides from 4-Methoxy-3-nitrobenzylmercaptan and 2,4,6-Trimethoxyphenylacetylene and (*E*)-Styrylbenzyl Sulfoxide and Sulfone[a]



[a] Reagents and conditions: (a) Et_3B—hexane, benzene, 25 °C, 2 h; (b) 1,1,1,3,3,3-hexafluoro-2-propanol, 30% H_2O_2, 25 °C, 2 h; (c) acetone/water (2:1), sodium hydrosulfite, 50 °C, 30 min; (d) 30% H_2O_2, AcOH, room temp, 24 h; (e) *m*-CPBA, CH_2Cl_2, 0 °C to room temp, 3 h.

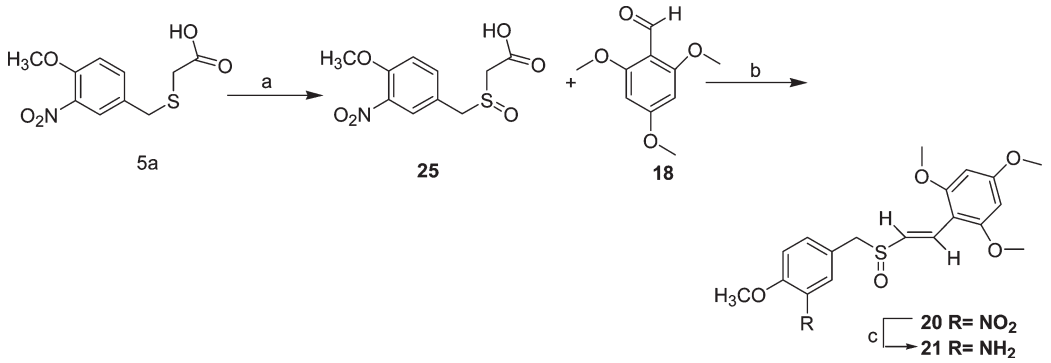
Scheme 6. Synthesis of 2,4,6-Trimethoxyphenylacetylene[a]



[a] Reagents and conditions: (a) triphenylphosphine, tetrabromomethane, CH_2Cl_2, 5 °C, 30 min; (b) *n*-BuLi, dry THF, −78 °C, 15 min.

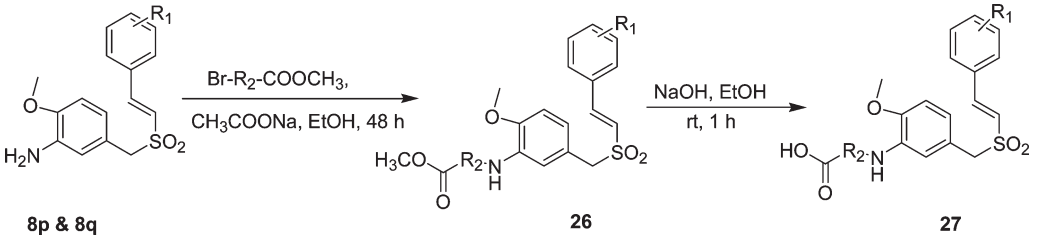
aromatic ring at different positions. A moderate cytotoxicity in tumor cells was seen in a compound when an amino group and methoxy group are at third and fourth positions of the benzyl ring and a methoxy group at the fourth position of the styryl ring (**8d**). By introduction of a second methoxy group on the styryl ring of **8d**, the cytotoxicity of the resulting compounds **8g**, **8h**, and **8i** was further enhanced by several fold. Whereas the results are quite surprising for the molecules that are disubstituted with methoxy groups on the styryl aromatic ring compared to **8d**, the results obtained in cytotoxicity assays using these compounds (**8g**, **8h**, **8i**, **8j**, and **8k**) clearly show that the methoxy group, when present at 2 and 6 positions (**8i**), enhances the activity of the molecule by greater than 10-fold when compared to other disubstituted methoxy groups (**8g** and **8h**). It is also clear from the cytotoxicity profile of the compounds **8j** and **8k** that when amino and methoxy groups are placed at other than third and fourth positions, the compounds exhibit decreased cell killing activity: 15- to 500-fold. Because the introduction of two methoxy groups on the styryl aromatic ring enhanced the biological activity, we have synthesized some trimethoxystyryl analogues to determine if this further enhances their cytotoxic properties. Analysis of these compounds (**8n**, **8o**, **8p**, **8q**, and **8r**) in cell-killing assays showed that (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (**8p**) exhibited the best activity in the entire series. This compound, **8p**, is almost 11-fold more active than **8i** in both cell lines. These results also show that when 2, 4, and 6 positions of the styryl ring are occupied by methoxy groups (**8p**), the molecule attains optimum biological activity

Scheme 7. Synthesis of (*E*)-Styryl-4-methoxy-3-nitrobenzyl Sulfoxide from 4-Methoxy-3-nitrobenzyl Sulfoxide Acetic Acid[a]

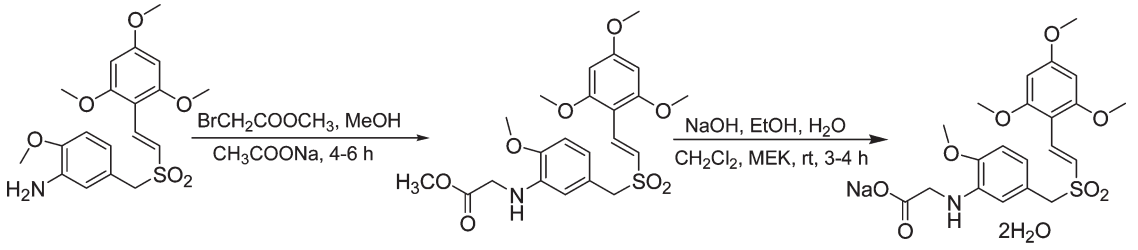


[a] Reagents and conditions: (a) NaOH/deionized H_2O, $NaHCO_3$, acetone, Oxone solution, sodium bisulfite, 6 N HCl; (b) benzylamine, AcOH, reflux, 2−8 h; (c) acetone/water (2:1), sodium hydrosulfite, 50 °C, 30 min.

Scheme 8. Synthesis of Amine Esters and Acids of 4-Methoxy-3-aminostyrylbenzylsulfones (8p and 8q)



Scheme 9. Synthesis of 28



compared to other trimethoxy substituted styrylsulfones (**8n**, **8o**, **8q**, and **8r**). To validate the critical requirement of the methoxy group at the fourth position of the 2′,4′,6′-trimethoxystyryl moiety, we have replaced the methoxy group at the fourth postion by a hydroxy (**8t**) and a carboxypropoxy group (**8u**). Both replacements in **8p** caused severe loss of cytotoxicity in the molecules, indicating the indispensability of a methoxy group at the fourth position of the ring. Further replacing the methoxy group with halogen atoms or changing the position of the amino group in the benzyl aromatic ring resulted in molecules (**8w**, **8x**, **8y**, and **8aa**) that suffered substantial loss of cytotoxicity. Also the compounds formed by replacing all three methoxy groups of the styryl ring by fluorine atoms (**8ab** and **8ac**) in **8p** have reduced level of cytotoxicity. The SAR analysis clearly shows that all the compounds with nitro substitutions on the benzylic ring (**8a**, **8c**, **8e**, **8f**, **8l**, **8m**, **8s**, **8v**, and **8z**) are far less active than the corresponding amino compounds, indicating that the amino group in that position is critical for the interaction of the compounds with their target and activity.

Once we established that 3-amino-4-methoxy groups on benzyl aromatic ring and 2,4,6-trimethoxy groups on styryl ring produced a compound (**8p**) with the best cytotoxic activity, we then analyzed the role of sulfone in the activity of the molecule (Table 2). To understand the oxidative state of sulfur in the molecule, we have made sulfide (**24**) and sulfoxide (**21**) analogues of **8p**. Both sulfide (**24**) and sulfoxide (**21**) analogues are 10-fold less active than sulfone (**8p**), indicating complete oxidative state of sulfur in the compound is required for optimum activity.

The compound **8p**, which has a high potency, has very low solubility in aqueous buffers and solutions. In order to enhance its water solubility and bioavailability, the amino group in third position was converted to amino acids (**27a**−**l**). From Table 3, it is clear that all 3-substituted amino acids (**27a**−**l**) are more active than the corresponding esters (**26a**−**l**). As the 3-glycine substituted

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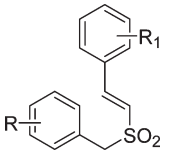
Table 1. In Vitro Cytotoxicity of (*E*)-Styrylbenzylsulfones 8



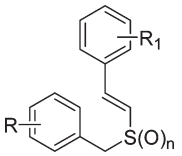
			IC_{50} (μM)	
compd	R	R_1	DU145	K562
8a	3-NO_2, 4-CH_3O	2-CH_3O	20	20
8b	3-NH_2, 4-CH_3O	2-CH_3O	7.5	7.5
8c	3-NO_2, 4-CH_3O	4-CH_3O	25	25
8d	3-NH_2, 4-CH_3O	4-CH_3O	2.5	2.5
8e	3-NO_2, 4-CH_3O	2,6-$(CH_3O)_2$	20	20
8f	2-NO_2, 4-CH_3O	2,6-$(CH_3O)_2$	50	50
8g	3-NH_2, 4-CH_3O	2,4-$(CH_3O)_2$	0.5	0.5
8h	3-NH_2, 4-CH_3O	2,5-$(CH_3O)_2$	0.75	0.75
8i	3-NH_2, 4-CH_3O	2,6-$(CH_3O)_2$	0.05	0.05
8j	2-NH_2, 4-CH_3O	2,6-$(CH_3O)_2$	0.75	0.75
8k	3-NH_2, 6-CH_3O	2,6-$(CH_3O)_2$	25	25
8l	3-NO_2, 4-CH_3O	2,4,6-$(CH_3O)_3$	2.5	2.5
8m	2-NO_2, 4-CH_3O	2,4,6-$(CH_3O)_3$	20	20
8n	2-NH_2, 4-CH_3O	2,4,6-$(CH_3O)_3$	0.025	0.025
8o	3-NH_2, 4-CH_3O	2,4,5-$(CH_3O)_3$	0.25	0.25
8p	3-NH_2, 4-CH_3O	2,4,6-$(CH_3O)_3$	0.004	0.003
8q	3-NH_2, 4-CH_3O	3,4,5-$(CH_3O)_3$	3.0	0.25
8r	3-NH_2, 6-CH_3O	2,4,6-$(CH_3O)_3$	7.5	7.5
8s	3-NO_2, 4-CH_3O	2,6-$(CH_3O)_2$, 4-OH	5.0	5.0
8t	3-NH_2, 4-CH_3O	2,6-$(CH_3O)_2$, 4-OH	0.2	0.3
8u	3-NH_2, 4-CH_3O	2,6-$(CH_3O)_2$, 4-O-$(CH_2)_3$COOH	25	20
8v	3-NO_2, 4-Br	2,4,6-$(CH_3O)_3$	25	25
8w	3-NH_2, 4-Br	2,4,6-$(CH_3O)_3$	0.75	0.75
8x	3-NH_2, 4-Cl	2,4,6-$(CH_3O)_3$	0.01	0.01
8y	2-NH_2, 4-Cl	2,4,6-$(CH_3O)_3$	2.5	2.5
8z	3-NO_2, 4-F	2,4,6-$(CH_3O)_3$	25	25
8aa	3-NH_2, 4-F	2,4,6-$(CH_3O)_3$	2.5	2.5
8ab	3-NH_2, 4-CH_3O	2,4,6-F_3	2.0	0.8
8ac	3-NH_2, 4-CH_3O	2,4,5-F_3	5.0	15

compound **27a** has superior activity over other molecules (**27b**−**l**) and as it does not have a chiral center at glycine carbon, we have made a water-soluble sodium analogue of it (**28**) to carry out our preclinical and clinical studies. Compound **28** has 28 mg/mL solubility in water and other aqueous buffers, which makes it suitable for intravenous, intraperitoneal, and oral administration of the compound.

BIOLOGICAL RESULTS AND DISCUSSION

In Vitro Antitumor Effects of 8p and 28 Compounds. We next tested the activity of two of the most active compounds (**8p** and **28**) listed in Tables 1−3 against 94 different human tumor cell lines, and surprisingly, they were found to induce apoptosis of all of these cell lines with very similar GI_{50} values (selected data shown in Table 4). These compounds (such as **8p**, and **28**) were also tested by the National Cancer Institute, USA, through its

Table 2. In Vitro Cytotoxicity of (*E*)-Styrylbenzyl Sulfides (24) and Sulfoxides (21)



				IC_{50} (μM)	
compd	R	R_1	*n*	DU145	K562
17	3-NO_2, 4-OCH_3	2,4,6-$(OCH_3)_3$	0	5.0	5.0
20	3-NO_2, 4-OCH_3	2,4,6-$(OCH_3)_3$	1	15	15
21	3-NH_2, 4-OCH_3	2,4,6-$(OCH_3)_3$	1	0.04	0.02
24	3-NH_2, 4-OCH_3	2,4,6-$(OCH_3)_3$	0	0.05	0.03

Developmental Therapeutics Program (DTP) against their panel of 60 human cancer cell lines.[18] Their results showed that these compounds exhibited broad-spectrum activity and inhibited the growth of all of the tested cell lines, including drug-resistant cell lines, at nanomolar concentrations. The finding that such a large number of tumor cell lines are sensitive to these compounds suggests that the target is essential for the proliferation and survival of cancer cells. Statistical comparison (using the NCI algorithm COMPARE) revealed that these drugs are mitotic blockers of tumor cells. This statistical observation was further substantiated by flow cytometry analysis shown in Figure 2.

8p and 28 Compounds Are Highly Active against Drug Resistant Tumor Cell Lines. Development of multidrug resistance (MDR) to classical chemotherapeutic agents is a clinical problem oncologists face as patients fail first round treatment or become resistant during or following recurrent tumor growth. The MDR phenotype is caused by the overexpression of ATP-binding cassette (ABC) transporters divided into seven subfamily members. The overexpression of various members of this family enables the tumor cells to actively pump out a wide range of amphipathic drugs such that the intracellular concentrations are no longer cytotoxic. To further investigate the activity of these compounds against MDR positive tumor types, we determined the IC_{50} values of **8p** and **28** using two classical MDR positive cell lines (Table 5). The results shown in Figure 1A show a 96 h dose response of the uterine sarcoma cell line MES-SA and the multidrug resistant subline MES-SA/DX5[19] treated with **28** compared to a dose response against paclitaxel, a known substrate for P-glycoprotein. This cell line has been shown to express high levels of P-glycoprotein (ABCB1) and is resistant to a number of hydrophobic compounds including doxorubicin, paclitaxel, vincristine, vinblastine, etoposide, mitoxantrone, dactinomycin, and daunorubucin. Our results show that the parental cell line was very sensitive to paclitaxel (IC_{50} = 4 nM) but the MDR positive subline was greater than 100-fold resistant (IC_{50} = 750 nM). When the two cell lines were treated with **28**, both the parental and the MDR positive cell lines were equally sensitive to the cell killing activity of the compound with an IC_{50} of 0.1 μM (Table 5). A second MDR cell line, derived from an ovarian tumor, was also tested. Once again, both the parental and the resistant cell lines were equally sensitive to compound **28** (Table 5). We also investigated as to whether atypical multidrug resistant cells are sensitive to **28**. For these studies, we employed the parental leukemic cell line CEM and its MDR subline CEM/C2 (Figure 1B).[20] CEM/C2

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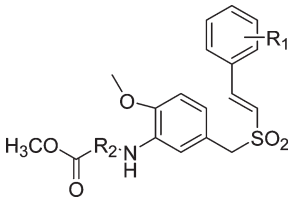
Table 3. In Vitro Cytotoxicity of 3-Amino Substituted Esters 26 and Acids 27 and Sodium Salt 28



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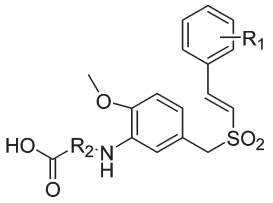

27

			IC_{50} (μM)	
compd	R_1	R_2	DU145	K562
26a	2,4,6-$(CH_3O)_3$	CH_2	0.1	0.1
26b	3,4,5-$(CH_3O)_3$	CH_2	75	30
26c	2,4,6-$(CH_3O)_3$	CH_2CH_2	1.5	1.0
26d	2,4,6-$(CH_3O)_3$	$CH(CH_3)$	0.75	0.2
26e	2,4,6-$(CH_3O)_3$	CF_2	0.25	0.25
26f	2,4,6-$(CH_3O)_3$	$CH(CF_3)$	0.25	0.25
26g	2,4,6-$(CH_3O)_3$	$C(CH_3)_2$	2.5	0.80
26h	2,4,6-$(CH_3O)_3$	$CH(C_6H_5)$	0.075	0.03
26i	2,4,6-$(CH_3O)_3$	$CH(4\text{-}FC_6H_4)$	0.3	0.8
26j	2,4,6-$(CH_3O)_3$	$CH(4\text{-}ClC_6H_4)$	0.4	0.2
26k	2,4,6-$(CH_3O)_3$	$CH(4\text{-}BrC_6H_4)$	0.3	0.2
26l	2,4,6-$(CH_3O)_3$	$CH(4\text{-}MeOC_6H_4)$	0.25	0.15
27a	2,4,6-$(CH_3O)_3$	CH_2	0.075	0.0075
27b	3, 4, 5-$(CH_3O)_3$	CH_2	5.0	3.0
27c	2,4,6-$(CH_3O)_3$	CH_2CH_2	5.0	5.0
27d	2,4,6-$(CH_3O)_3$	$CH(CH_3)$	0.025	0.015
27e	2,4,6-$(CH_3O)_3$	CF_2	0.15	0.15
27f	2,4,6-$(CH_3O)_3$	$CH(CF_3)$	0.02	0.075
27g	2,4,6-$(CH_3O)_3$	$C(CH_3)_2$	0.15	0.0075
27h	2,4,6-$(CH_3O)_3$	$CH(C_6H_5)$	0.02	0.015
27i	2,4,6-$(CH_3O)_3$	$CH(4\text{-}FC_6H_4)$	0.15	0.08
27j	2,4,6-$(CH_3O)_3$	$CH(4\text{-}ClC_6H_4)$	0.4	0.25
27k	2,4,6-$(CH_3O)_3$	$CH(4\text{-}BrC_6H_4)$	0.3	0.2
27l	2,4,6-$(CH_3O)_3$	$CH(4\text{-}OMeC_6H_4)$	0.1	0.015
28	ON 01910.Na		0.1	0.015

was selected and subcloned for resistance to camptothecin and has cross-resistance to etoposide, dactinimycin, bleomycin, mitoxantrone, doxorubicin, and daunorubicin. As shown in Figure 1B and Table 5, compound **28** was active against both the parental and the camptothecin resistant subclone, with the CEM/C2 clone being 2-fold more sensitive than the parental. These studies clearly demonstrate that this chemotype will not be a substrate for ABC transport proteins and therefore be a suitable treatment option for tumors expressing both classical and atypical MDR resistant markers.

Effects of 28 on Cell Cycle Progression of Normal and Tumor Cells. We next examined the effect of these compounds on normal and tumor cell cycle progression using FACS analysis. Figure 2A shows the effect of **28** on the cell cycle progression of normal diploid human fetal lung (HFL-1) and DU145 (prostate cancer) cells (Figure 2B). The results of this study show that the addition of the **28** to DU145 cells resulted in a block of their cell cycle progression in G2/M phase of the cell cycle in a dose

Table 4. Evaluation of 8p and 28 against a Panel of Human Tumor Cell Lines and Normal Fibroblasts

		IC_{50} (μM)	
cell line	tumor type	**8p**	**28**
BT20	breast (ER−)	0.03	0.08
T47D	breast (ER+)	0.003	0.17
MCF-7	breast (ER+)	0.001	0.075
SK-BR-3	breast (ER−)	0.003	0.075
BT474	breast (ER+)	0.002	0.05
MDA-MB-231	breast (triple neg)	ND	0.025
MDA-MB-157	breast (triple neg)	ND	0.075
Hcc70	breast	ND	0.075
HCC1428	breast	ND	0.06
DU145	prostate (AR−)	0.005	0.1
PC-3	prostate (AR+)	0.006	0.15
OV-CAR-3	ovarian	0.003	0.075
MIA-Paca2	pancreatic	0.003	0.05
BxPC-3	pancreatic	ND	0.075
PANC-1	pancreatic	ND	0.04
U87	glioblastoma	0.003	0.08
H157	NSCLC	0.004	0.08
A549	NSCLC	0.003	0.09
H1975	NSCLC	0.003	0.09
H187	SCLC	0.004	0.08
N417	SCLC	0.003	0.08
AGS	gastric	0.003	0.08
RF1	gastric	0.002	0.05
RF48	gastric	0.001	0.05
HELA	cervical	ND	0.1
COLO-205	colorectal	0.005	0.15
DLD-1	colorectal	0.005	0.15
HCT-116	colorectal	0.003	0.075
HCT-15	colorectal	0.003	0.09
COLO-320	colorectal	0.003	0.06
SW480	colorectal	0.005	0.06
RPMI-7951	melanoma	ND	0.025
WM983A	melanoma	ND	0.04
WM3211	melanoma	ND	0.075
WM1341D	melanoma	ND	0.1
WM278	melanoma	ND	0.15
WM239A	melanoma	ND	0.075
WM-793	melanoma	ND	0.075
451-LU	melanoma	ND	0.025
DND-1A	melanoma	ND	0.075
K562	CML	0.0025	0.015
MOLT-4	T-lymphoblastic: all	0.004	0.04
Z138C	mantle cell lymphoma	0.003	0.075
GRANTA-519	mantle cell lymphoma	0.003	0.075
Bel-7402	hepatoma	ND	0.1
KB	nasopharyngeal	ND	0.07
HELA	cervical	ND	0.1
U937	lymphoma	ND	0.01
LP-1	multiple myeloma	0.003	0.03
U266	multiple myeloma	0.003	0.025
OPM-2	multiple myeloma	0.003	0.015

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Table 4. Continued

cell line	tumor type	IC_{50} (μM) 8p	28
RPMI-8266	multiple myeloma	0.003	0.01
HL-60	AML M3	ND	0.02
KG1a	AML M1	ND	0.03
HEL	AML M6	ND	0.05
Daudi	Burkitt's lymphoma (B-cell)	0.003	0.15
Raji	Burkitt's lymphoma (B-cell)	0.002	0.075
Namalwa	Burkitt's lymphoma (B-cell)	0.005	0.075
fibroblast	PS-41	ND	>100
endothelial	Hu-VEC	ND	>100

Table 5. Evaluation of 8p and 28 against a Panel of Multidrug-Resistance Human Tumor Cell Lines

cell line	tumor type	IC_{50} (μM) 8p	28
MES-SA	sarcoma	0.004	0.1
MES-SA/DXS[a]	resistant sarcoma	0.004	0.1
CEM	leukemic	0.01	0.1
CEM/C2[a]	resistant leukemic	0.01	0.05
2008	ovarian	0.003	0.15
2008/17/4	resistant ovarian	0.003	0.1

[a] These cell lines constitute multidrug-resistance cell lines and show up-regulation of MDR and in the case of CEM/C2, additional mutations in the Topo-2 gene.[19,20]

dependent manner. In addition, treatment of the tumor cells resulted in an accumulation of cells containing subG1 content of DNA, which is an indication of cell death. On the other hand, treatment of normal diploid fibroblasts cells (HFL-1) with **28** resulted in a block of their cell cycle progression in the G_1 and G2/M phases of the cell cycle, without the corresponding induction of cell death. We further investigated the selective nature of cell killing by running studies aimed at studying the activation of the apoptotic pathway. Tumor and normal cell lines were then treated with **28** and activation of apoptotic pathways, as judged by PARP [poly(ADP-ribose) polymerase-1] cleavage,[21] is shown in (Figure 3). Treatment of **28** selectively induced PARP cleavage in the tumor cell line, while there was no PARP cleavage in the treated normal cell line. Since it is well-known that PARP cleavage is the result of activation of caspase 3, we further investigated the activation of the apoptotic pathway by looking at cellular viability together with the activity of caspases 3 and 7. A dual viability and caspase activation assay was performed in A549 cells treated with **28** which showed the concentrations at which **28** activated the apoptotic machinery to induce a cytotoxic effect (Figure 4). These data show that treatment with 0.25 μM induced loss of viability with the concomitant induction of caspase 3/7 within 24 h of tumor cell treatment. Taken together, these data show that **28** selectively induces G2/M cell cycle block with the induction of apoptosis in tumor cells.

In Vivo Antitumor Effect of 28. In order to determine in vivo efficacy, we utilized the nude mouse model system. A highly aggressive human estrogen negative breast carcinoma cell line (BT20) was xenografted into athymic nude mice. The animals were treated with 200 mg/kg of **28** using Q2D × 20 schedules. The animals were treated when the tumors were approximately 70 mm^3 in size. Figure 5A shows that an intraperitoneal (ip) injection of **28** was able to significantly inhibit the growth of the tumors. The tumors of vehicle treated mice, on average, increased in volume over the 22 day period by 5-fold (70−480 mm^3), while the Q2D **28** treated tumors increased in volume by only 2.5-fold (70−180 mm^3). **28** was well tolerated at these doses as determined by body weights and physical observations (Figure 5B). These studies show that **28** is efficacious against human tumor xenografts while showing no signs of toxicity at the schedules tested under this study.

CONCLUSION

In this communication, we describe the synthesis of a group of (*E*)-styrylbenzylsulfones that induce apoptotic death of a wide variety of human tumor cell lines at subnanomolar concentrations while exhibiting relatively low toxicity to normal human cells. Our studies show that the cytoxic activity of the (*E*)-styrylbenzylsulfones is completely dependent on the nature and position of the substituents on the two aromatic rings. These structure−function studies show that a molecule with a benzyl moiety having 3-amino and 4-methoxy groups and a styryl ring with methoxy groups at 2-, 4-, and 6-positions showed optimum biological activity (**8p**). Biological evaluation of the activity of these compounds shows that these compounds are highly active against a wide variety of human tumor cell lines including those that are resistant to the activity of many of the currently used chemotherapeutic agents.

The low toxicity profile, both in vitro and in vivo, and their potent tumor inhibitory activity as seen in nude mouse xenograft assays point to the potential value of these compounds as safe therapies for cancer, lacking many of the side effects normally associated with current chemotherapeutic agents. Recent studies with **28** show that this compound altered the growth and cell cycle status of mantle cell lymphoma cell lines and potently inhibited the expression of several important proteins, including cyclin D1, p-mTOR, and PI3-K.[6] Since **28** is highly effective in various combinations with conventional chemotherapy,[6] the lack of overt hematotoxicity of this compound is beneficial for testing novel combinations for advanced cancers, including tumors resistant to conventional chemotherapy. In addition, its safety profile seen with normal hematopoietic cells suggests that these compounds have a potential use in in vitro purging of tumor cells from patient bone marrow for use in autologous bone marrow transplantation. Clinical studies in MDS (phase III) and pancreatic (phase II/III) patients currently underway will reveal the best way to utilize this compound in cancer therapy.

EXPERIMENTAL SECTION

Chemistry: General Experimental Procedures. All reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen, and solvents were dried using standard procedures. Reagents and solvents were obtained in the highest available purity and used without further purification unless indicated. Reactions were monitored by thin layer chromatography (TLC) on preloaded silica gel 60 glass-backed plates with F^{254} plates as the indicator (Sigma-Aldrich), developed using mobile phases of varying compositions of ethyl acetate/hexane and methanol/chloroform, and the spots were visualized by a UV indicator. Column chromatography was performed with Merck 70−320

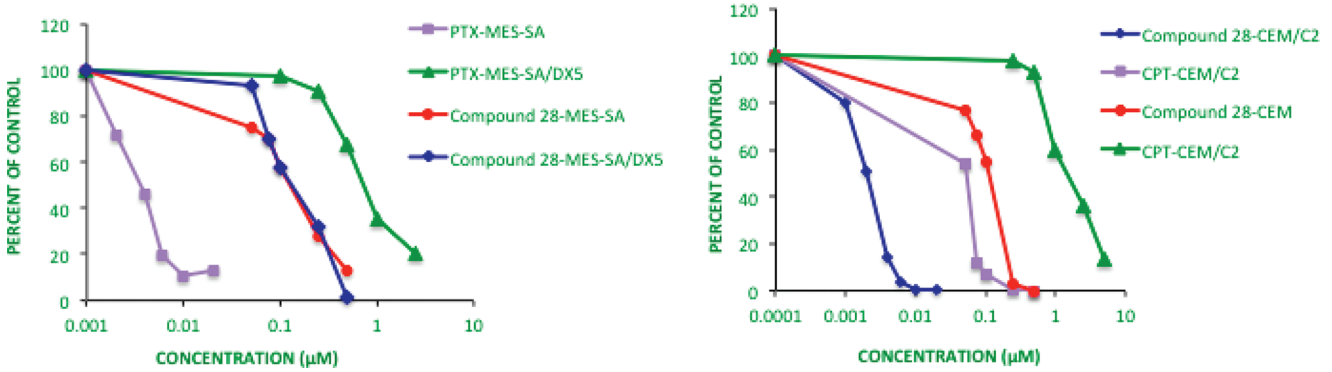

Figure 1. **28** is active against multidrug resistant cells (MDR). (A, left) The MDR-1 positive MES-SA/DX5 clone and an atypical MDR resistant to topoisomerase inhibitors CEM/C2 (B, right) and their respective sensitive parental controls were plated into six-well dishes and treated with increasing concentrations of **28** or a representative chemotherapeutic agent, paclitaxel (PTX) or camptothecin (CPT), for 96 h. The number of viable cells from duplicate plates was determined by trypan blue exclusion. As expected, the parentals are sensitive to both **28** and the chemotherapeutic agent, but while the resistant clones are over 500-fold resistant to PTX or CPT, they remain sensitive to the cytotoxic action of **28**.

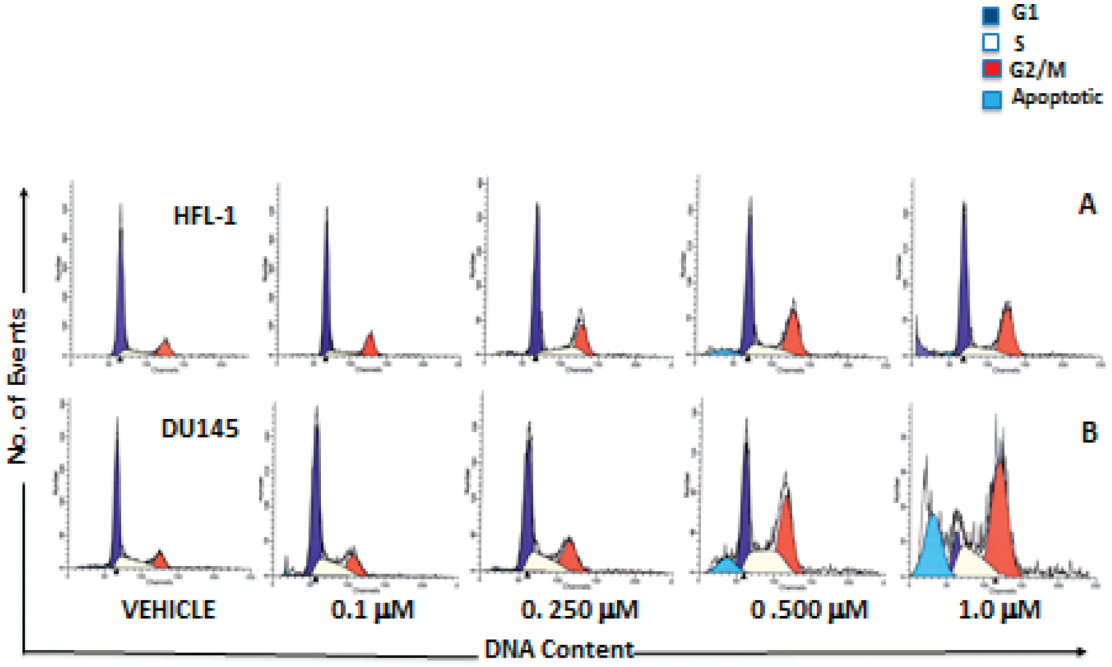

Figure 2. **28** selectively induces mitotic G2/M arrest and apoptosis in cancer cells. (A) Normal diploid fibroblasts HFL-1 cells or (B) human prostate cells (DU145) were treated with increasing concentrations of **28** and incubated in medium containing 10% fetal bovine serum for 24 h. The cells were fixed, stained with propidium iodide, and then subjected to FACS analysis and analyzed for their DNA content. **28** induces a mitotic arrest and induction of a subG1 population (blue) indicative of apoptosis in the cancer cell line while only inducing a small mitotic block in the normal cells.

mesh silica gel. Melting points were determined using an Electrothermal MEL-Temp 3.0 micro melting point apparatus with a Fluka 51 K/J electronic thermometer and are uncorrected. Nuclear magnetic resonance spectra for proton (^{1}H NMR) were recorded on Bruker Avance III (300 MHz), Varian INOVA (400 MHz), and GE (500 MHz) spectrometers. ^{13}C NMR spectra (75 MHz) were obtained on a Bruker Avance III 300 MHz spectrometer. The chemical shift values are expressed in ppm (parts per million) relative to tetramethylsilane as an internal standard: s, singlet; d, doublet; dd, doublet of a doublet; t, triplet; m, multiplet; br s, broad singlet. Coupling constants (*J*) were measured in hertz (Hz). Compounds purity was determined by elemental analyses (0.4%) or LC/MS analysis and was confirmed to be >95% for all compounds. All LC/MS data were gathered on an Agilent 1200 LC with Agilent 6410 triple quadrupole mass spectrometer detectors. The compound solution was infused into the electron spray ionization source operating in positive and negative modes.

General Procedure for the Preparation of Benzyl Bromides (2). Method A (Scheme 2). To a well stirred solution of substituted toluene **1** (40 mmol) in carbon tetrachloride (150 mL) were added benzoyl peroxide (4.0 mmol) and *N*-bromosuccinimide (48 mmol). The reaction mixture was heated at reflux for 18 h. After completion of the reaction (TLC monitoring, hexane/ethyl acetate, 9:1, on silica gel plate), the contents were cooled to room temperature, water was added, and the product was isolated by extraction with dichloromethane. The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain the desired crude product **2**. The pure compound **2** was obtained following purification by silica gel flash column chromatography (hexane/ethyl

acetate, 9:1). The following benzyl bromides **2** were prepared using the above procedure.

4-Methoxy-3-nitrobenzyl Bromide (2a). Radical benzylic bromination of 4-methyl-2-nitroanisole yielded the corresponding 4-methoxy-3-nitrobenzyl bromide. The yield of this reaction was 68%, giving a light yellow solid with a melting point of 106−108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.97 (s, 3H, OCH_3), 4.47 (s, 2H, CH_2), 7.08 (d, J = 8.7 Hz, 1H, Ar−H), 7.58 (dd, J = 8.7, 2.1 Hz, 1H, Ar−H), 7.89 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 245.9688; found 245.9682. Anal. ($C_8H_8BrNO_3$) C, H, N.

4-Methoxy-2-nitrobenzyl Bromide (2b). Radical benzylic bromination of 4-methyl-3-nitroanisole yielded the corresponding 4-methoxy-2-nitrobenzyl bromide. The yield of this reaction was 65%, giving a yellow solid with a melting point of 60−62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H, OCH_3), 4.81 (s, 2H, CH_2), 7.14 (dd, J = 8.4, 2.7 Hz, 1H, Ar−H), 7.48 (d, J = 8.7 Hz, 1H, Ar−H), 7.56 (d, J = 2.7 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 245.9688; found 245.9681. Anal. ($C_8H_8BrNO_3$) C, H, N.

4-Bromo-3-nitrobenzyl Bromide (2c). Radical benzylic bromination of 4-bromo-3-nitrotoluene yielded the corresponding 4-bromo-3-nitrobenzyl bromide. The yield of this reaction was 78%, giving a yellow solid with a melting point of 62−63 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.45 (s, 2H, CH_2), 7.47 (dd, J = 8.4, 2.4 Hz, 1H, Ar−H), 7.73 (d, J = 8.4 Hz, 1H, Ar−H), 7.89 (d, J = 2.0 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 295.8667; found 295.8662. Anal. ($C_7H_5Br_2NO_2$) C, H, N.

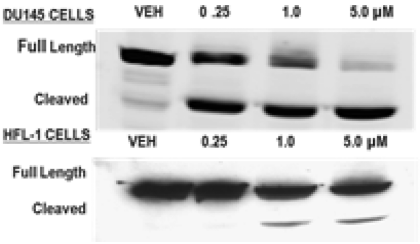

Figure 3. DU145 and HFL-1 (normal human fibroblasts) cells were treated with increasing concentrations of **28** or DMSO (vehicle) for 48 h. Cells were harvested, and total protein was resolved by 10% SDS−PAGE, Western blotted and hybridized to anti-PARP (Cell Signaling no. 542) antibody. The blot was then washed and treated with anti-rabbit secondary labeled with infrared dye (700) and scanned using the Odyssey scanner (LiCor).

4-Chloro-3-nitrobenzyl Bromide (2d). Radical benzylic bromination of 4-chloro-3-nitrotoluene yielded the corresponding 4-chloro-3-nitrobenzyl bromide. The yield of this reaction was 87%, giving a pale yellow liquid with a boiling point of 115−120 °C (0.25 mmHg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.60 (s, 2H, CH_2), 7.42 (dd, J = 8.4, 2.4 Hz, 1H, Ar−H), 7.68 (d, J = 8.4 Hz, 1H, Ar−H), 7.86 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 249.9192; found 249.9186. Anal. ($C_7H_5BrClNO_2$) C, H, N.

4-Chloro-2-nitrobenzyl Bromide (2e). Radical benzylic bromination of 4-chloro-2-nitrotoluene yielded the corresponding 4-chloro-2-nitrobenzyl bromide. The yield of this reaction was 69%, giving a pale yellow solid with a melting point of 40−42 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.80 (s, 2H, CH_2), 7.54 (d, J = 8.3 Hz, 1H, Ar−H), 7.61 (dd, J = 8.3, 2.1 Hz, Ar−H), 8.07 (d, J = 2.1 Hz, Ar−H). HRMS: m/z calcd [M + H] 249.9192; found 249.9189. Anal. ($C_7H_5BrClNO_2$) C, H, N.

4-Fluoro-3-nitrobenzyl Bromide (2f). Radical benzylic bromination of 4-fluoro-3-nitrotoluene yielded the corresponding 4-fluoro-3-nitrobenzyl bromide. The yield of this reaction was 84%, giving a yellow solid with a melting point of 50−52 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.49 (s, 2H, CH_2), 7.32(dd, J = 8.7, 1.8 Hz, 1H, Ar−H), 7.66−7.71 (m, 1H, Ar−H), 8.11 (dd, J = 6.9, 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 233.9488; found 233.9481. Anal. ($C_7H_5BrFNO_2$) C, H, N.

General Procedure for the Preparation of Benzyl Alcohols (4). Method B (Scheme 2). Sodium borohydride (20 mmol) was added in small portions to an ice-cold solution of aldehyde **3** (20 mmol) in dry methanol (100 mL) with stirring. The reaction mixture was left at 0−5 °C for 1 h. After completion of the reaction (TLC monitoring, hexane/ethyl acetate, 9:1 on silica gel plate), the solvent was evaporated. Then the chloroform (100 mL) was added to the residue obtained. The organic layer was washed with 5% sodium bicarbonate (50 mL) and water (75 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain the desired crude product **4**. The pure compound **4** was obtained after recrystallization from benzene/hexane. The following benzyl alcohols **4** were prepared using the above procedure.

4-Methoxy-3-nitrobenzyl Alcohol (4a). Reduction of 4-methoxy-3-nitrobenzaldehyde yielded the corresponding 4-methoxy-3-nitrobenzyl alcohol. The yield of this reaction was 78%, giving a yellow solid

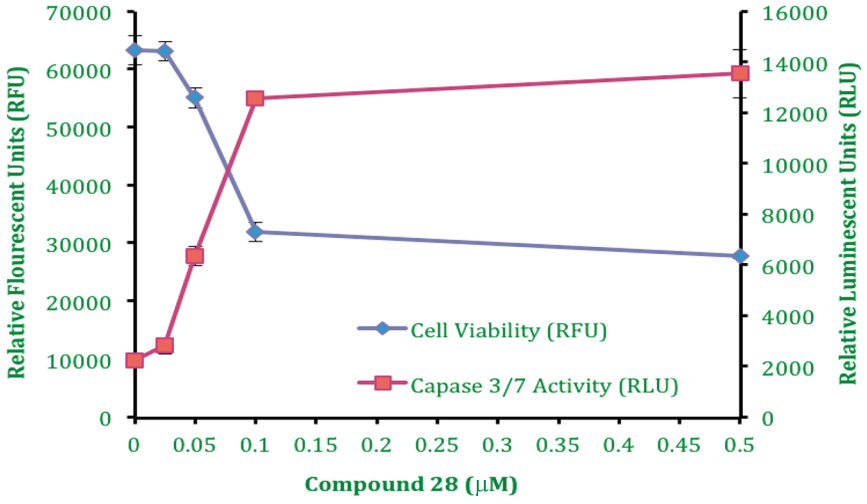

Figure 4. Cellular viability and the activity of caspases 3/7 were assayed concomitantly in A549 cells treated with **28** for 24 h (n = 3). Viability was measured after addition of CellTiter-Blue reagent (Promega Corporation). Caspase 3/7 activity was measured after addition of Caspase-Glo 3/7 reagent (Promega Corporation). Fluorescence and luminescence were plotted together to reveal the concentrations at which **28** activated the apoptotic machinery to induce a cytotoxic effect.

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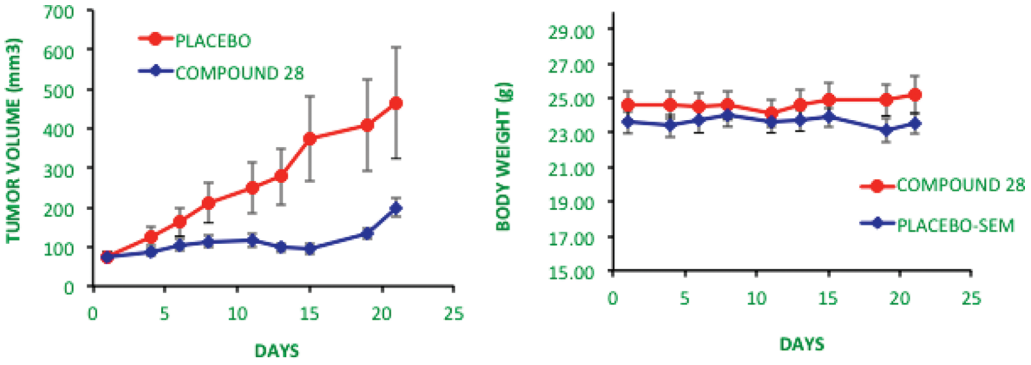

Figure 5. Human breast cancer cells (BT20) were injected subcutaneously into female nude mice. The mice were grouped and then treated with 200 mg/kg **28** by intraperitoneal injections Q2D × 20 formulated in phosphate buffered saline (PBS) or placebo (PBS) alone. Tumor volumes (A, left) and body weights (B, right) were determined, and the average (±SEM) for each group ($N = 9$) was determined and plotted. **28** significantly inhibited the in vivo growth of tumors. Placebo tumors doubled in 6 days, while it took over 18 days for the **28** treated tumors to double in size. There was no sign of toxicity or body weight loss.

with a melting point of 69−70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.65 (br s, 1H, OH), 3.96 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2), 7.12 (d, J = 8.4 Hz, 1H, Ar−H), 7.61 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.84 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 184.0532; found 184.0522. Anal. ($C_8H_9NO_4$) C, H, N.

4-Methoxy-2-nitrobenzyl Alcohol (4b). Reduction of 4-methoxy-2-nitrobenzaldehyde yielded the corresponding 4-methoxy-2-nitrobenzyl alcohol. The yield of this reaction was 73%, giving colorless needles with a melting point of 80−82 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.53 (t, J = 6.8 Hz, 1H, OH), 3.88 (s, 3H, OCH_3), 4.86 (d, J = 6.7 Hz, 2H, CH_2), 7.19 (dd, J = 8.6, 2.7 Hz, 1H, Ar−H), 7.58 (d, J = 8.6 Hz, 1H, Ar−H), 7.60 (d, J = 2.7 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 184.0532; found 184.0523. Anal. ($C_8H_9NO_4$) C, H, N.

4-Bromo-3-nitrobenzyl Alcohol (4c). Reduction of 4-bromo-3-nitrobenzaldehyde yielded the corresponding 4-bromo-3-nitrobenzyl alcohol. The yield of this reaction was 89%, giving a yellow solid with a melting point of 60−62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.61 (br s, 1H, OH), 4.71 (s, 2H, CH_2), 7.38 (d, J = 8.5 Hz, 1H, Ar−H), 7.67 (d, J = 8.3 Hz, 1H, Ar−H), 7.81 (s, 1H, Ar−H). HRMS: m/z calcd [M + H] 231.9531; found 231.9533. Anal. ($C_7H_6BrNO_3$) C, H, N.

4-Chloro-3-nitrobenzyl Alcohol (4d). Reduction of 4-chloro-3-nitrobenzaldehyde yielded the corresponding 4-chloro-3-nitrobenzyl alcohol. The yield of this reaction was 81%, giving a yellow solid with a melting point of 63−65 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.63 (br s, 1H, OH), 4.49 (s, 2H, CH_2), 7.48 (dd, J = 8.0, 2.0 Hz, 1H, Ar−H), 7.53 (d, J = 8.0 Hz, 1H, Ar−H), 7.85 (d, J = 2.0 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 188.0036; found 188.0031. Anal. ($C_7H_6ClNO_3$) C, H, N.

4-Chloro-2-nitrobenzyl Alcohol (4e). Reduction of 4-chloro-2-nitrobenzaldehyde yielded the corresponding 4-chloro-2-nitrobenzyl alcohol. The yield of this reaction was 78%, giving a pale yellow solid with a melting point of 89−91 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.91 (br s, 1H, OH), 4.92 (s, 2H, CH_2), 7.47(d, J = 8.7 Hz, 1H, Ar−H), 7.72 (dd, J = 8.7, 2.4 Hz, Ar−H), 8.09 (d, J = 2.1 Hz, Ar−H). HRMS: m/z calcd [M + H] 188.0036; found 188.0029. Anal. ($C_7H_6ClNO_3$) C, H, N.

4-Fluoro-3-nitrobenzyl Alcohol (4f). Reduction of 4-fluoro-3-nitrobenzaldehyde yielded the corresponding 4-fluoro-3-nitrobenzyl alcohol. The yield of this reaction was 91%, giving a colorless solid with a melting point of 42−44 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.69 (br s, 1H, OH), 4.76 (s, 2H, CH_2), 7.28 (dd, J = 10.7, 8.6 Hz, 1H, Ar−H), 7.61−7.66 (m, 1H, Ar−H), 8.06 (dd, J = 10.7, 8.6 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 172.0732; found 172.0713. Anal. ($C_7H_6FNO_3$) C, H, N.

6-Methoxy-3-nitrobenzyl Alcohol (4g). Reduction of 6-methoxy-3-nitrobenzaldehyde yielded the corresponding 6-methoxy-3-nitrobenzyl alcohol. The yield of this reaction was 77%, giving a white solid with a melting point of 123−125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (br s, 1H, OH), 3.97 (s, 3H, OCH_3), 4.73 (d, J = 4.1 Hz, 2H, CH_2), 6.93 (d, J = 9.0 Hz, 1H, Ar−H), 8.19 (dd, J = 9.0, 2.8 Hz, 1H, Ar−H), 8.26 (d, J = 2.8 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 184.0532; found 184.0521. Anal. ($C_8H_9NO_4$) C, H, N.

General Procedure for the Preparation of Benzyl Bromides (2). Method B (Scheme 2). Phosphorus tribromide (24 mmol) was added to a stirred solution of alcohol **4** (20 mmol) and toluene (40 mL) at 40 °C. The solution was heated to 100 °C for 30 min, and after completion of the reaction (TLC monitoring, hexane/ethyl acetate, 9:1 on silica gel plate), the contents were cooled to ambient temperature. The liquid was decanted and washed with water (2 × 50 mL) and brine (50 mL). The combined aqueous washes were extracted with ether (2 × 75 mL), and the combined organic fractions were dried and evaporated to give crude residue. The residue was dissolved in ether (100 mL) and washed with water (2 × 50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated to get the crude product **2**, which on silica gel flash chromatography (hexane/ethyl acetate, 9:1) resulted in pure benzyl bromide **2**. The following benzyl bromides **2** were prepared using the above procedure.

4-Methoxy-3-nitrobenzyl Bromide (2a). Bromination of the alcohol **4a** with phosphorus tribromide yielded the corresponding **2a**. The yield of this reaction was 52%. The analytical data are in accord with above method A procedure.

4-Methoxy-2-nitrobenzyl Bromide (2b). Bromination of the alcohol **4b** with phosphorus tribromide yielded the corresponding **2b**. The yield of this reaction was 58%. The analytical data are in accord with above method A procedure.

4-Bromo-3-nitrobenzyl Bromide (2c). Bromination of the alcohol **4c** with phosphorus tribromide yielded the corresponding **2c**. The yield of this reaction was 62%. The analytical data are in accord with above method A procedure.

4-Chloro-3-nitrobenzyl Bromide (2d). Bromination of the alcohol **4d** with phosphorus tribromide yielded the corresponding **2d**. The yield of this reaction was 59%. The analytical data are in accord with above method A procedure.

4-Chloro-2-nitrobenzyl Bromide (2e). Bromination of the alcohol **4e** with phosphorus tribromide yielded the corresponding **2e**. The yield of this reaction was 63%. The analytical data are in accord with above method A procedure.

4-Fluoro-3-nitrobenzyl Bromide (2f). Bromination of the alcohol **4f** with phosphorus tribromide yielded the corresponding **2f**.

The yield of this reaction was 54%. The analytical data are in accord with above method A procedure.

6-Methoxy-3-nitrobenzyl Bromide (2g). Bromination of the 6-methoxy-3-nitrobenzyl alcohol **4g** with phosphorus tribromide yielded the corresponding 6-methoxy-3-nitrobenzyl bromide **2g**. The yield of this reaction was 55%, giving a white solid with a melting point of 76−78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.97 (s, 3H, OCH_3), 4.73 (s, 2H, CH_2), 6.93 (d, J = 9.0 Hz, 1H, Ar−H), 8.19 (dd, J = 9.0, 2.8 Hz, 1H, Ar−H), 8.26 (d, J = 2.8 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 245.9688; found 245.9674. Anal. ($C_8H_8BrNO_3$) C, H, N.

General Procedure for the Preparation of Benzylthioacetic Acids (5). (Scheme 1). The following benzylthioacetic acids were prepared according to the procedure reported in the literature.[7]

4-Methoxy-3-nitrobenzylthioacetic Acid (5a). Condensation of 4-methoxy-3-nitrobenzyl bromide **2a** with mercaptoacetic acid yielded the corresponding 4-methoxy-3-nitrobenzylthioacetic acid. The yield of this reaction was 96%, giving a pale yellow solid with a melting point of 129−133 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.12 (s, 2H, $-SCH_2$), 3.82 (s, 2H, CH_2S), 3.90 (s, 3H, OCH_3), 7.32 (d, J = 8.4 Hz, 1H, Ar−H), 7.59 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.82 (d, J = 2.1 Hz, 1H, Ar−H), 12.60 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 256.0358; found 256.0346. Anal. ($C_{10}H_{11}NO_5S$) C, H, N.

4-Methoxy-2-nitrobenzylthioacetic Acid (5b). Condensation of 4-methoxy-2-nitrobenzyl bromide **2b** with mercaptoacetic acid yielded the corresponding 4-methoxy-2-nitrobenzylthioacetic acid. The yield of this reaction was 86%, giving a light yellow solid with a melting point of 86−88 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.05 (s, 2H, $-SCH_2$), 3.81 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2S), 7.04 (dd, J = 8.4, 2.7 Hz, 1H, Ar−H), 7.33 (d, J = 8.7 Hz, 1H, Ar−H), 7.49 (d, J = 2.7 Hz, 1H, Ar−H), 12.41 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 256.0358; found 256.0349. Anal. ($C_{10}H_{11}NO_5S$) C, H, N.

4-Bromo-3-nitrobenzylthioacetic Acid (5c). Condensation of 4-bromo-3-nitrobenzyl bromide **2c** with mercaptoacetic acid yielded the corresponding 4-bromo-3-nitrobenzylthioacetic acid. The yield of this reaction was 92%, giving a yellow solid with a melting point of 133−135 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.15 (s, 2H, $-SCH_2$), 4.05 (s, 2H, CH_2S), 7.51 (d, J = 8.1, Hz, 1H, Ar−H), 7.91 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 8.21 (d, J = 1.8 Hz, 1H, Ar−H), 12.60 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 303.9357; found 303.9348. Anal. ($C_9H_8BrNO_4S$) C, H, N.

4-Chloro-3-nitrobenzylthioacetic Acid (5d). Condensation of 4-chloro-3-nitrobenzyl bromide **2d** with mercaptoacetic acid yielded the corresponding 4-chloro-3-nitrobenzylthioacetic acid. The yield of this reaction was 90%, giving a yellow solid 110−114 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.15 (s, 2H, $-SCH_2$), 3.86 (s, 2H, CH_2S), 7.42 (d, J = 8.1 Hz, 1H, Ar−H), 7.69 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.92 (d, J = 1.8 Hz, 1H, Ar−H), 12.70 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 259.9863; found 259.9856. Anal. ($C_9H_8ClNO_4S$) C, H, N.

4-Chloro-2-nitrobenzylthioacetic Acid (5e). Condensation of 4-chloro-2-nitrobenzyl bromide **2e** with mercaptoacetic acid yielded the corresponding 4-chloro-2-nitrobenzylthioacetic acid. The yield of this reaction was 92%, giving a yellow solid with a melting point of 103−105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13 (s, 2H, $-SCH_2$), 4.22 (s, 2H, CH_2S), 7.47 (d, J = 8.1 Hz, 1H, Ar−H), 7.57 (dd, J = 8.1, 2.1 Hz, 1H, Ar−H), 8.04 (d, J = 2.1 Hz, 1H, Ar−H), 12.73 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 259.9863; found 259.9851. Anal. ($C_9H_8ClNO_4S$) C, H, N.

4-Fluoro-3-nitrobenzylthioacetic Acid (5f). Condensation of 4-fluoro-2-nitrobenzyl bromide **2f** with mercaptoacetic acid yielded the corresponding 4-fluoro-3-nitrobenzylthioacetic acid. The yield of this reaction was 88%, giving a pale yellow solid with a melting point of 74−76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.12 (s, 2H, $-SCH_2$), 3.92 (s, 2H, CH_2S), 7.28 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.61−7.68 (m, 1H, Ar−H), 8.07 (dd, J = 6.9, 2.4 Hz, 1H, Ar−H), 12.61 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 244.0158; found 244.0143. Anal. ($C_9H_8FNO_4S$) C, H, N.

6-Methoxy-3-nitrobenzylthioacetic Acid (5g). Condensation of 6-methoxy-3-nitrobenzyl bromide **2g** with mercaptoacetic acid yielded the corresponding 6-methoxy-3-nitrobenzylthioacetic acid. The yield of this reaction was 86%, giving a pale yellow solid with a melting point of 76−78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.08 (s, 2H, $-SCH_2$), 3.74 (s, 2H, CH_2S), 3.98 (s, 3H, OCH_3), 7.29 (d, J = 9.0 Hz, 1H, Ar−H), 8.21 (m, 1H, Ar−H), 8.30 (d, J = 3.0 Hz, 1H, Ar−H). HRMS: m/z calcd [M − H] 256.0358; found 256.0349. Anal. ($C_{10}H_{11}NO_5S$) C, H, N.

General Procedure for the Preparation of Benzylsulfonylacetic Acids (6). (Scheme 1). The following benzylsulfonylacetic acids were prepared according to the procedure reported in the literature.[7]

4-Methoxy-3-nitrobenzylsulfonylacetic Acid (6a). Oxidation of 4-methoxy-3-nitrobenzylthioacetic acid **5a** with 30% hydrogen peroxide yielded the corresponding 4-methoxy-3-nitrobenzylsulfonylacetic acid. The yield of this reaction was 51%, giving a yellow solid with a melting point of 137−139 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.79 (s, 2H, SCH_2), 3.86 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2S), 7.08 (d, J = 9.0 Hz, 1H, Ar−H), 7.59 (dd, J = 8.5, 2.5 Hz, 1H, Ar−H), 7.86 (d, J = 2.5 Hz, 1H, Ar−H), 13.42 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 288.0256; found 288.0251. Anal. ($C_{10}H_{11}NO_7S$) C, H, N.

4-Methoxy-2-nitrobenzylsulfonylacetic Acid (6b). Oxidation of 4-methoxy-2-nitrobenzylthioacetic acid **5b** with 30% hydrogen peroxide yielded the corresponding 4-methoxy-2-nitrobenzylsulfonylacetic acid. The yield of this reaction was 63%, giving a pale yellow solid with a melting point of 158−161 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.87 (s, 3H, OCH_3), 4.27 (s, 2H, $-SCH_2$), 5.02 (s, 2H, CH_2S), 7.36 (dd, J = 8.4, 2.7 Hz, 1H, Ar−H), 7.53 (d, J = 8.7 Hz, 1H, Ar−H), 7.57 (d, J = 2.4 Hz, 1H, Ar−H), 13.53 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 288.0256; found 288.0244. Anal. ($C_{10}H_{11}NO_7S$) C, H, N.

4-Bromo-3-nitrobenzylsulfonylacetic Acid (6c). Oxidation of 4-bromo-3-nitrobenzylthioacetic acid **5c** with 30% hydrogen peroxide yielded the corresponding 4-bromo-3-nitrobenzylsulfonylacetic acid. The yield of this reaction was 62%, giving a yellow solid with a melting point of 172−174 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.30 (s, 2H, $-SCH_2$), 4.81(s, 2H, CH_2S), 7.65 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 8.01 (d, J = 8.4 Hz, 1H, Ar−H), 8.08 (d, J = 1.8 Hz, 1H, Ar−H), 13.58 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 335.9256; found 335.9252. Anal. ($C_9H_8BrNO_6S$) C, H, N.

4-Chloro-3-nitrobenzylsulfonylacetic Acid (6d). Oxidation of 4-chloro-3-nitrobenzylthioacetic acid **5d** with 30% hydrogen peroxide yielded the corresponding 4-chloro-3-nitrobenzylsulfonylacetic acid. The yield of this reaction was 68%, giving a yellow solid with a melting point of 161−163 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.27 (s, 2H, $-SCH_2$), 4.77 (s, 2H, CH_2S), 7.61 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.98 (d, J = 8.4 Hz, 1H, Ar−H), 8.04 (d, J = 1.8 Hz, 1H, Ar−H), 13.60 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 291.9761; found 291.9755. Anal. ($C_9H_8ClNO_6S$) C, H, N.

4-Chloro-2-nitrobenzylsulfonylacetic Acid (6e). Oxidation of 4-chloro-2-nitrobenzylthioacetic acid **5e** with 30% hydrogen peroxide yielded the corresponding 4-chloro-2-nitrobenzylsulfonylacetic acid. The yield of this reaction was 64%, giving a yellow solid with a melting point of 113−115 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.36 (s, 2H, $-SCH_2$), 5.00 (s, 2H, CH_2S), 7.65 (dd, J = 8.4, 3.0 Hz, 1H, Ar−H), 7.80 (d, J = 8.4 Hz, 1H, Ar−H), 8.18 (d, J = 1.8 Hz, 1H, Ar−H), 13.70 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 291.9761; found 291.9753. Anal. ($C_9H_8ClNO_6S$) C, H, N.

4-Fluoro-3-nitrobenzylsulfonylacetic Acid (6f). Oxidation of 4-fluoro-3-nitrobenzylthioacetic acid **5f** with 30% hydrogen peroxide yielded the corresponding 4-fluoro-3-nitrobenzylsulfonylacetic acid. The yield of this reaction was 69%, giving a yellow solid with a melting point of 120−122 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.24 (s, 2H,

$-SCH_2$), 4.75 (s, 2H, CH_2S), 7.64 (dd, J = 8.4, 2.7 Hz, 1H, Ar−H), 7.79−7.84 (m, 1H, Ar−H), 8.20 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 13.40 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 276.0056; found 276.0046. Anal. ($C_9H_8FNO_6S$) C, H, N.

6-Methoxy-3-nitrobenzylsulfonylacetic Acid (6g). Oxidation of 6-methoxy-3-nitrobenzylthioacetic acid **5g** with 30% hydrogen peroxide yielded the corresponding 6-methoxy-3-nitrobenzylsulfonylacetic acid. The yield of this reaction was 67%, giving a pale yellow solid with a melting point of 166−168 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.93 (s, 3H, OCH_3), 4.28 (s, 2H, $-SCH_2$), 4.79 (s, 2H, CH_2S), 7.30 (d, J = 9.0 Hz, 1H, Ar−H), 8.26−8.28 (m, 1H, Ar−H), 8.31 (d, J = 3.0 Hz, 1H, Ar−H), 13.40 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 288.0256; found 288.0248. Anal. ($C_{10}H_{11}NO_7S$) C, H, N.

General Procedure for the Preparation of (*E*)-Styrylbenzylsulfone (8). Method A (Scheme 1). A mixture of benzylsulfonylacetic acid **6** (10 mmol), araldehyde **7** (10 mmol), glacial acetic acid (15 mL), and a catalytic amount of benzylamine (200 μL) was refluxed for about 2−8 h. After completion of the reaction (TLC monitoring, chloroform on silica gel plate), with the contents cooled to room temperature, the precipitated product was filtered and washed with 2-propanol. If solid was not formed, the reaction mixture was diluted with ether and washed successively with saturated sodium bicarbonate, dilute hydrochloric acid, and water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain the desired crude product **8**. The crude product was recrystallized in 2-propanol to yield an analytically pure sample of **8**. The following (*E*)-styrylbenzylsulfones **8** were prepared using the above procedure.

(*E*)-2′-Methoxystyryl-4-methoxy-3-nitrobenzylsulfone (8a). The title compound was obtained from 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** and 2-methoxybenzaldehyde following the procedure as described in method A. Yield, 56%; yellow solid, mp 169−171 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.92−6.99 (m, 2H, Ar−H), 7.01 (d, J = 15.6 Hz, 1H, ═CH), 7.12 (d, J = 8.7 Hz, 1H, Ar−H), 7.35−7.45 (m, 2H, Ar−H), 7.62 (d, J = 15.6 Hz, 1H, CH═), 7.63 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.87 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 364.0777; found 364.0780. Anal. ($C_{17}H_{17}NO_6S$) C, H, N.

(*E*)-2′-Methoxystyryl-4-methoxy-3-aminobenzylsulfone (8b). (*E*)-2′-Methoxystyryl-4-methoxy-3-nitrobenzylsulfone **8a** (900 mg, 2.5 mmol) was dissolved in acetone/water (40:20 mL) and heated to 50 °C. After 30 min sodium hydrosulfite (8.79 g, 50.0 mmol) was added slowly, and temperature was maintained at 50 °C for a further 30 min. After completion of reaction (TLC monitoring, chloroform on silica gel plate), the contents were cooled to room temperature, water was added, and the product was isolated by extraction with ethyl acetate. The organic phase was washed with water (3 × 100 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to obtain the desired crude product **8b**. The pure compound **8b** was obtained following purification by silica gel flash column chromatography (chloroform). Yield, 51%; white solid, mp 140−142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H,OCH_3), 3.83 (s, 3H, OCH_3), 4.15 (s, 2H, CH_2), 6.95−7.02 (m, 2H, Ar−H), 6.98 (d, J = 15.6 Hz, 1H, ═CH), 7.12 (d, J = 8.7 Hz, 1H, Ar−H), 7.37−7.45 (m, 2H, Ar−H), 7.62 (d, J = 15.6 Hz, 1H, CH═), 7.63 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.87 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 334.1035; found 334.1066. Anal. ($C_{17}H_{19}NO_4S$) C, H, N.

(*E*)-4′-Methoxystyryl-4-methoxy-3-nitrobenzylsulfone (8c). The title compound was obtained from 4′-methoxy-3-nitrobenzylsulfonylacetic acid **6a** and 4-methoxybenzaldehyde following the procedure as described in method A. Yield, 58%; yellow solid, mp 172−174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.88 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.93−6.98 (m, 2H, Ar−H), 6.95 (d, J = 15.5 Hz, 1H, ═CH), 7.12 (d, J = 9.0 Hz, 1H, Ar−H), 7.36 (dd, J = 7.5, 1.5 Hz, 1H, Ar−H), 7.42−7.49 (m, 2H, Ar−H), 7.61 (d, J = 15.5 Hz, 1H, CH═), 7.86 (d, J = 2.0 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 364.0777; found 364.0765. Anal. ($C_{17}H_{17}NO_6S$) C, H, N.

(*E*)-4′-Methoxystyryl-4-methoxy-3-aminobenzylsulfone (8d). The title compound was obtained by the reduction of (*E*)-4′-methoxystyryl-4-methoxy-3-nitrobenzylsulfone **8c** following the procedure as described for compound **8b**. Yield, 49%; yellow solid, mp 152−154 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.92−6.99 (m, 2H, Ar−H), 7.01 (d, J = 15.6 Hz, 1H, ═CH), 7.12 (d, J = 8.7 Hz, 1H, Ar−H), 7.35−7.45 (m, 2H, Ar−H), 7.62 (d, J = 15.6 Hz, 1H, CH═), 7.63 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.87 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 334.1035; found 334.1068. Anal. ($C_{17}H_{19}NO_4S$) C, H, N.

(*E*)-2′,6′-Dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone (8e). The title compound was obtained from 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** and 2,6-dimethoxybenzaldehyde following the procedure as described in method A. Yield, 53%; yellow solid, mp 188−190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 6H, 2 × OCH_3), 3.90 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.48 (d, J = 8.7 Hz, 2H, Ar−H), 7.03 (d, J = 8.7 Hz, 1H, Ar−H), 7.13 (d, J = 15.6 Hz, 1H, ═CH), 7.26 (t, J = 8.4 Hz, 1H, Ar−H), 7.56 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.82 (d, J = 2.4 Hz, 1H, Ar−H), 7.84 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M + H] 394.0882; found 394.0889. Anal. ($C_{18}H_{19}NO_7S$) C, H, N.

(*E*)-2′,6′-Dimethoxystyryl-4-methoxy-2-nitrobenzylsulfone (8f). The title compound was obtained from 4-methoxy-2-nitrobenzylsulfonylacetic acid **6b** and 2,6-dimethoxybenzaldehyde following the procedure as described in method A. Yield, 52%; yellow solid, mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 6H, 2 × OCH_3), 3.80 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2), 6.47 (d, J = 8.7 Hz, 2H, Ar−H), 7.09 (dd, J = 8.4, 2.7 Hz, 1H, Ar−H), 7.16 (d, J = 15.6 Hz, 1H, ═CH), 7.25 (t, J = 8.4 Hz, 1H, Ar−H), 7.45 (m, 2H, Ar−H), 7.72 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M + H] 394.0882; found 394.0869. Anal. ($C_{18}H_{19}NO_7S$) C, H, N.

(*E*)-2′,4′-Dimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8g). Step 1: (*E*)-2′,4′-Dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 2,4-dimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′-dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. Yield, 50%; yellow solid, mp 148−150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 6H, 2 × OCH_3), 3.90 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.48 (d, J = 8.7 Hz, 2H, Ar−H), 7.03 (d, J = 8.7 Hz, 1H, Ar−H), 7.13 (d, J = 15.6 Hz, 1H, ═CH), 7.26 (t, J = 8.4 Hz, 1H, Ar−H), 7.56 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.84 (d, J = 2.4 Hz, 1H, Ar−H), 7.82 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M + H] 394.0882; found 394.0877. Anal. Calcd for $C_{18}H_{19}NO_7S$: C, 54.95%; H, 4.87%; N, 3.56%. Found: C, 55.06%; H, 4.82%; N, 3.43%.

Step 2: (*E*)-2′,4′-Dimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8g). The title compound was obtained by the reduction of (*E*)-2′,4′-dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 47%; yellow solid, mp 136−138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 6H, 2 × OCH_3), 3.98 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 6.46 (d, J = 2.4 Hz, 1H, Ar−H), 6.85 (d, J = 15.3 Hz, 1H, ═CH), 7.12 (d, J = 8.7 Hz, 1H, Ar−H), 7.29 (d, J = 8.7 Hz, 1H, Ar−H), 7.51 (d, J = 15.3 Hz, 1H, CH═), 7.63 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.86 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z [M + H] 364.1140; found 364.1129. Anal. ($C_{18}H_{21}NO_5S$) C, H, N.

(*E*)-2′,5′-Dimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8h). Step 1: (*E*)-2′,5′-Dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 2,5-dimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,5′-dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. Yield, 52%; yellow solid, mp 174−175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (s, 6H, 2 × OCH_3), 3.94 (s, 3H, OCH_3), 4.19 (s, 2H, CH_2), 6.54 (d, J = 8.7 Hz,

2H, Ar−H), 7.13 (d, J = 8.7 Hz, 1H, Ar−H), 7.17 (d, J = 15.6 Hz, 1H, =CH), 7.30 (t, J = 8.4 Hz, 1H, Ar−H), 7.59 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.78 (d, J = 2.4 Hz, 1H, Ar−H), 7.82 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 394.0882; found 394.0881. Anal. Calcd for $C_{18}H_{19}NO_7S$: C, 54.95%; H, 4.87%; N, 3.56%. Found: C, 54.86%; H, 4.75%; N, 3.47%.

Step 2: (*E*)-2′,5′-Dimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8h). The title compound was obtained by the reduction of (*E*)-2′,5′-dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 49%; yellow solid, mp 130−132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.18 (s, 2H, CH_2), 6.68−6.77 (m, 3H, Ar−H), 6.86 (d, J = 9.0 Hz, 2H, Ar−H), 6.91 (d, J = 15.6 Hz, 1H, =CH), 6.93−7.02 (m, 1H, Ar−H), 7.64 (d, J = 15.9 Hz, 1H, CH=). HRMS: m/z [M + H] 364.1140; found 364.1131. Anal. ($C_{18}H_{21}NO_5S$) C, H, N.

(*E*)-2′,6′-Dimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8i). The title compound was obtained by the reduction of (*E*)-2′,6′-dimethoxystyryl-4-methoxy-3-nitrobenzylsulfone **8e** following the procedure as described for compound **8b**. Yield, 48%; pale yellow solid, mp 106−108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 3H, OCH_3), 3.86 (s, 6H, 2 × OCH_3), 4.16 (s, 2H, CH_2), 6.52−6.59 (m, 2H, Ar−H), 6.71−6.79 (m, 2H, Ar−H), 7.17 (t, J = 8.1 Hz, 1H, Ar−H), 7.23 (d, J = 15.9 Hz, 1H, =CH), 7.32 (t, J = 8.4 Hz, 1H, Ar−H), 7.94 (d, J = 15.9 Hz, 1H, CH=). HRMS: m/z [M + H] 364.1140; found 364.1131. Anal. ($C_{18}H_{21}NO_5S$) C, H, N.

(*E*)-2′,6′-Dimethoxystyryl-4-methoxy-2-aminobenzylsulfone (8j). The title compound was obtained by the reduction of (*E*)-2′,6′-dimethoxystyryl-4-methoxy-2-nitrobenzylsulfone **8f** following the procedure as described for compound **8b**. Yield, 49%; yellow solid, mp 160−164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (s, 3H, OCH_3), 3.79 (s, 6H, 2 × OCH_3), 4.19 (s, 2H, CH_2), 6.24−6.29 (m, 2H, Ar−H), 6.49 (d, J = 8.4 Hz, 2H, Ar−H), 6.91 (d, J = 8.1 Hz, 1H, Ar−H), 7.23 (d, J = 15.9 Hz, 1H, =CH), 7.29 (t, J = 6.3 Hz, 1H, Ar−H), 7.94 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z [M + H] 364.1140; found 364.1151. Anal. ($C_{18}H_{21}NO_5S$) C, H, N.

(*E*)-2′,6′-Dimethoxystyryl-6-methoxy-3-aminobenzylsulfone (8k). Step 1: (*E*)-2′,6′-Dimethoxystyryl-6-methoxy-3-nitrobenzylsulfone. The condensation of 6-methoxy-3-nitrobenzylsulfonylacetic acid **6g** with 2,6-dimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,6′-dimethoxystyryl-6-methoxy-3-nitrobenzylsulfone. Yield, 55%; pale yellow solid, mp 189−191 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.85 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3), 4.44 (s, 2H, CH_2), 6.55 (d, J = 8.5 Hz, 2H, Ar−H), 6.93 (d, J = 9.0 Hz, 1H, Ar−H), 7.27 (d, J = 16.0 Hz, 1H, =CH), 7.33 (t, J = 8.5 Hz, 1H, Ar−H), 7.79 (d, J = 16.0 Hz, 1H, CH=), 8.21 (dd, J = 9.0, 3.0 Hz, 1H, Ar−H), 8.31 (d, J = 3.0 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 394.0882; found 394.0891. Anal. Calcd for $C_{18}H_{19}NO_7S$: C, 54.95%; H, 4.87%; N, 3.56%. Found: C, 55.10%; H, 4.92%; N, 3.63%.

Step 2: (*E*)-2′,6′-Dimethoxystyryl-6-methoxy-3-aminobenzylsulfone (8k). The title compound was obtained by the reduction of (*E*)-2′,6′-dimethoxystyryl-6-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 47%; light yellow solid, mp 172−174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.63 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3), 4.33 (s, 2H, CH_2), 6.53 (d, J = 8.5 Hz, 2H, Ar−H), 6.93 (d, J = 9.0 Hz, 1H, Ar−H), 7.27 (d, J = 16.0 Hz, 1H, =CH), 7.33 (t, J = 8.5 Hz, 1H, Ar−H), 7.85 (d, J = 16.0 Hz, 1H, CH=), 8.21 (dd, J = 9.0, 3.0 Hz, 1H, Ar−H), 8.31 (d, J = 3.0 Hz, 1H, Ar−H). HRMS: m/z [M + H] 364.1140; found 364.1134. Anal. ($C_{18}H_{21}NO_5S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone (8l). The title compound was obtained from 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** and 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A. Yield, 56%; yellow solid, mp 184−186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.23 (s, 2H, CH_2), 6.09 (s, 2H, Ar−H), 7.03 (d, J = 15.6 Hz, 1H, =CH), 7.10 (d, J = 8.7 Hz, 1H, Ar−H), 7.63 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.80 (d, J = 15.6 Hz, 1H, CH=), 7.85 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 424.0988; found 424.0982. Anal. ($C_{19}H_{21}NO_8S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-2-nitrobenzylsulfone (8m). The title compound was obtained from 4-methoxy-2-nitrobenzylsulfonylacetic acid **6b** and 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A. Yield, 54%; yellow solid, mp 158−160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.80 (s, 2H, CH_2), 6.10 (s, 2H, Ar−H), 7.05 (d, J = 15.6 Hz, 1H, =CH), 7.16 (dd, J = 8.7, 2.7 Hz, 1H, Ar−H), 7.50−7.53 (m, 2H, Ar−H), 7.70 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 424.0988; found 424.0972. Anal. ($C_{19}H_{21}NO_8S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-2-aminobenzylsulfone (8n). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-2-nitrobenzylsulfone **8m** following the procedure as described for compound **8b**. Yield, 50%; pale yellow solid, mp 147−149 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H, OCH_3), 3.85 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 6.11 (s, 2H, Ar−H), 6.32−6.36 (m, 2H, Ar−H), 6.98 (d, J = 8.1 Hz, 1H, Ar−H), 7.13 (d, J = 15.6 Hz, 1H, =CH), 7.93 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 394.1246; found 394.1261. Anal. ($C_{19}H_{23}NO_6S$) C, H, N.

(*E*)-2′,4′,5′-Trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8o). Step 1: (*E*)-2′,4′,5′-Trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 2,4,5-trimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′,5′-trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. Yield, 56%; pale yellow solid, mp 200−202 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), 6.49 (s, 1H, Ar−H), 6.79 (d, J = 15.6 Hz, 1H, =CH) 6.84 (s, 1H, Ar−H), 7.14 (d, J = 8.7 Hz, 1H, Ar−H), 7.56 (d, J = 15.6 Hz, 1H, CH=), 7.63 (dd, J = 8.7, 2.1 Hz, 1H, Ar−H), 7.86 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 424.0988; found 424.1001. Anal. Calcd for $C_{19}H_{21}NO_8S$: C, 53.89%; H, 5.00%; N, 3.31%. Found: C, 53.76%; H, 4.91%; N, 3.25%.

Step 2: (*E*)-2′,4′,5′-Trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8o). The title compound was obtained by the reduction of (*E*)-2′,4′,5′-trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 48%; pale yellow solid, mp 112−114 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2), 6.50 (s, 1H, Ar−H), 6.69 (d, J = 2.1 Hz, 1H, Ar−H), 6.73 (dd, J = 8.4, 2.1 Hz, 2H, Ar−H), 6.77 (d, J = 2.1 Hz, 1H, Ar−H), 6.81 (d, J = 15.0 Hz, 1H, =CH), 7.61 (d, J = 15.6 Hz, 1H, =CH). HRMS: m/z calcd [M + H] 394.1246; found 394.1268. Anal. ($C_{19}H_{23}NO_6S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8p). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone **8l** following the procedure as described for compound **8b**. Yield, 48%; light yellow solid, mp 146−148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2), 4.33 (br s, 2H, NH_2), 6.10 (s, 2H, Ar−H), 6.31−6.35 (m, 2H, Ar−H), 6.97 (d, J = 8.3 Hz, 1H, Ar−H), 7.12 (d, J = 15.6 Hz, 1H, =CH), 7.93 (d, J = 15.6 Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.7, 161.4, 147.6, 136.4, 135.1, 122.8, 121.1, 121.0, 117.2, 110.2, 103.8, 90.3, 61.7, 55.7, 55.5, 55.4. HRMS: m/z calcd [M + H] 394.1246; found 394.1246. Anal. ($C_{19}H_{23}NO_6S$) C, H, N.

(*E*)-3′,4′,5′-Trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8q). Step 1: (*E*)-3′,4′,5′-Trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 3,4,5-trimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-3′,4′,5′-trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone. Yield, 52%; pale yellow solid, mp 170−172 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 6H, 2 × OCH_3), 3.90 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 6.63 (d, J = 15.3 Hz, 1H, =CH), 6.68 (s, 2H, Ar−H), 7.13 (d, J = 8.7 Hz, 1H, Ar−H), 7.39 (d, J = 15.3 Hz, 1H, CH=), 7.62 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.86 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 424.0988; found 424.0998. Anal. Calcd for $C_{19}H_{21}NO_8S$: C, 53.89%; H, 5.00%; N, 3.31%. Found: C, 53.71%; H, 4.93%; N, 3.37%.

Step 2: (*E*)-3′,4′,5′-Trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (8q). The title compound was obtained by the reduction of (*E*)-3′,4′,5′-trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 48%; light orange solid, mp 108−110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H, OCH_3), 3.79 (s, 6H, 2 × OCH_3), 3.82 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 6.55 (d, J = 15.4 Hz, 1H, =CH), 6.58 (s, 2H, Ar−H), 6.61 (dd, J = 8.2, 2.1 Hz, 1H, Ar−H), 6.67 (d, J = 8.2 Hz, 1H, Ar−H), 6.70 (d, J = 2.1 Hz, 1H, Ar−H), 7.29 (d, J = 15.4 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 394.1246; found 394.1246. Anal. ($C_{19}H_{23}NO_6S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-6-methoxy-3-aminobenzylsulfone (8r). Step 1: (*E*)-2′,4′,6′-Trimethoxystyryl-6-methoxy-3-nitrobenzylsulfone. The condensation of 6-methoxy-3-nitrobenzylsulfonylacetic acid **6g** with 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′,6′-trimethoxystyryl-6-methoxy-3-nitrobenzylsulfone. Yield, 55%; yellow solid, mp 144−146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.83 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.42 (s, 2H, CH_2), 6.08 (s, 2H, Ar−H), 6.92 (d, J = 9.0 Hz, 1H, Ar−H), 7.09 (d, J = 15.5 Hz, 1H, =CH), 7.69 (d, J = 16.0 Hz, 1H, CH=), 8.11 (dd, J = 9.0, 2.5 Hz, 1H, Ar−H), 8.30 (d, J = 2.5 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 424.0988; found 424.0998. Anal. Calcd for $C_{19}H_{21}NO_8S$: C, 53.89%; H, 5.00%; N, 3.31%. Found: C, 53.76%; H, 4.94%; N, 3.37%.

Step 2: (*E*)-2′,4′,6′-Trimethoxystyryl-6-methoxy-3-aminobenzylsulfone (8r). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-6-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 49%; orange solid, mp 124−128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.57 (s, 3H, OCH_3), 3.76 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 6.01 (s, 2H, Ar−H), 6.59 (dd, J = 8.2, 2.1 Hz, 2H, Ar−H), 6.77 (d, J = 8.2 Hz, 1H, Ar−H), 7.02 (d, J = 15.9 Hz, 1H, =CH), 7.69 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 394.1246; found 394.1266. Anal. ($C_{19}H_{23}NO_6S$) C, H, N.

(*E*)-2′,6′-Dimethoxy-4′-hydroxystyryl-4-methoxy-3-nitrobenzylsulfone (8s). A mixture of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** (2.05 g, 5 mmol), 2,6-dimethoxy-4-hydroxybenzaldehyde (1.02 g, 5.5 mmol), benzoic acid (92 mg, 0.75 mmol), and piperidine (55 mg, 0.65 mmol) in toluene (50 mL) was refluxed for 2−4 h with continuous removal of water using a Dean−Stark water separator. Reaction completion was determined by TLC (9:1 chloroform/methanol on silica gel plate). The solvent was evaporated. To the residue water was added and extracted with ethyl acetate. The organic phase was washed with saturated sodium bicarbonate solution, dilute hydrochloric acid, and water and dried over anhydrous sodium sulfate. The organic phase was filtered, and evaporation of the solvent under vacuo yielded a crude product **8s**. The pure compound **8s** was obtained following purification by silica gel flash column chromatography (chloroform). Yield, 48%; light yellow solid, mp 222−224 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.77 (s, 6H, 2 × OCH_3), 3.91 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2), 5.79 (s, 1H, OH), 6.11 (s, 2H, Ar−H), 6.99 (d, J = 15.6 Hz, 1H, =CH), 7.37 (d, J = 9.0 Hz, 1H, Ar−H), 7.48 (d, J = 15.6 Hz, 1H, CH=), 7.62 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.86 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 410.08; found 410.09. Anal. ($C_{18}H_{19}NO_8S$) C, H, N.

(*E*)-2′,6′-Dimethoxy-4′-hydroxystyryl-4-methoxy-3-aminobenzylsulfone (8t). The title compound was obtained by the reduction of (*E*)-2′,6′-dimethoxy-4′-hydroxystyryl-4-methoxy-3-nitrobenzylsulfone **8s** following the procedure as described for compound **8b**. Yield, 45%; light yellow solid, mp 132−134 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.67 (s, 6H, 2 × OCH_3), 3.76 (s, 3H, OCH_3), 4.07 (s, 2H, CH_2), 5.75 (bs, 1H, OH), 5.95 (s, 2H, Ar−H), 6.65−6.69 (m, 3H, Ar−H), 6.92 (d, J = 15.6 Hz, 1H, =CH), 7.73 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 380.1090; found 380.0184. Anal. ($C_{18}H_{21}NO_6S$) C, H, N.

(*E*)-2′,6′-Dimethoxy-4′-phenoxybutanoicacidstyryl-4-methoxy-3-aminobenzylsulfone (8u). Step 1: (*E*)-2′,6′-Dimethoxy-4′-phenoxybutanoic acid styryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 4-(4-formyl-3,5-dimethoxyphenoxy)butyric acid following the procedure as described in method A resulted in the desired product (*E*)-2′,6′-dimethoxy-4′-phenoxybutanoic acid styryl-4-methoxy-3--nitrobenzylsulfone. Yield, 56%; pale yellow solid, mp 198−200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.11−2.18 (m, 2H, CH_2), 2.61 (t, J = 7.1 Hz, 2H, CH_2), 3.83 (s, 6H, 2 × OCH_3), 3.97 (s, 3H, OCH_3), 4.08 (t, J = 6.1 Hz, 2H, CH_2), 4.23 (s, 2H, CH_2), 6.09 (s, 2H, Ar−H), 7.02 (d, J = 15.6 Hz, 1H, =CH), 7.11 (d, J = 8.7 Hz, 1H, Ar−H), 7.63 (dd, J = 8.7, 2.3 Hz, 1H, Ar−H), 7.78 (d, J = 15.6 Hz, 1H, CH=), 7.84 (d, J = 2.2 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 496.1199; found 496.1984. Anal. Calcd for $C_{22}H_{25}NO_{10}S$: C, 53.33%; H, 5.09%; N, 2.83%. Found: C, 53.42%; H, 5.01%; N, 2.87%.

Step 2: (*E*)-2′,6′-Dimethoxy-4′-phenoxybutanoic acid styryl-4-methoxy-3-aminobenzylsulfone (8u). The title compound was obtained by the reduction of (*E*)-2′,6′-dimethoxy-4′-phenoxybutanoic acidstyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 48%; light yellow solid, mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04−2.10 (m, 2H, CH_2), 2.53 (t, J = 7.1 Hz, 2H, CH_2), 3.75 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 4.00 (t, J = 6.0 Hz, 2H, CH_2), 4.06 (s, 2H, CH_2), 6.02 (s, 2H, Ar−H), 6.66−6.70 (m, 3H, Ar−H), 6.99 (d, J = 15.6 Hz, 1H, =CH), 7.77 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 466.1457; found 466.1443. Anal. ($C_{22}H_{27}NO_8S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-bromo-3-nitrobenzylsulfone (8v). The title compound was obtained from 4-bromo-3-nitrobenzylsulfonylacetic acid **6c** and 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A. Yield, 56%; yellow solid, mp 186−188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 4.73 (s, 2H, CH_2), 6.10 (s, 2H, Ar−H), 7.03 (d, J = 15.9 Hz, 1H, =CH), 7.10 (d, J = 8.7 Hz, 1H, Ar−H), 7.63 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.80 (d, J = 15.6 Hz, 1H, CH=), 7.85 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 471.9987; found 471.9972. Anal. ($C_{18}H_{18}BrNO_7S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-bromo-3-aminobenzylsulfone (8w). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-bromo-3-nitrobenzylsulfone **8v** following the procedure as described for compound **8b**. Yield, 49%; white solid, mp 162−164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 4.63 (s, 2H, CH_2), 6.01 (s, 2H, Ar−H), 6.70−6.77 (m, 2H, Ar−H), 7.06 (d, J = 15.9 Hz, 1H, =CH), 7.27 (s, 1H, Ar−H), 7.85 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 442.0174; found 442.0189. Anal. ($C_{18}H_{20}BrNO_5S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-chloro-3-aminobenzylsulfone (8x). Step 1: (*E*)-2′,4′,6′-Trimethoxystyryl-4-chloro-3-nitrobenzylsulfone. The condensation of 4-chloro-3-nitrobenzylsulfonylacetic acid **6d** with 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′,6′-trimethoxystyryl-4-chloro-3-nitrobenzylsulfone. Yield, 51%; pale

yellow solid, mp 173−174 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2), 6.02 (s, 2H, Ar−H), 6.59 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar−H), 6.77 (d, *J* = 2.1 Hz, 1H, Ar−H), 7.00 (d, *J* = 15.6 Hz, 1H, ═CH), 7.13 (d, *J* = 8.1 Hz, Ar−H), 7.75 (d, *J* = 15.9 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 428.0489; found 428.0476. Anal. Calcd for $C_{18}H_{18}ClNO_7S$: C, 50.53%; H, 4.24%; N, 3.27%. Found: C, 50.72%; H, 4.29%; N, 3.24%.

Step 2: (*E*)-2′,4′,6′-Trimethoxystyryl-4-chloro-3-aminobenzylsulfone (8x). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-chloro-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 50%; pale yellow solid, mp 138−140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, OCH_3), 4.00 (br s, 2H, NH_2), 4.06 (s, 2H, CH_2), 6.02 (s, 2H, Ar−H), 6.59 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar−H), 6.77 (d, *J* = 2.1 Hz, 1H, Ar−H), 6.95 (d, *J* = 15.6 Hz, 1H, ═CH), 7.13 (d, *J* = 8.1 Hz, Ar−H), 7.75 (d, *J* = 15.9 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 398.0842; found 398.0848. Anal. ($C_{18}H_{20}ClNO_5S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-chloro-2-aminobenzylsulfone (8y). Step 1: (*E*)-2′,4′,6′-Trimethoxystyryl-4-chloro-2-nitrobenzylsulfone. The condensation of 4-chloro-2-nitrobenzylsulfonylacetic acid **6e** with 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′,6′-trimethoxystyryl-4-chloro-2-nitrobenzylsulfone. Yield, 54%; pale yellow solid, mp 206−208 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.10 (s, 2H, Ar−H), 6.59 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar−H), 6.84 (d, *J* = 2.1 Hz, 1H, Ar−H), 7.10 (d, *J* = 15.6 Hz, 1H, ═CH), 7.21 (d, *J* = 8.1 Hz, Ar−H), 7.82 (d, *J* = 15.9 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 428.0489; found 428.0469. Anal. Calcd for $C_{18}H_{18}ClNO_7S$: C, 50.53%; H, 4.24%; N, 3.27%. Found: C, 50.45%; H, 4.20%; N, 3.22%.

Step 2: (*E*)-2′,4′,6′-Trimethoxystyryl-4-chloro-2-aminobenzylsulfone (8y). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-chloro-2-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 48%; yellow solid, mp 184−186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 4.50 (br s, 2H, NH_2),6.12 (s, 2H, Ar−H), 6.74 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar−H), 6.79 (d, *J* = 2.1 Hz, 1H, Ar−H), 6.99 (d, *J* = 8.1 Hz, Ar−H), 7.11 (d, *J* = 15.9 Hz, 1H, ═CH), 7.92 (d, *J* = 15.6 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 398.0842; found 398.0836. Anal. ($C_{18}H_{20}ClNO_5S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-fluoro-3-nitrobenzylsulfone (8z). The title compound was obtained from 4-fluoro-3-nitrobenzylsulfonylacetic acid **6f** and 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A. Yield, 53%; light yellow solid, mp 161−163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 6H, 2 × OCH_3), 3.87 (s, 3H, OCH_3), 4.28 (s, 2H, CH_2), 6.10 (s, 2H, Ar−H), 7.02 (d, *J* = 15.6 Hz, 1H, ═CH), 7.31 (dd, *J* = 8.7, 1.8 Hz, 1H, Ar−H), 7.69−7.74 (m, 1H, Ar−H), 7.75 (d, *J* = 15.3 Hz, 1H, CH═), 8.07 (dd, *J* = 6.9, 2.1 Hz, 1H, Ar−H). HRMS: *m*/*z* calcd [M + H] 412.0791; found 412.0774. Anal. ($C_{18}H_{18}FNO_7S$) C, H, N.

(*E*)-2′,4′,6′-Trimethoxystyryl-4-fluoro-3-aminobenzylsulfone (8aa). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-fluoro-3-nitrobenzylsulfone **8z** following the procedure as described for compound **8b**. Yield, 46%; pale yellow solid, mp 129−131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, OCH_3), 4.09 (s, 2H, CH_2), 6.02 (s, 2H, Ar−H), 6.57−6.62 (m, 1H, Ar−H), 6.80 (dd, *J* = 8.4, 2.1 Hz, 1H, Ar−H), 6.85 (dd, *J* = 8.4, 2.7 Hz, 1H, Ar−H), 6.96 (d, *J* = 15.9 Hz, 1H, ═CH), 7.27 (s, 1H, Ar−H), 7.76 (d, *J* = 15.6 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 382.1087; found 382.1105. Anal. ($C_{18}H_{20}FNO_5S$) C, H, N.

(*E*)-2′,4′,6′-Trifluorostyryl-4-methoxy-3-aminobenzylsulfone (8ab). Step 1: (*E*)-2′,4′,6′-Trifluorostyryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 2,4,6-trifluorobenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′,6′-trifluorostyryl-4-methoxy-3-nitrobenzylsulfone. Yield, 52%; yellow solid, mp 141−143 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H, OCH_3), 4.28 (s, 2H, CH_2), 6.20 (s, 2H, Ar−H), 6.80−6.90 (m, 2H, Ar−H), 6.97−7.05 (m, 1H, Ar−H), 7.10 (d, *J* = 15.9 Hz, 1H, ═CH), 7.62 (d, *J* = 15.6 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 388.0388; found 388.0379. Anal. Calcd for $C_{16}H_{12}F_3NO_5S$: C, 49.61%; H, 3.12%; N, 3.62%. Found: C, 49.75%; H, 3.17%; N, 3.68%.

Step 2: (*E*)-2′,4′,6′-Trifluorostyryl-4-methoxy-3-aminobenzylsulfone (8ab). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trifluorostyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 48%; light yellow solid, mp 110−112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H, OCH_3), 4.18 (s, 2H, CH_2), 6.67−6.83 (m, 5H, Ar−H), 7.01 (d, *J* = 16.2 Hz, 1H, ═CH), 7.50 (d, *J* = 15.9 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 358.0646; found 358.0637. Anal. ($C_{16}H_{14}F_3NO_3S$) C, H, N.

(*E*)-2′,4′,5′-Trifluorostyryl-4-methoxy-3-aminobenzylsulfone (8ac). Step 1: (*E*)-2′,4′,5′-Trifluorostyryl-4-methoxy-3-nitrobenzylsulfone. The condensation of 4-methoxy-3-nitrobenzylsulfonylacetic acid **6a** with 2,4,5-trifluorobenzaldehyde following the procedure as described in method A resulted in the desired product (*E*)-2′,4′,5′-trifluorostyryl-4-methoxy-3-nitrobenzylsulfone. Yield, 51%; pale yellow solid, mp 161−163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H, OCH_3), 4.19 (s, 2H, CH_2), 6.67 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar−H), 6.74−6.77 (m, 2H, Ar−H), 6.80 (d, *J* = 15.6 Hz, 1H, ═CH), 6.97−7.05 (m, 1H, Ar−H), 7.17−7.24 (m, 1H, Ar−H), 7.43 (d, *J* = 15.6 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 388.0388; found 388.0394. Anal. Calcd for $C_{16}H_{12}F_3NO_5S$: C, 49.61%; H, 3.12%; N, 3.62%. Found: C, 49.50%; H, 3.16%; N, 3.69%.

Step 2: (*E*)-2′,4′,5′-Trifluorostyryl-4-methoxy-3-aminobenzylsulfone (8ac). The title compound was obtained by the reduction of (*E*)-2′,4′,5′-trifluorostyryl-4-methoxy-3-nitrobenzylsulfone following the procedure as described for compound **8b**. Yield, 46%; white solid, mp 132−134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H, OCH_3), 4.19 (s, 2H, CH_2), 6.67 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar−H), 6.74−6.77 (m, 2H, Ar−H), 6.80 (d, *J* = 15.6 Hz, 1H, ═CH), 6.97−7.05 (m, 1H, Ar−H), 7.17−7.24 (m, 1H, Ar−H), 7.43 (d, *J* = 15.6 Hz, 1H, CH═). HRMS: *m*/*z* calcd [M + H] 358.0646; found 358.0627. Anal. ($C_{16}H_{14}F_3NO_3S$) C, H, N.

Preparation of 3-Nitro-4-methoxybenzylmercaptan (9) (Scheme 4). Step 1: 3-Nitro-4-methoxybenzylisothiouronium Salt (12). A solution of 3-nitro-4-methoxybenzyl bromide **2a** (10.0 g, 41 mmol) and thiourea (10.0 g, 131 mmol) in 50 mL water was heated under reflux for 2 h. The reaction mixture was cooled and stirred at room temperature for 2 h, and the solid was filtered. The resulting dried product was used in next step without further purification. The yield of this reaction was 90%, giving a white solid with a melting point of 174−176 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.91 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2), 7.39 (d, *J* = 8.7 Hz, 1H, Ar−H), 7.72 (dd, *J* = 8.7, 2.4 Hz, 1H, Ar−H), 7.98 (d, *J* = 2.1 Hz, 1H, Ar−H), 9.12 (br s, 4H, 2 × NH_2). HRMS: *m*/*z* calcd [M + H] 323.9939; found 323.9929. Anal. ($C_9H_{14}BrN_3O_3S$) C, H, N.

Step 2: 3-Nitro-4-methoxybenzylmerccaptan (9). The isothiouronium salt **12** was decomposed by boiling several times with concentrated ammonia and hexane (100 mL, 15:85). Concentration of the combined hexane extracts provided crude **9**. The pure compound **9** was obtained on silica gel flash column chromatography (hexane/ethyl acetate, 4:1). The yield of this reaction was 55%, giving a yellow solid with a melting point of 48−49 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.74 (t, *J* = 7.5 Hz, SH), 3.67 (d, *J* = 7.5 Hz, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.98 (d, *J* = 8.4 Hz, 1H, Ar−H), 7.45 (dd, *J* = 8.4, 2.1 Hz, 1H, Ar−H), 7.76 (d, *J* = 2.4 Hz, 1H, Ar−H). HRMS: *m*/*z* calcd [M − H] 198.0303; found 198.0320. Anal. ($C_8H_9NO_3S$) C, H, N.

General Procedure for the Preparation of (*E*)-Styrylbenzylsulfone (8). Method B (Scheme 3). Preparation of 4′-Methoxyphenacyl-3-nitro-4-methoxybenzyl Sulfide (11). To a cooled solution of sodium hydroxide (100 mmol) in absolute methanol (50 mL), taken in a 250 mL round-bottomed flask, 3-nitro-4-methoxybenzylmercaptan **9** (100 mmol) was added slowly, and the reaction mixture was stirred for 5 min. An appropriate 4-methoxyphenacyl bromide **10** (100 mmol) was added in portions to the contents of the flask, and the mixture was stirred for 2 h. After completion of the reaction (TLC, monitoring, hexane/ethyl acetate, 8:2 on silica gel plate), the contents of the flask were poured into crushed ice and the compound formed was washed with ice-cold water and dried to get 4′-methoxyphenacyl-3-nitro-4-methoxybenzyl sulfide **11**. The yield of this reaction was 95%, giving a yellow solid with a melting point of 87−89 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.55 (s, 2H, CH_2), 3.67 (s, 2H, CH_2), 3.81(s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.87 (d, J = 9.0 Hz, 2H, Ar−H), 6.96 (d, J = 8.4 Hz, 2H, Ar−H), 7.49 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.79 (d, J = 2.4 Hz, 1H, Ar−H), 7.85 (d, J = 8.7 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 348.0827; found 348. 0811. Anal. ($C_{17}H_{17}NO_5S$) C, H, N.

Preparation of 4′-Methoxyphenacyl-3-nitro-4-methoxybenzylsulfone (13). The crude 4′-methoxyphenacyl-3-nitro-4-methoxybenzyl sulfide **11** (50 mmol) in glacial acetic acid (100 mL) was taken in a 250 mL round-bottomed flask, and 30% hydrogen peroxide (60 mL) was added in portions at frequent intervals. Then the reaction mixture was kept at room temperature for 24 h. The solid, if any formed, was separated by filtration, and the filtrate was poured onto crushed ice. The compound separated was filtered, washed with water, dried, and added to the first crop, if any. The total product on recrystallization from methanol afforded pure 4′-methoxyphenacyl-3-nitro-4-methoxybenzylsulfone (**13**). Yield, 76%; white solid, mp 172−174 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 6.87 (d, J = 9.0 Hz, 2H, Ar−H), 7.06 (d, J = 8.7 Hz, 2H, Ar−H), 7.67 (dd, J = 8.7, 2.1 Hz, 1H, Ar−H), 7.90 (d, J = 9.0 Hz, 1H, Ar−H), 7.98 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 380.0726; found 380.0709. Anal. ($C_{17}H_{17}NO_7S$) C, H, N.

Preparation of 2-(3-Nitro-4-methoxybenzylsulfonyl)-1-(4′-methoxyphenyl)ethanol (14). To anhydrous tetrahydrofuran (THF) solution (20 mL) of 4-methoxyphenacylbenzylsulfone **13** (10 mmol) maintained at 0 °C was added $NaBH_4$ (10 mmol) slowly under N_2 atmosphere. The reaction mixture was maintained at 0 °C for 1 h. After completion of the reaction monitored by TLC (hexane/ethyl acetate, 8:2 on silica gel plate), the contents were poured onto crushed ice. The solid that separated out was filtered, washed with water, and dried under vacuum to yield **14**. Yield, 56%; white solid, mp 152−154 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.43 (dd, J = 9.9, 4.6 Hz, 2H, CH−C$\underline{H}_2$), 3.73 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.58 (dd, J = 15.7, 13.6 Hz, 2H, $SO_2C\underline{H}_2$), 5.05 (m, 1H, CHO$\underline{H}$), 6.02 (d, J = 4.2 Hz, 1H, CH), 6.90 (d, J = 8.6 Hz, 2H, Ar−H), 7.32 (d, J = 8.6 Hz, 2H, Ar−H), 7.42 (d, J = 9.0 Hz, 1H, Ar−H), 7.69 (dd, J = 8,7, 1.8 Hz, 1H, Ar−H), 7.93 (d, J = 1.8 Hz, 1H, Ar−H) . HRMS: m/z calcd [M + H] 382.0882; found 382.0916. Anal. ($C_{17}H_{19}NO_7S$) C, H, N.

Preparation of (*E*)-4′-Methoxystyryl-3-nitro-4-methoxybenzylsulfone (8c). *p*-Toluenesulfonic acid (1 mmol) was added in one portion to a mixture of 2-(3-nitro-4-methoxybenzylsulfonyl)-1-(4′-methoxyphenyl)ethanol **14** (5 mmol) in anhydrous toluene (25 mL) at room temperature and under N_2 atmosphere. The temperature was raised to 120 °C, and the mixture was refluxed for 2−4 h using a Dean−Stark water separator. After completion of the reaction monitored by TLC (chloroform, on silica gel plate), the reaction mixture was concentrated under reduced pressure and then quenched by the addition of water (25 mL). The aqueous layer was neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to afford crude product, which on recrystallization in 2-propanol afforded the desired product **8c**. Yield: 65%; white solid, 184−186 °C. Analytical data are the same as for **8c** obtained by method A.

General Procedure for the Preparation of 2,4,6-Trimethoxyphenylacetylene (15, Scheme 6). Step 1: 2-(2′,2′-Dibromovinyl)-1,3,5-trimethoxybenzene (19). To a solution of 2,4,6- trimethoxybenzaldehyde **18** (5.0 g, 25.5 mmol) and triphenylphosphine (13.37 g, 51.0 mmol) in anhydrous dichloromethane (60 mL) was added a solution of tetrabromomethane (9.8 g, 30.0 mmol) in dichloromethane (10 mL), keeping the temperature below 5 °C. The reaction mixture was stirred for an additional 30 min. After completion of the reaction monitored by TLC (hexane/ethyl acetate, 9:1 on silica gel plate), the reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/ethyl acetate, 9:1), resulting in pure **19**. The yield of this reaction was 72%, giving a white solid with a melting point of 128−130 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 6H, 2 × OCH_3), 3.83 (s, 3H, OCH_3), 6.12 (s, 2H, Ar−H), 7.19 (s, 1H, CH═). HRMS: m/z calcd [M +H] 352.9133; found 352.9112. Anal. ($C_{11}H_{12}Br_2O_3$) C, H.

Step 2: 2,4,6-Trimetoxyphenylacetylene (15). A solution of 2-(2′,2′-dibromovinyl)-1,3,5-trimethoxybenzene **19** (7.42 g, 21.3 mmol) in dry tetrahydrofuran (135 mL) was cooled to −78 °C, and *n*-butyllithium (18.0 mL, 45.0 mmol) was slowly added. The mixture was stirred for a further 15 min at −78 °C. After completion of the reaction monitored by TLC (hexane/ethyl acetate, 9:1 on silica gel plate), water was added (60 mL) and extracted with ethyl acetate (2 × 100 mL). The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo and the residue was purified by flash column chromatography (hexane/ethyl acetate, 9:1), resulting in pure **15**. The yield of this reaction was 67%, giving a white solid with a melting point of 119−122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.43 (s, 1H, CH), 3.77 (s, 3H, OCH_3), 3.82 (s, 6H, 2 × OCH_3), 6.04 (s, 2H, Ar−H). HRMS: m/z calcd [M + H] 193.0786; found 193.0764. Anal. ($C_{11}H_{12}O_3$) C, H.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzyl Sulfide (17) and (*Z*)-2′,4′,6′-Trimethoxystyry-4-methoxy-3-nitrolbenzyl Sulfide (16) (Scheme 5). A hexane solution of triethylborane (10.5 mL, 10.1 mmol) was added to a solution of 2,4,6-trimethoxyphenylacetylene **15** (5.0 g, 10.1 mmol) and 4-methoxy-3-nitrobenzylthiol **9a** (2.49 g, 12.12 mmol) in benzene (100 mL) at 25 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 25 °C. After completion of the reaction monitored by TLC (hexane/ethyl acetate, 9:1 on silica gel plate), the reaction mixture was quenched with 1 M ammonium chloride solution and the aqueous portion was extracted with ethyl acetate. The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo and the residue was purified by column chromatography (hexane/ethyl acetate, 9:1, and with gradual increase in polarity), resulting in a stereoisomeric mixture (E/Z = 60/40).

(*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzyl Sulfide (17). The yield of this reaction was 60%, giving a white solid with a melting point of 121−123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (s, 6H, 2 × OCH_3), 3.81 (s, 3H, OCH_3), 3.93 (s, 2H, $C\underline{H}_2S$), 3.96 (s, 3H, OCH_3), 6.10 (s, 2H, Ar−H), 6.83 (d, J = 15.6 Hz, 1H, CH═), 7.00 (d, J = 15.6 Hz, 1H, ═CH), 7.05 (d, J = 8.7 Hz, 1H, Ar−H), 7.59 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.80 (d, J = 2.4 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 392.1090; found 392.1084. Anal. ($C_{19}H_{21}NO_6S$) C, H, N.

(*Z*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzyl Sulfide (16). The yield of this reaction was 40%, giving a white solid with a melting point of 102−104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 12H, 4 × OCH_3), 3.86 (s, 2H, $C\underline{H}_2S$), 6.06 (s, 2H, Ar−H), 6.14 (d, J = 10.2 Hz, 1H, CH═), 6.49 (d, J = 10.5 Hz, 1H, ═CH), 6.94 (d, J = 8.4 Hz, 1H, Ar−H), 7.43

(dd, J = 8.7, 2.1 Hz, 1H, Ar−H), 7.75 (d, J = 1.8 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 392.1090; found 392.1084. Anal. ($C_{19}H_{21}NO_6S$) C, H, N.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-aminobenzyl Sulfide (24). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzyl sulfide **17** following the procedure as described for compound **8b**. Yield, 43%; pale yellow solid, mp 106−108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.73 (s, 6H, 2 × OCH_3), 3.76 (s, 6H, 2 × OCH_3), 3.80 (s, 2H, CH_2S), 6.03 (s, 2H, Ar−H), 6.63−6.71 (m, 2H, Ar−H), 6.74 (d, J = 15.6 Hz, 1H, CH═), 7.01 (d, J = 15.9 Hz, 1H, ═CH), 7.30 (s, 1H, Ar−H). HRMS: m/z calcd [M + H] 362.1348; found 362.1339. Anal. ($C_{19}H_{23}NO_4S$) C, H, N.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzyl Sulfoxide (20). An aqueous 30% hydrogen peroxide (0.56 mL, 5.2 mmol) was added to a stirred solution of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzyl sulfide **17** (1.0 g, 2.6 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (10 mL) at 25 °C. The reaction was monitored by TLC. After the complete disappearance of the sulfide (2 h), the excess hydrogen peroxide was quenched with saturated sodium sulfite (Na_2SO_3) solution (5.0 mL) and the fluorous organic phase containing the sulfoxide was separated. After removal of the solvent under vacuo, sulfoxide **20** was obtained as a semisolid. Flash column chromatography (chloroform) gave pure **20**. The yield of this reaction was 91%, giving a white solid with a melting point of 148−150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.96−4.00 (d, J = Hz, 2H, CH_2S), 6.01 (s, 2H, Ar−H), 6.96 (d, J = 15.9 Hz, 1H, CH═), 7.02 (d, J = 8.7 Hz, 1H, Ar−H), 7.36 (d, J = 15.6 Hz, 1H, ═CH), 7.46 (dd, J = 8.7, 2.1 Hz, 1H, Ar−H), 7.71 (d, J = 2.1 Hz, 1H, Ar−H). HRMS: m/z calcd [M + H] 408.1039; found 408.1022. Anal. ($C_{19}H_{21}NO_7S$) C, H, N.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-aminobenzyl Sulfoxide (21). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzyl sulfoxide **20** following the procedure as described for compound **8b**. Yield, 46%; pale yellow solid, mp 131−133 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77 (br s, 12H, 4 × OCH_3), 3.81 (br s, 2H, NH_2), 3.92 (d, J = 12.6 Hz, 2H, CH_2S), 6.04 (s, 2H, Ar−H), 6.60−6.69 (m, 3H, Ar−H), 7.08 (d, J = 15.6 Hz, 1H, CH═), 7.43 (d, J = 15.6 Hz, 1H, ═CH). HRMS: m/z calcd [M + H] 378.1297; found 378.1280. Anal. ($C_{19}H_{23}NO_5S$) C, H, N.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone (22 and 8l). The title compound was obtained by the oxidation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzyl sulfoxide **20** according to the procedure reported in the literature.[7] The yield of this reaction was 62%; yellow solid, mp 184−186 °C. The analytical data are in accord with **8l**.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-aminobenzylsulfone (23 and 8p). *Method A.* The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzylsulfone **22** following the procedure as described for compound **8b**. The yield of this reaction was 52%; light yellow solid, mp 146−148 °C. The analytical data are in accord with **8p**.

Method B. The title compound was obtained by the oxidation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzyl sulfide **24**. To a solution of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzyl sulfide **24** (903 mg, 2.5 mmol) in anhydrous dichloromethane (20 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (1.29 g, 7.5 mmol) slowly under nitrogen atmosphere, and the resulting mixture was stirred at 0 °C to room temperature for 3 h. After completion of the reaction (TLC monitoring, chloroform on silica gel plate), 10% sodium hydrogen carbonate solution (25 mL) was added slowly. The mixture was stirred for 10 min, and the aqueous layer was separated. The organic layer washed with water (2 × 25 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (chloroform) to obtain the title compound **24**. The yield of this reaction was 64%; light yellow solid, mp 146−148 °C. The analytical data are in accord with **8p**.

Synthesis of (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-aminobenzyl Sulfoxide (21, Scheme 7). Step 1: 4-Methoxy-3-nitrobenzylsulfinylacetic Acid (25). A vigorously stirred solution of sodium hydroxide (0.58 g, 14.5 mmol) and deionized water (30 mL) was treated with 4-methoxy-3-nitrobenzylthioacetic acid **5a** (3,30 g, 12.1 mmol). The resulting suspension was stirred at ambient temperature for 10 min. To this was added sodium bicarbonate (8.00 g, 95 mmol) and acetone (10 mL), and the mixture was cooled to 0 °C. The Oxone solution (4.85 g in 20 mL of 4 × 10^{-4} M EDTA) was added over 10 min, keeping the mixture below 5 °C. The suspension was stirred for 5 min and immediately quenched at 2 °C with sodium bisulfate (3 g in 6 mL of deionized water) and stirred for 15 min. Ethyl acetate (75 mL) was added, and the solution was acidified with 6 N (aq) HCl (18 mL). The aqueous phase was isolated, treated with sodium chloride (15.0 g), and re-extracted with ethyl acetate (75 mL). The organic layers were combined and washed with deionized water (50 mL), washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuo. The crystals formed were dried under vacuum to afford pure **25**. The yield of this reaction was 89%, giving a white solid with a melting point of 122−124 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.42 (s, 2H, −SCH_2), 3.90 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2S), 7.42 (d, J = 8.4 Hz, 1H, Ar−H), 7.69 (dd, J = 8.7, 2.4 Hz, 1H, Ar−H), 7.92 (d, J = 2.1 Hz, 1H, Ar−H), 12.90 (br s, 1H, COOH). HRMS: m/z calcd [M − H] 272.0307; found 272.0300. Anal. Calcd for $C_{10}H_{11}NO_6S$: C, 43.95%; H, 4.06%; N, 5.13%. Found: C, 44.06%; H, 4.09%; N, 5.17%.

Step 2: (*E*)-2′,4′,6′-Trimethoxystyryl-4-methoxy-3-nitrobenzyl Sulfoxide (20). The title compound was obtained from 4-methoxy-3-nitrobenzylsulfinylacetic acid **25** and 2,4,6-trimethoxybenzaldehyde following the procedure as described in method A and Scheme 1. The yield of this reaction was 48%. The analytical data are in accord with **20** as reported in Scheme 5.

Step 3: (*E*)-2′, 4′, 6′-Trimethoxystyryl-4-methoxy-3-aminobenzyl Sulfoxide (21). The title compound was obtained by the reduction of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-nitrobenzyl sulfoxide **20** following the procedure as described for compound **8b**. The yield of this reaction was 42%. The analytical data are in accord with **21** as reported in Scheme 5.

General Procedure for the Preparation of Amino Esters (26, Scheme 8). Sodium acetate (32.8 g, 400 mmol) was dissolved in ethanol (200 mL). Methyl 2-bromoacetate (61.1 g, 400 mmol) was added to the above solution and refluxed for 10 min. To the cooled reaction mixture compound (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** or (*E*)-3′,4′,5′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8q** (39.35 g, 100 mmol) was added and then refluxed for 48 h. After completion of the reaction monitored by TLC (chloroform/methanol, 9:1 on silica gel plate), the reaction mixture was concentrated under vacuum and poured into ice−water. The solid formed was filtered, washed with water, and dried under vacuum. The crude product on purification from ethanol resulted in analytical pure product **26**. The following amino esters were prepared using the above procedure.

(*E*)-Methyl 2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (26a). Sodium acetate (3.28 g, 39 mmol) was dissolved in methanol (20 mL). Methyl 2-bromoacetate (6.11 g, 40 mmol) was added to the above solution and refluxed for 10 min. To the cooled reaction mixture compound (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** (3.95 g, 10 mmol) was added, and then the mixture was refluxed for 4−6 h. The reaction mixture was concentrated under vacuum and poured into ice−water. The formed precipitate was filtered, washed with water, and dried under vacuum. The crude product on

recrystallization from ethanol resulted in pure product **26a**. Yield, 70%; white solid, mp 150−152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.69 (s, 3H, OCH_3), 3.75 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81 (d, J = 5.4 Hz, 2H, CH_2), 4.09 (s, 2H, CH_2), 4.74 (t, J = 5.4 Hz, 1H, NH), 6.01(s, 2H, Ar−H), 6.41 (d, J = 1.8 Hz, 1H, Ar−H), 6.61−6.68 (m, 2H, Ar−H), 6.97 (d, J = 15.6 Hz, 1H, =CH), 7.73 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 466.1457; found 466.1446. Anal. ($C_{22}H_{27}NO_8S$) C, H, N.

(*E*)-Methyl 2-(2-Methoxy-5-((3′,4′,5′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (26b). The title compound was obtained by the alkylation of (*E*)-3′,4′,5′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8q** with methyl 2-bromoacetate following the procedure as described for compound **26**. Yield, 63%; light brown solid, mp 82−84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.67 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 6H, 2 × OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (d, J = 5.4 Hz, 2H, CH_2), 4.14 (s, 2H, CH_2), 4.53 (t, J = 5.4 Hz, 1H, NH), 6.52 (d, J = 15.5 Hz, 1H, =CH), 6.57 (s, 2H, Ar−H), 6.62 (dd, J = 8.2, 2.1 Hz, 1H, Ar−H), 6.67 (d, J = 8.2 Hz, 1H, Ar−H), 6.70 (d, J = 2.1 Hz, 1H, Ar−H), 7.24 (d, J = 15.4 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 466.1457; found 466.1465. Anal. ($C_{22}H_{27}NO_8S$) C, H, N.

(*E*)-Ethyl 3-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoate (26c). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with ethyl 3-bromopropionate following the procedure as described for compound **26**. Yield, 59%; light green solid, mp 72−74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.2 Hz, 3H, CH_3), 2.58 (t, J = 6.3 Hz, 2H, CH_2), 3.41 (t, J = 6.6 Hz, 2H, CH_2), 3.82 (s, 9H, 3 × OCH_3), 3.84 (s, 3H, OCH_3), 4.04−4.10 (m, 2H, OCH_2), 4.17 (s, 2H, CH_2), 5.06 (t, J = 5.4 Hz, 1H, NH), 6.09 (s, 2H, Ar−H), 6.61−6.64 (m, 1H, Ar−H), 6.66−6.71 (m, 2H, Ar−H), 7.06 (d, J = 15.6 Hz, 1H, =CH), 7.84 (d, J = 15.9 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 480.1614; found 480.1647. Anal. ($C_{23}H_{29}NO_8S$) C, H, N.

(*E*)-Methyl 2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoate (26d). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromopropionate following the procedure as described for compound **26**. Yield, 60%; white solid, mp 178−180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (d, J = 6.9 Hz, 3H, CH_3), 3.50 (s, 3H, OCH_3), 3.61 (s, 6H, 2 × OCH_3), 3.63 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.90−3,92 (m, 1H, CH), 3.94 (s, 2H, CH_2), 4.52 (br s, 1H, NH), 5.88 (s, 2H, Ar−H), 6.32 (d, J = 1.7 Hz, 1H, Ar−H), 6.47 (dd, J = 8.1, 1.7 Hz, 1H, Ar−H), 6.52 (d, J = 8.1 Hz, 1H, Ar−H), 6.81 (d, J = 15.6 Hz, 1H, =CH), 7.59 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 480.1579; found 480.1568. Anal. ($C_{23}H_{29}NO_8S$) C, H, N.

(*E*)-Methyl 2″,2″-Difluoro-2(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (26e). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-chloro-2,2-difluoroacetate following the procedure as described for compound **26**. Yield, 57%; white solid, mp 186−188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.74 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.22 (s, 2H, CH_2), 6.09 (s, 2H, Ar−H), 6.86 (d, J = 8.4 Hz, 1H, Ar−H), 7.09 (d, J = 15.6 Hz, 1H, =CH), 7.11 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.19 (s, 1H, Ar−H), 7.84 (d, J = 15.6 Hz, 1H, CH=), 8.08 (brs, 1H, NH). HRMS: m/z calcd [M + H] 502.1269; found 502.1284. Anal. ($C_{22}H_{25}F_2NO_8S$) C, H, N.

(*E*)-Methyl 3″,3″,3″-Trifluoro-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoate (26f). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromo-3,3,3-trifluoropropanoate following the procedure as described for compound **26**. Yield, 56%; white solid, mp 192−194 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.49 (s, 3H, OCH_3), 3.51 (s, 6H, 2 × OCH_3), 3.55 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.95−4.16 (m, 1H, CH), 4.22 (s, 2H, CH_2), 4.85 (t, J = 9.0 Hz, 1H, NH), 5.92 (s, 2H, Ar−H), 6.23 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 6.40 (d, J = 8.1 Hz, 1H, Ar−H), 6.53 (d, J = 2.1 Hz, 1H, Ar−H), 6.80 (d, J = 15.6 Hz, 1H, =CH), 7.55 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 534.1345; found 534.1339. Anal. ($C_{23}H_{26}F_3NO_8S$) C, H, N.

(*E*)-Methyl 2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-methylpropanoate (26g). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromo2-methylpropionate following the procedure as described for compound **26**. Yield, 60%; white solid, mp 170−172 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.52 (s, 6H, 2 × CH_3), 3.68 (s, 3H, OCH_3), 3.81 (s, 6H, 2 × OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 6.06 (s, 2H, Ar−H), 6.41 (s, 1H, Ar−H), 6.69−6.71 (m, 2H, Ar−H), 7.02 (d, J = 15.5 Hz, 1H, =CH), 7.80 (d, J = 15.5 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 494.1770; found 494.1761. Anal. ($C_{24}H_{31}NO_8S$) C, H, N.

(*E*)-Methyl 2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-phenylacetate (26h). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl α-bromophenylacetate following the procedure as described for compound **26**. Yield, 63%; white solid, mp 94−96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.71 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2), 4.99 (d, J = 6.0 Hz, 1H, CH), 5.43(d, J = 6.3 Hz, 1H, NH), 6.10 (s, 2H, Ar−H), 6.36 (d, J = 1.8 Hz, 1H, Ar−H), 6.67 (dd, J = 8.1, 1.8 Hz, 1H, Ar−H), 6.73 (d, J = 8.1 Hz, 1H, Ar−H), 6.99 (d, J = 15.6 Hz, 1H, =CH), 7.29−7.35 (m, 3H, Ar−H), 7.42 (dd, J = 8.1, 1.8 Hz, 2H, Ar−H), 7.77 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 542.1770; found 542.1778. Anal. ($C_{28}H_{31}NO_8S$) C, H, N.

(*E*)-Methyl 2-(4″-Fluorophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (26i). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromo-2- (4-fluorophenyl)acetate following the procedure as described for compound **26**. Yield, 60%; white solid, mp 152−154 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.72 (s, 3H, OCH_3), 3.82 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 4.98 (d, J = 2.5 Hz, 1H, CH), 6.10 (s, 2H, Ar−H), 6.33 (d, J = 2.0 Hz, 1H, Ar−H), 6.69 (dd, J = 8.5, 2.0 Hz, 1H, Ar−H), 6.73 (d, J = 8.5 Hz, 1H, Ar−H), 6.96−6.99 (m, 2H, Ar−H), 7.00 (d, J = 15.5 Hz, 1H, =CH), 7.37−7.40 (m, 2H, Ar−H), 7.76 (d, J = 16.0 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 560.1676; found 560.1656. Anal. ($C_{28}H_{30}FNO_8S$) C, H, N.

(*E*)-Methyl 2-(4″-Chlorophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (26j). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromo-2- (4-chlorophenyl)acetate following the procedure as described for compound **26**. Yield, 64%; white solid, mp 154−156 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.72 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 4.96 (s, 1H, CH), 6.11 (s, 2H, Ar−H), 6.31 (s, 1H, Ar−H), 6.67−6.75 (m, 2H, Ar−H), 6.99 (d, J = 15.6 Hz, 1H, =CH), 7.25−7.28 (m, 2H, Ar−H), 7.54 (d, J = 8.4 Hz, 2H, Ar−H), 7.76 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 576.1381; found 576.1367. Anal. ($C_{28}H_{30}ClNO_8S$) C, H, N.

(*E*)-Methyl 2-(4″-Bromophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (26k). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromo-2- (4-bromophenyl)acetate following the procedure as described for compound **26**. Yield, 62%; white solid, mp 150−152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.48 (s, 3H, OCH_3), 3.59 (s, 6H, 2 × OCH_3), 3.62 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.81 (s, 2H, CH_2), 4.71(s, 1H, CH), 5.87 (s, 2H, Ar−H), 6.07 (d, J = 1.8 Hz, 1H, Ar−H),

6.44 (dd, J = 8.1, 1.8 Hz, 1H, Ar−H), 6.50 (d, J = 8.1 Hz, 1H, Ar−H), 6.75 (d, J = 15.6 Hz, 1H, =CH), 7.05−7.08 (m, 2H, Ar−H), 7.16−7.19 (m, 2H, Ar−H), 7.53 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 620.0876; found 620.0859. Anal. ($C_{28}H_{30}BrNO_8S$) C, H, N.

(*E*)-Methyl 2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-(4″-methoxyphenyl)acetate (26l). The title compound was obtained by the alkylation of (*E*)-2′,4′,6′-trimethoxystyryl-4-methoxy-3-aminobenzylsulfone **8p** with methyl 2-bromo-2-(4-methoxyphenyl)acetate following the procedure as described for compound **26**. Yield, 61%; white solid, mp 182−184 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2), 4.91(s, 1H, CH), 6.10 (s, 2H, Ar−H), 6.37 (d, J = 1.5 Hz, 1H, Ar−H), 6.68 (dd, J = 8.1, 1.5 Hz, 1H, Ar−H), 6.73 (d, J = 8.1 Hz, 1H, Ar−H), 6.84 (d, J = 9.0 Hz, 2H, Ar−H), 7.00 (d, J = 15.5 Hz, 1H, =CH), 7.33 (d, J = 8.0 Hz, 2H, Ar−H), 7.77 (d, J = 16.0 Hz, 1H, CH=). HRMS: m/z calcd [M + H] 572.1876; found 572.1896. Anal. ($C_{29}H_{33}NO_9S$) C, H, N.

General Procedure for the Preparation of Amino Acids (27, Scheme 8). To a solution of amine ester **26** (46.5 g, 100 mmol) in ethanol (200 mL), 20% aqueous sodium hydroxide solution (200 mL) was added. The reaction mixture was refluxed for 2.5 h. After completion of the reaction (TLC, monitoring, chloroform/methanol, 9:1 on silica gel plate), the solvent was removed under vacuum and the remainder was acidified by acetic acid to pH 4. The solid that formed was filtered and dried to get the crude amino acid **27** which on crystallization from acetone (2 × 25 mL) resulted in analytically pure amino acid **27** as white crystals.

(*E*)-2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetic Acid (27a). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate **26a** following the procedure as described for compound **27**. Yield, 50%; pale yellow solid, mp 172−174 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.78 (s, 2H, NH−CH_2), 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 6H, 2 × OCH_3), 4.33 (s, 2H, CH_2), 6.35 (s, 2H, Ar−H), 6.48 (d, J = 1.8 Hz, 1H, Ar−H), 6.65 (dd, J = 8.1, 1.8 Hz, 1H, Ar−H), 6.86 (d, J = 8.1 Hz, 1H, Ar−H), 7.17 (d, J = 15.9 Hz, 1H, =CH), 7.62 (d, J = 15.6 Hz, 1H, CH=). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 172.1, 163.5, 160.8, 146.3, 136.9, 132.7, 123.6, 121.3, 119.2, 111.9, 109.3, 102.5, 90.6, 60.3, 55.9, 55.5, 55.4, 44.4, 30.6. HRMS: m/z calcd [M − H] 450.1301; found 450.1311. Anal. ($C_{21}H_{25}NO_8S$) C, H, N.

(*E*)-2-(2-Methoxy-5-((3′,4′,5′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetic Acid (27b). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(2-methoxy-5-((3′,4′,5′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate **26b** following the procedure as described for compound **27**. Yield, 55%; light yellow solid, mp 112−114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H, OCH_3), 3.79 (s, 6H, 2 × OCH_3), 3.81 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 4.15 (s, 2H, CH_2), 6.44 (d, J = 1.8 Hz, 1H, Ar−H), 6.55 (d, J = 15.4 Hz, 1H, =CH), 6.59 (s, 2H, Ar−H), 6.62−6.66 (m, 1H, Ar−H), 6.69 (d, J = 8.2 Hz, 1H, Ar−H), 7.26 (d, J = 15.5 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 450.1301; found 450.1314. Anal. ($C_{21}H_{25}NO_8S$) C, H, N.

(*E*)-3-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoic Acid (27c). The title compound was obtained by the hydrolysis of (*E*)-ethyl 3-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoate **26c** following the procedure as described for compound **27**. Yield, 51%; white solid, mp 130−132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (t, J = 6.3 Hz, 2H, CH_2), 3.34 (t, J = 6.3 Hz, 2H, CH_2), 3.75 (s, 6H, 2 × OCH_3), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 6.01 (s, 2H, Ar−H), 6.57 (s, 1H, Ar−H), 6.64−6.71 (m, 2H, Ar−H), 6.99 (d, J = 15.9 Hz, 1H, =CH), 7.76 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 464.1457; found 464.1471. Anal. ($C_{22}H_{27}NO_8S$) C, H, N.

(*E*)-2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoic Acid (27d). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoate **26d** following the procedure as described for compound **27**. Yield, 57%; light yellow solid, mp 116−118 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.07 (d, J = 6.6 Hz, 3H,CH_3), 3.57 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.64 (s, 6H, 2 × OCH_3), 3.79−3.83 (m, 1H, CH), 4.06 (s, 2H, CH_2), 6.08 (s, 2H, Ar−H), 6.26 (s, 1H, Ar−H), 6.35(d, J = 7.5 Hz, 1H, Ar−H), 6.58 (d, J = 8.1 Hz, 1H, Ar−H), 6.90 (d, J = 15.6 Hz, 1H, =CH), 7.35 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 464.1457; found 464.1446. Anal. ($C_{22}H_{27}NO_8S$) C, H, N.

(*E*)-2″,2″-Difluoro-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetic Acid (27e). The title compound was obtained by the hydrolysis of (*E*)-methyl 2″,2″-difluoro-2(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-acetate **26e** following the procedure as described for compound **27**. Yield, 59%; white solid, mp 196−198 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 6H, 2 × OCH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 6.12 (s, 2H, Ar−H), 6.58 (d, J = 8.1 Hz, 1H, Ar−H), 6.89 (d, J = 8.4 Hz, 1H, Ar−H), 7.06 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.29 (d, J = 15.6 Hz, 1H, =CH), 7.84 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 486.1112; found 486.1101. Anal. ($C_{21}H_{23}F_2NO_8S$) C, H, N.

(*E*)-3″,3″,3″-Trifluoro-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)propanoic Acid (27f). The title compound was obtained by the hydrolysis of (*E*)-methyl 3″,3″,3″-trifluoro-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)-phenylamino)propanoate **26f** following the procedure as described for compound **27**. Yield, 53%; white solid, mp 180−182 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.78 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 3.87 (s, 3H, OCH_3), 4.05 (d, J = 6.3 Hz, CH), 4.12 (s, 2H, CH_2), 6.28 (s, 2H, Ar−H), 6.61 (d, J = 8.4 Hz, 1H, Ar−H), 6.76 (dd, J = 8.4, 2.1 Hz, 1H, Ar−H), 7.01−7.09 (m, 1H, Ar−H), 7.10 (d, J = 15.6 Hz, 1H, =CH), 7.57 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 518.1175; found 518.1186. Anal. ($C_{22}H_{24}F_3NO_8S$) C, H, N.

(*E*)-2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-methylpropanoic Acid (27g). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-methyl-propanoate **26g** following the procedure as described for compound **27**. Yield, 61%; white solid, mp 142−144 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (s, 6H, 2 × CH_3), 3.83 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2), 6.07 (s, 2H, Ar−H), 6.52 (s, 1H, Ar−H), 6.79 (d, J = 8.0 Hz, 1H, Ar−H), 6.85 (d, J = 8.1 Hz, 1H, Ar−H), 7.05 (d, J = 16.0 Hz, 1H, =CH), 7.78 (d, J = 15.5 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 478.1614; found 478.1605. Anal. ($C_{23}H_{29}NO_8S$) C, H, N.

(*E*)-2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-phenylacetic Acid (27h). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-2-phenylacetate **26h** following the procedure as described for compound **27**. Yield, 60%; white solid, mp 124−126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.75 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.00(s, 2H, CH_2), 4.86 (s, 1H, CH), 6.03 (s, 2H, Ar−H), 6.32 (d, J = 1.4 Hz, 1H, Ar−H), 6.66−6.69 (m, 2H, Ar−H), 6.94 (d, J = 15.6 Hz, 1H, =CH), 7.22−7.26 (m, 3H, Ar−H), 7.32−7.34 (m, 2H, Ar−H), 7.69 (d, J = 15.6 Hz, 1H, CH=). HRMS: m/z calcd [M − H] 526.1614; found 526.1604. Anal. ($C_{27}H_{29}NO_8S$) C, H, N.

(*E*)-2-(4″-Fluorophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetic Acid (27i). The title compound was obtained by the hydrolysis of (*E*)-methyl

2-(4″-fluorophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate **26i** following the procedure as described for compound **27**. Yield, 60%; light yellow solid, mp 82−84 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2), 4.42(s, 1H, CH), 6.29 (s, 2H, Ar−H), 6.33 (d, J = 2.0 Hz, 1H, Ar−H), 6.69 (dd, J = 8.5, 2.0 Hz, 1H, Ar−H), 6.73 (d, J = 8.5 Hz, 1H, Ar−H), 6.96−6.99 (m, 2H, Ar−H), 7.00 (d, J = 15.5 Hz, 1H, ═CH), 7.37−7.40 (m, 2H, Ar−H), 7.76 (d, J = 16.0 Hz, 1H, CH═). HRMS: m/z calcd [M − H] 544.1520; found 544.1434. Anal. ($C_{27}H_{28}FNO_8S$) C, H, N.

(*E*)-2-(4″-Chlorophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetic Acid (27j). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(4″-chlorophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)-phenylamino)acetate **26j** following the procedure as described for compound **27**. Yield, 60%; white solid, mp 172−174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.55 (s, 6H, 2 × OCH_3), 3.57 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2), 4.69(s, 1H, CH), 5.83 (s, 2H, Ar−H), 6.06 (d, J =1.8 Hz, 1H, Ar−H), 6.44 (dd, J = 8.1, 1.8 Hz, 1H, Ar−H), 6.47 (d, J = 8.1 Hz, 1H, Ar−H), 6.73 (d, J = 15.6 Hz, 1H, ═CH), 7.00 (d, J = 7.8 Hz, 2H, Ar−H), 7.08 (d, J = 8.5 Hz, 2H, Ar−H), 7.49 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M − H] 560.1224; found 560.1212. Anal. ($C_{27}H_{28}ClNO_8S$) C, H, N.

(*E*)-2-(4″-Bromophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetic Acid (27k). The title compound was obtained by the hydrolysis of (*E*)-methyl 2-(4″-bromophenyl)-2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)-phenylamino)acetate **26k** following the procedure as described for compound **27**. Yield, 60%; white solid, mp 178−179 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.93 (s, 6H, 2 × OCH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.25 (s, 2H, CH_2), 4.96 (s, 1H, CH), 6.39 (s, 2H, Ar−H), 6.41 (d, J = 1.8 Hz, 1H, Ar−H), 6.69 (dd, J = 8.1, 1.8 Hz, 1H, Ar−H), 6.91 (d, J = 8.1 Hz, 1H, Ar−H), 7.14 (d, J = 15.6 Hz, 1H, ═CH), 7.39 (d, J = 8.4 Hz, 2H, Ar−H), 7.57 (d, J = 8.4 Hz, 2H, Ar−H),7.61 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M − H] 604.0719; found 604.0731. Anal. ($C_{27}H_{28}BrNO_8S$) C, H, N.

(*E*)-2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)-methyl)phenylamino)-2-(4″-methoxyphenyl)acetic Acid (27l). The title compound was obtained by the hydrolysis of (*E*)-(4″-methoxyphenyl)-{2-methoxy-5-[2-(2′,4′,6′-trimethoxyphenyl)ethene-sulfonylmethyl]phenylamino}acetic acid methyl ester **26l** following the procedure as described for compound **27**. Yield, 60%; white solid, mp 174−175 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.72 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 6H, 2 × OCH_3), 3.87 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 4.80(s, 1H, CH), 6.31 (s, 2H, Ar−H), 6.37 (d, J = 1.5 Hz, 1H, Ar−H), 6.62 (dd, J = 8.1, 1.5 Hz, 1H, Ar−H), 6.71 (d, J = 8.1 Hz, 1H, Ar−H), 6.82 (d, J = 9.0 Hz, 2H, Ar−H), 7.08 (d, J = 15.6 Hz, 1H, ═CH), 7.27 (d, J = 8.7 Hz, 2H, Ar−H), 7.54 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M − H] 556.1720; found 556.1731. Anal. ($C_{28}H_{31}NO_9S$) C, H, N.

Sodium (*E*)- 2-(2-Methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)acetate (ESTYBON) (28). The title compound was obtained by the direct hydrolysis of (*E*)-methyl 2-(2-methoxy-5-((2′,4′,6′-trimethoxystyrylsulfonyl)methyl)phenylamino)-acetate **26a**. To a solution of sodium hydroxide (3.95 g, 99 mmol) in water (11.5 mL) at 20 °C was added ethanol (40 mL), (*E*)-methyl 2-(2-methoxy-5-((2′,4′,6′-trimethoxystyryl sulfonyl)methyl)phenylamino)-acetate **26a** and dichloromethane (200 mL). The resulting mixture was stirred at room temperature for 3−4 h. After completion of the reaction monitored by TLC (chloroform/methanol, 9:1 on silica gel plate), charcoal was added and the mixture was stirred for 30 min. The reaction mixture was filtered through Celite and washed with ethanol (2 × 20 mL). The combined filterate was distilled at 50 °C until most of the solvent was removed. Methyl ethyl ketone (70 mL) was added to the residue, and distillation of the methyl ethyl ketone was at 50 °C. To the residue, water (10 mL) was added. The resulting mixture was heated to 70 °C and maintained for 30 min. The reaction mixture was cooled to room temperature and stirred for 2 h at room temperature. The solid formed was filtered, washed with methyl ethyl ketone (2 × 20 mL), and dried to get the title compound **28**. Yield, 80%; white solid, mp 174−178 °C. ^{1}H NMR (D_2O, 300 MHz): δ 3.46 (s, 2H, NH−CH_2), 3.63 (s, 6H, 2 × OCH_3), 3.72 (s, 3H, OCH_3), 3.75(s, 3H, OCH_3), 4.23 (s, 2H, CH_2), 5.89 (s, 2H, Ar−H), 6.44 (d, J = 1.5 Hz, 1H, Ar−H), 6.59 (dd, J = 8.4, 1.5 Hz, 1H, Ar−H), 6.72 (d, J = 8.4 Hz, 1H, Ar−H), 6.91 (d, J = 15.6 Hz, 1H, ═CH), 7.39 (d, J = 15.6 Hz, 1H, CH═). HRMS: m/z calcd [M + H] 510.1365; found 510.1378. Anal. ($C_{21}H_{24}NNaO_8S\cdot 2H_20$) C, H, N.

Biology. Tissue Culture and Reagents. Paclitaxel was purchased from Sigma. Cell lines were purchased from ATCC. Cell lines were routinely grown in DMEM or RPM1 (CellGro) supplemented with 10% fetal bovine serum (Cell Generation Co.) and 1 unit/mL penicillin−streptomycin (Gibco).

Cytotoxicity Assay. We have tested a number of tumor cell lines using a dose response end point assay system. The cells were grown in either DMEM or RPMI supplemented with 10% fetal bovine serum and 1 unit/mL penicillin−streptomycin solution. The tumor cells were plated into six-well dishes at a cell density of 1.0 × 10^5 cells/mL/well, and compounds were added 24 h later at various concentrations. Cell counts were determined from duplicate wells after 96 h of treatment. The total number of viable cells was determined by trypan blue exclusion.

Flow Cytometry. Human prostate tumor cells, DU145 cells, and normal diploid human lung fibroblasts, HFL-1 cells, were grown in DMEM (Cellgro) supplemented with 10% fetal bovine serum and 1 unit/mL penicillin−streptomycin. The cells were plated onto 100 mm^2 dishes at a cell density of 1.0 × 10^6 cells/dish, and 24 h later, they were treated with 2.5 μM compound. The cells were harvested 24 h after treatment. The cells were removed from the plate by trypsin digestion and combined with the nonattached cells found in the medium. The cell pellets were washed in phosphate buffered saline (PBS) and fixed in ice cold 70% ethanol for at least 24 h. The fixed cells were then washed with room temperature PBS and stained with propidium iodide (50 mg/mL) and RNase A (0.5 mg) for 30 min at 37 °C. The stained cells were then analyzed on a Becton-Dickinson (BD) (FACScan) flow cytometer and the data analyzed by cell cycle analysis software (Modfit, BD).

PARP Western. DU145 and HFL-1 cells were plated at a density of 3.0 × 10^6 cells per 150 mm^2 plate and treated 24 h later with either DMSO or **28**. The cells were collected at 48 h of treatment, and cell pellets were frozen. The frozen cell pellets were lysed in 1% NP40/PBS lysis buffer containing protease inhibitors. Equal amounts of total cellular protein were then resolved on a 10% SDS−polyacrylamide gel. The gels were transferred onto nitrocellulose paper (S/S), hybridized with anti-PARP antibodies (BD), and developed using ECL (Perkin-Elmer, MA) solution.

Cellular Viability and Caspase 3/7 Activity. Exponentially growing A549 cells were seeded in a white walled 96-well plate at a density of 3600 cells/well in 100 μL of DMEM containing 10% FBS and 1% Pen/Strep. Cells were then allowed to adhere overnight at 37 °C in an incubator. The next day, cells were treated with varying concentrations of **28** or DMSO and then returned to the incubator. Twenty-four hours later, plates were removed from the incubator and 20 μL of CellTiter-Blue Reagent (Promega catalog no. G8080) was added individually to each well following the manufacturer's instructions. Plates were slowly shaken for 0.5 min and then returned to the incubator. After 3 h, fluorescence was read using a Glomax 96-well plate reader. Next, 120 μL of Caspase Glo 3/7 reagent (Promega catalog no. G8090) was added to each well per manufacturer's instructions. Plates were slowly shaken for 0.5 min and allowed to develop at room temperature

for 2 h. At the end of this period, luminescence was read using a Glomax 96-well plate reader.

Nude Mouse Assay. Female athymic (NCR-nu/nu, Taconic) nude mice were injected with (0.5−1.0) × 10^7 BT20 cells subcutaneously in the hind leg using a 1 mL tuberculin syringe equipped with a 271/2 gauge needle. Approximately 14 days later, mice were paired (N = 9) and injected with 200 mg/kg **28** or phosphate buffered saline as the vehicle control. The intravenous injections were performed in the mouse tail vein using a 1 mL tuberculin syringe equipped with a 30 gauge needle. The animals were injected following a Q2D × 20 schedule. Tumor measurements (two dimensions) were done three times per week using traceable digital vernier calipers (Fisher). Tumor volume was calculated using the following equation: $V = (L(S^2)p/6$, where L is the longer and S is the shorter of the two dimensions. Body weight was determined during each measurement. The animals were observed for signs of toxicity. The time of tumor volume doubling was calculated, and the $T - C$ value (difference in the average times after treatment for tumors of the treated groups to attain a doubling in volume compared to the average of the control group) was determined. We did not observe body weight loss of more than 10% in any group nor were there any animal deaths. All studies were performed under the guidelines of Temple University IACUC.

■ ASSOCIATED CONTENT

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

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Author Contributions

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Notes

Conflict of Interest Statement: Dr. E. P. Reddy is a stockholder, board member, grant recipient, and paid consultant of Onconova Therapeutics Inc. Dr. M. V. R. Reddy is a stockholder and paid consultant of Onconova Inc. Dr. S. Cosenza is a paid consultant of Onconova Therapeutics Inc.

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■ ABBREVIATIONS USED

MDS, myelodysplstic syndromes; AML, acute myeloid leukemia; PI3K, phosphoinositide 3-kinase; BIM, Bcl-2-interacting modulator of cell death; FDA, Food and Drug Administration; DNA, deoxyribonucleic acid; CDK, cyclin dependent kinase; JNK, Janus kinase; p-mTOR, mammalian target of rapamycin

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