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Design, synthesis, and biological evaluation of (*E*)- and (*Z*)-styryl-2-acetoxyphenyl sulfides and sulfones as cyclooxygenase-2 inhibitors

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Abstract—A new series of styryl acetoxyphenyl sulfides and sulfones possessing (*E*)- and (*Z*)-configurations were designed and prepared by stereospecific syntheses. All these compounds were evaluated for their ability to inhibit COX-2 enzyme in vitro. Structure–activity relationship studies on these compounds revealed that only sulfides with (*Z*)-configuration have potential COX-2 inhibitory activity. This inactivation of the enzyme is believed to be due to the selective covalent modification of COX-2 by the inhibitors.

1. Introduction

Cyclooxygenases (COXs) are key enzymes in the synthesis of prostaglandin H_2, which is a precursor for the biosynthesis of prostaglandins, thromboxanes, and prostacyclins.[1] COX enzymes exist in two isoforms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).[2] COX-1 enzyme is constitutively expressed and is critical for protection of gastric mucosa, platelet aggregation and renal blood flow whereas COX-2 enzyme is inducible and expressed during inflammation, pain, and oncogenesis.[3] Since COX-2 is involved in inflammation and pain, molecules that inhibit it's enzymatic activity would be of therapeutic value. Many nonsteroidal anti-inflammatory drugs (NSAIDs) were found to interact with these enzymes and inhibit their enzymatic activity.[4] These molecules include aspirin and indomethacin which are nonselective and inhibit both COX-1 and COX-2 enzymes. Aspirin inhibits COX-1 more strongly than COX-2[4] and inhibition of COX-1 by aspirin reduces the production of PGE_2 and PGI_2, which has an adverse ulcerogenic effect.[5]

Recently several new inhibitors were developed, which selectively inhibit COX-2 enzyme without interfering with COX-1 enzymatic activity. These molecules include celecoxib,[6] rofecoxib,[7] and valdecoxib,[8] which inhibit COX-2 enzyme without the side effects observed with traditional NSAIDs. These selective inhibitors take advantage of the larger enzymatic pocket in COX-2 active site where valine at 523 has a smaller side chain that accommodates the sulfur containing side chains of the inhibitors, where the isoleucine at 523 in COX-1 has a bigger side chain preventing the docking of the inhibitor at the active site.[9] This preferential binding of selective inhibitors to COX-2 enzyme over COX-1 enzyme prevents the side effects as seen in nonselective inhibitors.[10]

Aspirin is a unique NSAID that interacts with both cyclooxygenases but inhibits COX-1 10- to 100-fold more effectively than the COX-2 enzyme.[11] Aspirin's inhibitory activity is due to its ability to acetylate serine residues positioned at Ser^{530} in COX-1 and Ser^{516} in COX-2.[12,13] Acetylation of these residues prevents the positioning of arachidonic acid to its binding site thereby blocking the substrate to the active site of oxygenation. Because of its dual inhibitory activity, some of

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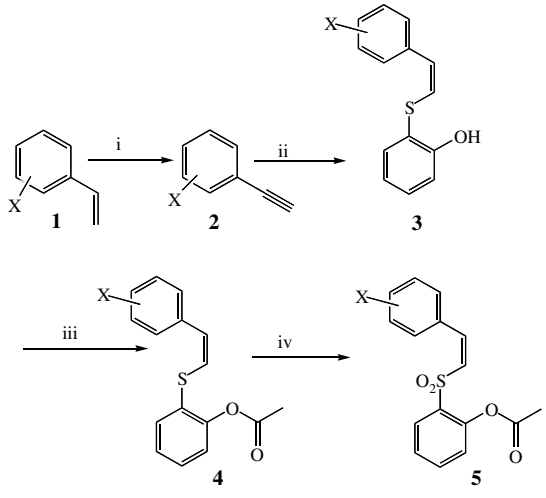
aspirin's therapeutic advantages can be attributed to its ability to reduce inflammation by acetylating COX-2 and prevent platelet aggregation and anti-thrombosis by acetylating COX-1.[14] Recent studies[15] on selective COX-2 inhibitors revealed that patients with heart disease are more prone to myocardial infarction and this may be due to TxA_2/PGI_2 imbalance created by selective COX-2 inhibitors.[16] These observations can be exploited in designing a novel aspirin like molecule, which can have all the benefits of COX-2 irreversible inhibition and retaining anti-thrombotic activity by selective acetylation of COX-1 enzyme. Recently, Kalgutkar and co-workers[17,18] have synthesized novel aspirin like analogs with variations at acyl group, alkyl group, aryl substitution pattern and heteroatom substitution and discovered a lead molecule that selectively acetylated, and irreversibly inactivated, COX-2.

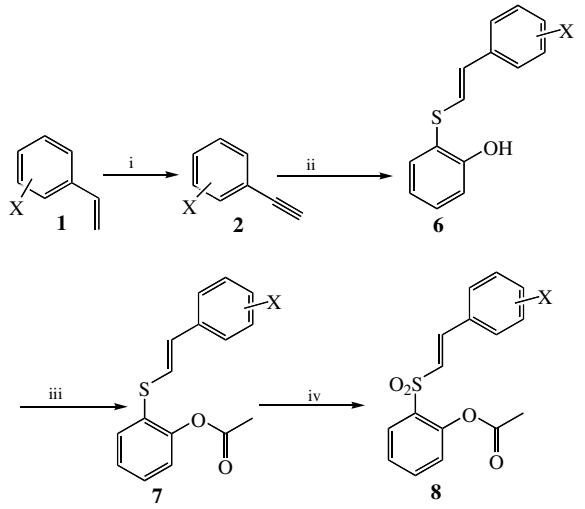
In this paper, we wish to report the synthesis of novel (*E*)- and (*Z*)-styryl-2-acetoxyphenyl sulfides, sulfones, and their selective inhibition of COX-2 enzyme. We believe that these compounds may be inhibiting COX-2 enzyme by modifying the serine residue located in the catalytic domain of the enzyme. The significance of this paper lies in the design and synthesis of new COX-2 inhibitors that may possess both anti-thrombotic activity of aspirin and anti-inflammatory activity of celecoxib and rofecoxib.

2. Chemistry

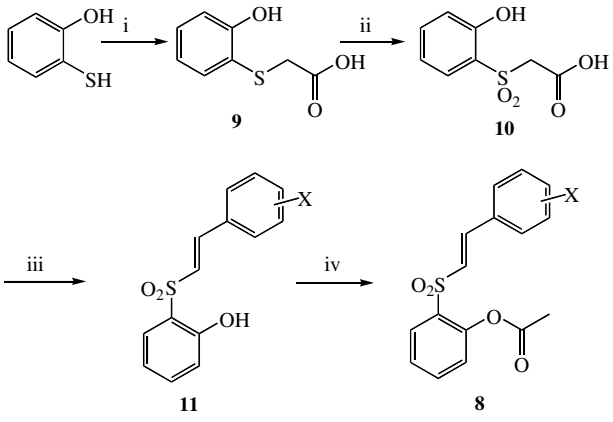
The title compounds were synthesized using the reaction sequence illustrated in Schemes 1–3. Accordingly, bromination and dehydrobromination of styrenes (**1**) in alcoholic potassium hydroxide solution yielded phenylacetylenes (**2**).[19] Nucleophilic addition of the thiol to phenylacetylenes in the presence of a base yielded a (*Z*)-styryl hydroxyphenyl sulfides (**3**) by *trans* addition.[20] Acetylation of (*Z*)-styryl hydroxyphenyl sulfides with acetic anhydride and pyridine gave (*Z*)-styryl acetoxyphenyl sulfides (**4**). Oxidation of these sulfides with hydrogen peroxide[21] in acetic acid resulted in the formation of (*Z*)-styryl acetoxyphenyl sulfones (**5**) (Scheme 1).



Scheme 1. Reagents and conditions: (i) Br_2, CCl_4, 4 °C, KOH, EtOH, reflux 12 h; (ii) 2-hydroxythiophenol, NaOH, MeOH, reflux 24 h; (iii) Ac_2O, pyridine/CH_2Cl_2, 6 h; (iv) 30% H_2O_2, AcOH, 16 h.



Scheme 2. Reagents and conditions: (i) Br_2, CCl_4, 4 °C, KOH, EtOH, reflux 12 h; (ii) 2-hydroxythiophenol, AcOH, $(Ac_2)_3Mn{\cdot}2H_2O$; (iii) Ac_2O, pyridine/CH_2Cl_2, 6 h; (iv) 30% H_2O_2, AcOH, 16 h.



Scheme 3. Reagents and conditions: (i) mercaptoacetic acid, NaOH, MeOH, reflux 5 h; (ii) 30%H_2O_2, AcOH, 16 h; (iii) aromatic aldehyde, benzoic acid, piperidine, toluene, reflux 4 h; (iv) Ac_2O, pyridine/CH_2Cl_2, 6 h.

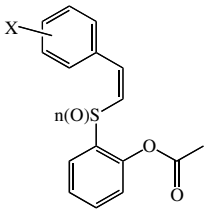
The corresponding (*E*)-isomers of styryl hydroxyphenyl sulfides (**6**) were synthesized by free radical addition of 2-hydroxy thiophenol to phenylacetylene.[22] Acetylation of the resulting sulfide (**7**) followed by the oxidation yielded (*E*)-styryl acetoxyphenyl sulfones (**8**) (Scheme 2). Alternately, (*E*)-styryl acetoxyphenyl sulfones were also synthesized by Knoevenagel type condensation[23] of 2-hydroxyphenylsulfonyl acetic acid (**10**) with various aromatic aldehydes followed by acetylation of the styryl sulfone (**11**) (Scheme 3). The (*E*)- and (*Z*)-configurations to these isomers were assigned by NMR. All (*Z*)-isomers have shown coupling constants between 10 and 11 Hz for their vinylic protons whereas the coupling constants for the vinylic protons in the (*E*)-isomers were found between 15 and 16 Hz.[24]

3. Results and discussion

We have synthesized a series of (*E*)- and (*Z*)-isomers of styryl acetoxyphenylsulfides (**4**, **7**) and sulfones (**5**, **8**) and evaluated their ability to inhibit COX-2 and COX-1 enzymes in vitro by using recombinant COX-1 and COX-2 enzymes. IC_{50} values for inhibition of ovine COX-1 and COX-2 by these compounds were determined by Enzyme Immuno Assay (Tables 1 and 2).[25]

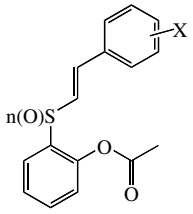
Inhibition of COX-2 enzyme by aspirin is due to its initial binding to an arginine residue (Arg^{499}) by its O-carboxylate group followed by the transfer of an acetyl moiety to the weakly nucleophilic hydroxyl group of the serine residue (Ser^{530} in COX-1 and Ser^{516} in COX-2).[26] Based on this, we have decided to synthesize a molecule capable of transferring an acetyl group to the serine residue to prevent the interaction of arachidonic acid with the COX-2 enzyme. Unlike aspirin, which inhibits COX-1 preferentially over COX-2, most of the (*Z*)-styryl acetoxyphenyl sulfides (**4**) inhibited COX-2 enzyme at lower concentrations as compared to COX-1 showing their specificity toward COX-2 enzyme (Table 1). It has been shown that the fatty acid binding site in COX-2 enzyme is larger than COX-1[27] and therefore designing a molecule that fits in COX-2 pocket and not in the COX-1 would result in specific inhibition of the COX-2 enzyme. Selectivity of (*Z*)-styryl acetoxyphenyl sulfides (**4**) for the COX-2 enzyme inhibition may be due to the presence of the bulkier (*Z*)-styryl thio group *ortho* to the acetate, which may fit well in the COX-2 enzyme pocket while not fitting into the COX-1 active site.

Table 1. In vitro COX-1 and COX-2 inhibition by (*Z*)-styryl acetoxyphenylsulfides and sulfones



Compound	*n*	X	IC_{50} (μM)	
			COX-2	COX-1
Celecoxib	—	—	1.7	>100
Aspirin	—	—	93	15.5
4a	0	H	10.8	>100
4b	0	4-F	18.9	>100
4c	0	2-F	10.6	>100
4d	0	4-Cl	27.9	>100
4e	0	4-Br	39.8	>100
4f	0	4-CH_3	27.8	>100
4g	0	4-CH_2CH_3	46.4	>100
4h	0	4-$(CH_2)_4CH_3$	73.7	>100
4i	0	3-$OCOCH_3$	2.8	>100
4j	0	4-OCH_3	53.8	>100
4k	0	2,4-F_2	27.4	>100
4l	0	4-CF_3	92.5	>100
5a	2	H	>100	>100
5b	2	4-Cl	>100	>100
5c	2	4-Br	>100	>100

Table 2. In vitro enzyme inhibition by (*E*)-styryl acetoxyphenylsulfides and sulfones



Compound	*n*	X	IC_{50} (μM)	
			COX-2	COX-1
7a	0	H	>100	>100
7b	0	4-Cl	>100	>100
7c	0	4-Br	>100	>100
8a	2	H	>100	>100
8b	2	4-Cl	>100	>100
8c	2	4-Br	>100	>100
8d	2	2,4,6-$(OCH_3)_3$	>100	>100

To study the structure–activity relationship of these molecules (**4**), we have made (*Z*)-styryl acetoxyphenyl sulfones (**5**), (*E*)-styryl acetoxyphenyl sulfide (**7**), and (*E*)-styryl acetoxyphenyl sulfones (**8**) by different methods (Schemes 1–3). Analysis of COX-2 enzyme inhibition data clearly shows that either oxidation of the thio group or the change in the configuration of the molecule from (*Z*) to (*E*) results in the loss of activity (Table 2). The oxidation of (*Z*)-styryl acetoxyphenyl sulfides (**4**) to sulfones (**5**) could make the aromatic ring more electron deficient and consequently may hinder the transfer of the acetyl group to the serine residue or the molecule may not fit in the fatty acid binding site because of the bulkier sulfone group. Another interesting aspect of the structure–activity relationship of the sulfides (**4**) is their geometrical configuration. Because of the presence of a double bond in the molecule, styryl acetoxyphenyl sulfides exist as *trans* (*E*) or *cis* (*Z*) isomers. Spatial arrangement of atoms in a molecule are critical for drug ligand interactions, which always determines the ability of a molecule to bind to its receptor. Some of the drugs, which are potent inhibitors of various targets, exist as chiral molecules.[28] Drugs such as desloratadine (Clarinex®), fexofenadine (Allegra®), esomeprazole (Nexium®), etc. are more active as an (*R*)- or (*S*)-isomer as compared to the corresponding racemates. This suggests that geometrical and stereoisomers differ in their drug property and the spatial distribution of atoms in a molecule is critical for the biological activity of the drug.

Our study shows that (*Z*)-styryl acetoxyphenyl sulfides are more potent inhibitors of COX-2 enzymatic activity than the corresponding (*E*)-isomers, which are inactive. Styryl acetoxyphenyl sulfides in (*Z*)-configuration may be a perfect fit for the fatty acid binding pocket of COX-2, whereas molecules with (*E*)-configuration that are more spatially distributed than (*Z*)-isomers may not fit into the active site.

Studies involving selective covalent modification of serine (Ser^{516}) in COX-2 and interaction of (*Z*)-styryl

acetoxyphenyl sulfide (**4a**) with other residues in the catalytic domain are in progress.

4. Conclusions

In this report, we have synthesized a series of novel (*Z*)- and (*E*)-styryl acetoxyphenyl sulfides and sulfones and examined their activity against COX-1 and COX-2 enzymes. Our results show that only the (*Z*)-styryl acetoxyphenyl sulfides selectively inhibit COX-2. Unlike celecoxib, rofecoxib, and valdecoxib, these molecules are likely to inhibit COX-2 enzyme by covalently modifying the serine residue (Ser^{516}) at the active site. The structure–activity relationship of styryl acetoxyphenyl sulfides and sulfones demonstrates that (*Z*)-configuration and the unoxidized thio group are critical for the COX-2 inhibitory activity. This work led to the discovery of a series of compounds that are mechanistically similar to aspirin but possessing higher degree of selectivity towards COX-2 enzyme inhibition unlike aspirin.

5. Experimental

5.1. COX-inhibition-EIA assay

Cyclooxygenase activity of ovine COX-1 and COX-2 was assayed using COX inhibitory screening assay kit (Cayman Chemicals, MI). This assay directly measures $PGF_{2\alpha}$, that was produced by stannous chloride reduction of COX derived PGH_2 by enzyme immunoassay (EIA). This assay is more accurate and reliable than the peroxidase inhibition assay as shown by Gierse et al.[25] All assays were conducted in duplicate and IC_{50} values are the average of duplicate determinations for each compound. In brief, for the inhibition assay, hematin reconstituted purified COX-1 and COX-2 enzymes (six units) in a reaction buffer containing Tris–HCl (0.1 M, pH 8.0), 5 mM EDTA, 2 mM phenol, were pre-incubated at room temperature for 1 h with inhibitor concentrations ranging from 0.001 to 100 μM in DMSO followed by the addition of arachidonic acid (100 μM) for 2 min at 37 °C. Reactions were terminated by adding 50 μL of 1 M HCl followed by the addition of 100 μL of saturated stannous chloride. The final product $PGF_{2\alpha}$ formed was measured by EIA and IC_{50} values were determined following the instructions given in the kit manual.

5.2. Chemistry

5.2.1. General information. Melting points were determined in open capillary tubes using a Mel-Temp® electro thermal apparatus and are uncorrected. Proton NMR (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were determined in $CDCl_3$ or DMSO-d_6 solution on a Bruker Avance 400 spectrometer. Proton chemical shifts (δ) are expressed in parts per million (ppm) relative to tetramethylsilane as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), br s (broad singlet), m (multiplet), and q (quartet). Coupling constants (*J*) are given in hertz (Hz). Elemental analyses were obtained by Quantitative Technologies Inc. (White House, New Jersey) and the results were within 0.4% of the calculated values unless otherwise mentioned.

5.2.2. Materials and methods. Reagents and solvents were purchased from common suppliers and were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (60 Å; Aldrich), visualized under 254 nm ultraviolet light or iodine spray. Column chromatography separations were performed using silica gel (70–230 mesh) obtained from the Aldrich Company. The solvents used for elution varied depending on the compound and included either one or a combination of the following: petroleum ether, ethylacetate, chloroform, and methanol. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. Yields were of purified product and were not optimized. Celecoxib was prepared according to the literature procedure.[6] Ethynylbenzenes were either purchased or prepared according to the procedure in the literature.[19]

5.2.3. General procedure for the synthesis of (*Z*)-styryl-2-hydroxyphenyl sulfides (3). To a stirred solution of sodium hydroxide (2 mmol) in absolute methanol (20 mL) was added dropwise 2-hydroxythiophenol (1 mmol) over a period of 0.75 h. On completion of the addition and when the reaction was no longer exothermic, phenylacetylene (1 mmol) was added, and the reaction mixture was refluxed for 24 h. The reaction mixture was then poured into ice-cold hydrochloric acid (10 mL) solution and was stirred for 10 min. The solution was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was collected, washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo, to afford the respective (*Z*)-styryl hydroxyphenyl sulfides. Products **3** were used without further purification for the preparation of compounds **4**.

5.2.3.1. (*Z*)-Styryl-2-hydroxyphenyl sulfide (3a). This compound was obtained as light yellow solid (78%) by reaction of 2-hydroxythiophenol with phenylacetylene. Mp 71–73 °C; ^{1}H NMR ($CDCl_3$): δ 6.03 (d, J = 10.6 Hz, 1H), 6.15 (br s, OH), 6.52 (d, J = 10.6 Hz, 1H), 6.86–7.51 (m, 9H). Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30. Found: C, 73.95; H, 5.29.

5.2.3.2. (*Z*)-4-Fluorostyryl-2-hydroxyphenyl sulfide (3b). This compound was obtained as light yellow solid (81%) by reaction of 2-hydroxythiophenol with 4-fluorophenylacetylene. Mp 55–57 °C; ^{1}H NMR ($CDCl_3$): δ 6.08 (d, J = 10.5 Hz, 1H), 6.18 (br s, OH), 6.57 (d, J = 10.5 Hz, 1H), 6.91–7.58 (m, 8H). Anal. Calcd for $C_{14}H_{11}FOS$: C, 68.27; H, 4.50. Found: C, 68.05; H, 4.53.

5.2.3.3. (*Z*)-2-Fluorostyryl-2-hydroxyphenyl sulfide (3c). This product was obtained as a colorless liquid (72% yield) by reaction of 2-hydroxythiophenol with 2-fluorophenylacetylene. ^{1}H NMR ($CDCl_3$): δ 6.12 (d, J = 10.7 Hz, 1H), 6.23 (br s, OH), 6.68 (d, J = 10.6 Hz, 1H), 7.01–7.90 (m, 8H). Anal. Calcd for $C_{14}H_{11}FOS$: C, 68.27; H, 4.50. Found: C, 68.29; H, 4.52.

5.2.3.4. (*Z*)-4-Chlorostyryl-2-hydroxyphenyl sulfide (3d). This product was obtained as a light yellow crystalline solid (78% yield) by reaction of 2-hydroxythiophenol with 4-chlorophenylacetylene. Mp 51–53 °C; ^{1}H NMR ($CDCl_3$): δ 6.06 (d, J = 10.7 Hz, 1H), 6.16 (br s, OH), 6.46 (d, J = 10.7 Hz, 1H), 6.87–7.47 (m, 8H). Anal. Calcd for $C_{14}H_{11}ClOS$: C, 63.99; H, 4.22. Found: C, 64.20; H, 4.21.

5.2.3.5. (*Z*)-4-Bromostyryl-2-hydroxyphenyl sulfide (3e). This product was obtained as a light yellow crystalline solid (85% yield) by reaction of 2-hydroxythiophenol with 4-bromophenylacetylene. Mp 54–57 °C; ^{1}H NMR ($CDCl_3$): δ 6.07 (d, J = 10.5 Hz, 1H), 6.21 (br s, OH), 6.52 (d, J = 10.6 Hz, 1H), 6.99–7.60 (m, 8H). Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.73; H, 3.61. Found: C, 54.58; H, 3.63.

5.2.3.6. (*Z*)-4-Methylstyryl-2-hydroxyphenyl sulfide (3f). This product was obtained as a colorless liquid (77% yield) by reaction of 2-hydroxythiophenol with 4-methylphenylacetylene. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 5.98 (d, J = 10.6 Hz, 1H), 6.21 (br s, OH), 6.52 (d, J = 10.6 Hz, 1H), 6.97–7.50 (m, 8H). Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82. Found: C, 74.56; H, 5.85.

5.2.3.7. (*Z*)-4-Ethylstyryl-2-hydroxyphenyl sulfides (3g). This product was obtained as a colorless liquid (69% yield) by reaction of 2-hydroxythiophenol with 4-ethylphenylacetylene. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H), 2.62 (q, 2H), 6.02 (d, J = 10.5 Hz, 1H), 6.18 (br s, OH), 6.50 (d, J = 10.6 Hz, 1H), 7.02–7.57 (m, 8H). Anal. Calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29. Found: C, 74.79; H, 6.31.

5.2.3.8. (*Z*)-4-Pentylstyryl-2-hydroxyphenyl sulfide (3h). This product was obtained as a colorless liquid (64% yield) by reaction of 2-hydroxythiophenol with 4-pentylphenylacetylene. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H), 1.28 (m, 4H), 1.45 (m, 2H), 2.55 (t, 2H), 5.97 (d, J = 10.6 Hz, 1H), 6.23 (br s, OH), 6.59 (d, J = 10.6 Hz, 1H), 6.86–7.48 (m, 8H). Anal. Calcd for $C_{19}H_{22}OS$: C, 76.47; H, 7.43. Found: C, 76.62; H, 7.39.

5.2.3.9. (*Z*)-3-Hydroxystyryl-2-hydroxyphenyl sulfide (3i). This product was obtained as a colorless liquid (66% yield) by reaction of 2-hydroxythiophenol with 3-hydroxyphenylacetylene. ^{1}H NMR ($CDCl_3$): δ 6.24 (br s, OH), 7.08–7.59 (m, 10H), 8.0 (br s, OH). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.51; H, 4.96.

5.2.3.10. (*Z*)-4-Methoxystyryl-2-acetoxyphenyl sulfide (3j). This product was obtained as a colorless liquid (74% yield) by reaction of 2-hydroxythiophenol with 4-methoxyphenylacetylene. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 6.11 (d, J = 10.5 Hz, 1H), 6.21 (br s, OH), 6.58 (d, J = 10.5 Hz, 1H), 6.91–7.55 (m, 8H). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.87; H, 5.48.

5.2.3.11. (*Z*)-2,4-Difluorostyryl-2-acetoxyphenyl sulfide (3k). This product was obtained as a colorless liquid (69% yield) by reaction of 2-hydroxythiophenol with 2,4-difluorophenylacetylene; ^{1}H NMR ($CDCl_3$: δ 6.26 (br s, OH), 6.35 (d, J = 10.5 Hz, 1H), 6.60 (d, J = 10.6 Hz, 1H), 6.80–7.79 (m, 7H). Anal. Calcd for $C_{14}H_{10}F_2OS$: C, 63.62; H, 3.81. Found: C, 63.41; H, 3.82.

5.2.3.12. (*Z*)-4-Trifluoromethylstyryl-2-acetoxyphenyl sulfide (3l). This product was obtained as a colorless semisolid (75% yield) by reaction of 2-hydroxythiophenol with 4-trifluorophenylacetylene. ^{1}H NMR ($CDCl_3$): δ 6.16 (br s, OH), 6.28 (d, J = 10.6 Hz,1H), 6.52 (d, J = 10.6 Hz, 1H), 7.14–7.78 (m, 8H). Anal. Calcd for $C_{15}H_{11}F_3OS$: C, 60.80; H, 3.74. Found: C, 60.58; H, 3.72.

5.2.4. General procedure for the synthesis of (*Z*)-styryl-2-acetoxyphenyl sulfides (4). A reaction mixture containing (*Z*)-styryl hydroxyphenyl sulfide (3 mmol), dry pyridine (3.2 mmol), and acetic anhydride (3.2 mmol) in 5 mL dry methylene chloride was stirred at room temperature for 6 h. Water was added to the reaction mixture, and the aqueous solution was extracted with methylene chloride (2×10 mL). The combined organic phase was washed with water, dried (Na_2SO_4), and filtered, and the solvent was concentrated in vacuo. Chromatography on silica gel (EtOAc/hexanes, 4:96) gave the desired product **4**.

5.2.4.1. (*Z*)-Styryl-2-acetoxyphenyl sulfide (4a). This product was obtained as a light yellow crystalline solid (59% yield) by reaction of acetylation with **3a**. Mp 54–56 °C; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, $COCH_3$), 6.34 (d, J = 10.5 Hz,1H), 6.62 (d, J = 10.5 Hz, 1H), 7.12–7.57 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 21.24 (CH_3), 122.37 (CH=CH), 128.58 (CH=CH), 123.27–150.31 (Ar–C), 169.62 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.30; H, 5.23.

5.2.4.2. (*Z*)-4-Fluorostyryl-2-acetoxyphenyl sulfide (4b). This product was obtained as a yellow crystalline solid (65% yield) by reaction of acetylation with **3b**. Mp 42–44 °C; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, $COCH_3$), 6.28 (d, J = 10.5 Hz, 1H), 6.58 (d, J = 10.5 Hz, 1H), 7.10–7.59 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 21.20 ($COCH_3$),123.40 (CH=CH), 128.36 (CH=CH), 115.64–150.27 (Ar–C), 169.55 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{13}FO_2S$: C, 66.65; H, 4.54. Found: C, 66.87; H, 4.53.

5.2.4.3. (*Z*)-2-Fluorostyryl-2-acetoxyphenyl sulfide (4c). This product was obtained as a colorless liquid (62% yield) by reaction of acetylation with **3c**. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, $COCH_3$), 6.46 (d, J = 12.0 Hz, 1H), 6.78 (d, J = 10.0 Hz, 1H), 7.06–7.90 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 21.18 ($COCH_3$), 123.59 (CH=CH), 128.95 (CH=CH), 115.63–150.37 (Ar–C), 169.57 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{13}FO_2S$: C, 66.65; H, 4.54. Found: C, 66.68; H, 4.55.

5.2.4.4. (*Z*)-4-Chlorostyryl-2-acetoxyphenyl sulfide (4d). This product was obtained as a light yellow crystalline solid (68% yield) by reaction of acetylation with **3d**. Mp 36–38 °C; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, $COCH_3$), 6.36 (d, J = 10.5 Hz, 1H), 6.55 (d, J = 10.5 Hz, 1H), 7.12–7.56 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 21.22 (CH_3), 123.57 (CH=CH), 128.96 (CH=CH), 126.17–150.32 (Ar–C), 169.55 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{13}ClO_2S$: C, 63.05; H, 4.30. Found: C, 62.91; H, 4.32.

5.2.4.5. (*Z*)-4-Bromostyryl-2-acetoxyphenyl sulfide (4e). This product was obtained as a light yellow crystalline solid (65% yield) by reaction of acetylation with **3e**. Mp 40–42 °C; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, $COCH_3$), 6.37 (d, J = 10.5 Hz, 1H), 6.52 (d, J = 10.0 Hz, 1H), 7.09–7.60 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 22.74 ($COCH_3$), 125.08 (CH=CH), 128.89 (CH=CH), 123.00–151.83 (Ar–C), 171.06 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{13}BrO_2S$: C, 55.03; H, 3.75. Found: C, 54.83; H, 3.76.

5.2.4.6. (*Z*)-4-Methylstyryl-2-acetoxyphenyl sulfide (4f). This product was obtained as a colorless liquid (67% yield) by reaction of acetylation with **3f**. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, $COCH_3$), 2.33 (s, 3H), 6.18 (d, J = 10.5 Hz, 1H), 6.56 (d, J = 10.5 Hz, 1H), 7.07–7.59 (m, 8H). Anal. Calcd for $C_{17}H_{15}O_2S$: C, 72.06; H, 5.34. Found: C, 71.79; H, 5.37.

5.2.4.7. (*Z*)-4-Ethylstyryl-2-acetoxyphenyl sulfide (4g). This product was obtained as a colorless liquid (59% yield) by reaction of acetylation with **3g**. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H), 2.31 (s, 3H, $COCH_3$), 2.66 (q, 2H), 6.15 (d, J = 10.5 Hz, 1H), 6.53 (d, J = 10.6 Hz, 1H), 7.02–7.67 (m, 8H). Anal. Calcd for $C_{18}H_{17}O_2S$: C, 72.70; H, 5.76. Found: C, 73.01; H, 5.77.

5.2.4.8. (*Z*)-4-Pentylstyryl-2-acetoxyphenyl sulfide (4h). This product was obtained as a colorless liquid (54% yield) by reaction of acetylation with **3h**. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H), 1.34 (m, 4H), 1.76 (m, 2H), 2.29 (s, 3H,$COCH_3$), 2.69 (t, 2H), 6.12 (d, J = 10.5 Hz, 1H), 6.59 (d, J = 10.6 Hz, 1H), 7.11–7.61 (m, 8H). Anal. Calcd for $C_{21}H_{24}O_2S$: C, 74.08; H, 7.10. Found: C, 74.30; H, 7.13.

5.2.4.9. (*Z*)-3-Acetoxystyryl-2-acetoxyphenyl sulfide (4i). A reaction mixture containing 3-hydroxystyryl-2-hydroxyphenyl sulfide (3 mmol), dry pyridine (6.4 mmol), and acetic anhydride (6.4 mmol) in 5 mL dry methylene chloride was stirred at room temperature for 6 h. Water was added to the reaction mixture, and the aqueous solution was extracted with methylene chloride (2×10 mL). The combined organic phase was washed with water, dried (Na_2SO_4), and filtered, and the solvent was concentrated in vacuo. Chromatography on silica gel (EtOAc/hexanes, 4:96) gave as a colorless liquid (63% yield). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, $COCH_3$), 2.41 (s, 3H, $COCH_3$), 7.08–7.59 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.14 (CH_3), 30.55 (CH_3), 123.69 (CH=CH), 128.46 (CH=CH), 121.77–151.68 (Ar–C), 169.32 ($COCH_3$), 173.52 ($COCH_3$); Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10. Found: C, 64.69; H, 5.07.

5.2.4.10. (*Z*)-4-Methoxystyryl-2-acetoxyphenyl sulfide (4j). This product was obtained as a colorless liquid (64% yield) by reaction of acetylation with **3j**. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 6.21 (d, J = 10.5 Hz, 1H), 6.58 (d, J = 10.5 Hz, 1H), 6.84–7.55 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 21.22 (CH_3), 55.45 (OCH_3), 123.45 (CH=CH), 128.67 (CH=CH), 122.42–155.23 (Ar–C), 169.60 ($OCOCH_3$). Anal. Calcd for $C_{17}H_{15}O_3S$: C, 68.20; H, 5.05. Found: C, 67.93; H, 5.06.

5.2.4.11. (*Z*)-2,4-Difluorostyryl-2-acetoxyphenyl sulfide (4k). This product was obtained as a colorless liquid (65% yield) by reaction of acetylation with **3l**. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, $COCH_3$), 6.45 (d, J = 10.5 Hz, 1H), 6.70 (d, J = 10.5 Hz, 1H), 6.80–7.79 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 21.18 ($COCH_3$), 123.22 (CH=CH), 128.67 (CH=CH), 120.76–150.30 (Ar–C), 169.53 ($COCH_3$). Anal. Calcd for $C_{16}H_{12}F_2O_2S$: C, 62.73; H, 3.95. Found: C, 62.74; H, 3.95.

5.2.4.12. (*Z*)-4-Trifluoromethylstyryl-2-acetoxyphenyl sulfide (4l). This product was obtained as a colorless semisolid (55% yield) by reaction of acetylation with **3m**. ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, $COCH_3$), 6.48 (d, J = 10.5 Hz,1H), 6.60 (d, J = 10.5 Hz, 1H), 7.14–7.78 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 21.14 ($COCH_3$), 123.65 (CH=CH), 128.88 (CH=CH), 120.55–150.44 (Ar–C), 169.58 ($OCOCH_3$). Anal. Calcd for $C_{17}H_{12}F_3O_2S$: C, 60.53; H, 3.58. Found: C, 60.69; H, 3.59.

5.2.5. General procedure for the synthesis of (*Z*)-styryl-2-acetoxyphenyl sulfone (5). To a solution containing (*Z*)-styryl-2-acetoxyphenyl sulfides (15 mmol) in 20 mL of glacial acetic acid was added 30% hydrogen peroxide (8 mL) dropwise at room temperature. After the addition was complete, the reaction mixture was allowed to stirr at room temperature for 16 h. The mixture was then poured into ice-cold water and stirred for 10 min. The separated solid filtered, and dried to give required compound **5**.

5.2.5.1. (*Z*)-Styryl-2-acetoxyphenyl sulfone (5a). This product was obtained as a white solid (88% yield) by oxidation of **4a**. Mp 98–100 °C; ^{1}H NMR ($CDCl_3$): δ 2.09 (s, 3H, $COCH_3$), 6.40 (d, J = 10.6 Hz, 1H), 6.94 (d, J = 10.6 Hz, 1H), 6.96–7.70 (m, 9H). Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.59; H, 4.64.

5.2.5.2. (*Z*)-4-Chlorostyryl-2-acetoxyphenyl sulfone (5b). This product was obtained as a white solid (81% yield) by oxidation of **4d**. Mp 84–86 °C; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, $COCH_3$), 6.42 (d, J = 10.5 Hz, 1H), 6.58 (d, J = 10.5 Hz, 1H), 7.09–7.92 (m, 8H). Anal. Calcd for $C_{16}H_{13}ClO_4S$: C, 57.06; H, 3.89. Found: C, 57.19; H, 3.87.

5.2.5.3. (*Z*)-4-Bromostyryl-2-acetoxyphenyl sulfone (5c). This product was obtained as a white solid (86% yield) by oxidation of **4e**. Mp 88–90 °C; ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H, $COCH_3$), 6.46 (d, J = 10.5 Hz, 1H), 6.62 (d, J = 10.5 Hz, 1H), 7.01–7.98 (m, 8H). Anal. Calcd for $C_{16}H_{13}BrO_4S$: C, 50.41; H, 3.44. Found: C, 50.53; H, 3.45.

5.2.6. General procedure for the synthesis of (*E*)-styryl-2-hydroxyphenyl sulfides (6). To a solution containing phenylacetylene (15 mmol) in 20 mL of glacial acetic acid was added manganese(III) acetate dihydrate (7.5 mmol) at room temperature. The mixture was stirred and heated in an oil bath, and then 2-hydroxy thiophenol (22.5 mmol) was added just before refluxing. The dark brown color of manganese(III) acetate dihydrate disappeared within 2 min. The solvent was removed in vacuo and the residue was triturated with water followed by extraction with chloroform. The extract was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The products were separated by silica gel column chromatography using chloroform as the eluting solvent, resulted the desired product (**6**).

5.2.6.1. (*E*)-Styryl-2-hydroxyphenyl sulfide (6a). This product was obtained as a solid (88% yield) by reaction of 2-hydroxythio phenol with phenylacetylene. Mp 92–94 °C; ^{1}H NMR ($CDCl_3$): δ 6.71 (d, J = 15.3 Hz, 1H), 7.42 (d, J = 15.3 Hz, 1H), 6.61–7.82 (m, 9H), 8.16 (br s, OH). Anal. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30. Found: C, 73.79; H, 5.31.

5.2.6.2. (*E*)-4-Chlorostyryl-2-hydroxyphenyl sulfide (6b). This product was obtained as a white solid (82% yield) by reaction of 2-hydroxythio phenol with 4-chlorophenyl acetylene. Mp 96–98 °C; ^{1}H NMR ($CDCl_3$): δ 6.86 (d, J = 15.3 Hz, 1H), 7.52 (d, J = 15.3 Hz, 1H), 6.93–7.91 (m, 8H), 8.21 (br s, OH). Anal. Calcd for $C_{14}H_{11}ClOS$: C, 63.99; H, 4.22. Found: C, 64.07; H, 4.23.

5.2.6.3. (*E*)-4-Bromostyryl-2-hydroxyphenyl sulfide (6c). This product was obtained as a white solid (81% yield) by reaction of acetylation with **6c**. Mp 102–104 °C; ^{1}H NMR ($CDCl_3$): δ 6.94 (d, J = 15.4 Hz, 1H), 7.60 (d, J = 15.0 Hz, 1H), 7.13–8.00 (m, 8H), 8.18 (br s, OH). Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.73; H, 3.61. Found: C, 54.69; H, 3.61.

5.2.7. General procedure for the synthesis of (*E*)-styryl-2-acetoxyphenyl sulfides (7). A reaction mixture containing styryl hydroxyphenyl sulfide (3 mmol), dry pyridine (3.2 mmol), and acetic anhydride (3.2 mmol) in 5 mL dry methylene chloride was stirred at room temperature for 6 h. Water was added to the reaction mixture, and the aqueous solution was extracted with methylene chloride (2×10 mL). The combined organic phase was washed with water, dried (Na_2SO_4), and filtered, and the solvent was concentrated in vacuo. Chromatography on silica gel (EtOAc/hexanes, 4:96) gave the desired acetate **7**.

5.2.7.1. (*E*)-Styryl-2-acetoxyphenyl sulfide (7a). This product was obtained as a solid (78% yield) by reaction of acetylation with **6a**. Mp 77–79 °C; ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, $COCH_3$), 6.79 (d, J = 15.3 Hz, 1H), 7.49 (d, J = 15.3 Hz, 1H), 6.69–7.87 (m, 9H). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 70.92; H, 5.20.

5.2.7.2. (*E*)-4-Chlorostyryl-2-acetoxyphenyl sulfide (7b). This product was obtained as a white solid (82% yield) by reaction of acetylation with **6b**. Mp 86–88 °C; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, $COCH_3$), 6.93 (d, J = 15.3 Hz, 1H), 7.62 (d, J = 15.3 Hz, 1H), 7.03–8.01 (m, 8H). Anal. Calcd for $C_{16}H_{13}ClO_2S$: C, 63.05; H, 4.30. Found: C, 63.09; H, 4.28.

5.2.7.3. (*E*)-4-Bromostyryl-2-acetoxyphenyl sulfide (7c). This product was obtained as a white solid (81% yield) by reaction of acetylation with **6c**. Mp 92–94 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, $COCH_3$), 6.94 (d, J = 15.4 Hz, 1H), 7.60 (d, J = 15.0 Hz, 1H), 7.13–8.00 (m, 8H). Anal. Calcd for $C_{16}H_{13}BrO_2S$: C, 55.03; H, 3.75. Found: C, 55.26; H, 3.74.

5.2.8. General procedure for the synthesis of (*E*)-styryl-2-acetoxyphenyl sulfones (8). To a solution containing (*E*)-styryl-2-acetoxyphenyl sulfides (15 mmol) in 20 mL of glacial acetic acid was added 30% hydrogen peroxide (8 mL) dropwise at room temperature. After the addition was complete, the reaction mixture was allowed to stir at room temperature for 16 h. The mixture was then poured into ice-cold water and stirred for 10 min. The separated solid filtered, and dried to give required compound **8**.

5.2.8.1. (*E*)-Styryl-2-acetoxyphenyl sulfone (8a). This product was obtained as a solid (81% yield) by oxidation of **7a**. Mp 114–116 °C; ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, $COCH_3$), 6.83 (d, J = 15.4 Hz, 1H), 7.59 (d, J = 15.4 Hz, 1H), 6.79–7.97 (m, 9H). Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.82; H, 4.66.

5.2.8.2. (*E*)-4-Chlorostyryl-2-acetoxyphenyl sulfone (8b). This product was obtained as a white solid (86% yield) by oxidation of **7b**. Mp 120–122 °C; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, $COCH_3$), 6.93 (d, J = 15.4 Hz, 1H), 7.62 (d, J = 15.4 Hz, 1H), 7.03–8.06 (m, 8H). Anal. Calcd for $C_{16}H_{13}ClO_4S$: C, 57.06; H, 3.89. Found: C, 56.96; H, 3.90.

5.2.8.3. (*E*)-4-Bromostyryl-2-acetoxyphenyl sulfone (8c). This product was obtained as a white solid (85% yield) by oxidation of **7c**. Mp 138–140 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, $COCH_3$), 6.97 (d, J = 15.5 Hz, 1H), 7.63 (d, J = 15.0 Hz, 1H), 7.23–8.07 (m, 8H). Anal. Calcd for $C_{16}H_{13}BrO_4S$: C, 50.41; H, 3.44. Found: C, 50.47; H, 3.43.

5.2.9. General procedure for the synthesis of 2-hydroxy phenylthio acetic acid (9). To a stirred solution of sodium hydroxide (12.8 g, 320 mmol) in absolute methanol (200 mL) was added dropwise 2-hydroxythio phenol

(20 g, 160 mmol) over a period of 0.75 h. On completion of the addition and when no longer the reaction was exothermic, chloroacetic acid (18.14 g, 192 mmol) was added portion wise, and the reaction mixture was refluxed for 5 h. This mixture was then poured into ice-cold hydrochloric acid solution (20 mL) and was stirred for 10 min. The solution was extracted with ethyl acetate (2×100 mL). The combined organic layer was collected, washed with water (2×50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuo, to afford as a oil in 98.4% yield. ^{1}H NMR ($CDCl_3$): δ 3.46 (s, 2H, CH_2), 6.79–7.46 (m, 4H), 8.41 (br s, OH). Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.29; H, 4.36. Product **9** was used immediately without further purification for the preparation of compound **10**.

5.2.10. General procedure for the synthesis of 2-hydroxyphenyl sulfonyl acetic acid (10). To a solution containing 2-hydroxyphenylthio acetic acid (15 g, 82 mmol) in 75 mL of glacial acetic acid was added 30% hydrogen peroxide (30 mL) dropwise at room temperature. After the addition was complete, the reaction was stirred for 16 h at room temperature. The solution was concentrated in vacuo, and the residue was filtered, washed with petroleum ether and dried to give a white powder. Yield 65%; Mp 125–126 °C; ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 2H, CH_2), 6.89–7.56 (m, 4H), 8.52 (br s, OH). Anal. Calcd for $C_8H_8O_5S$: C, 44.44; H, 3.73. Found: C, 44.36; H, 3.74. Product **10** was used without further purification for the preparation of compound **11**.

5.2.11. General procedure for the synthesis of (*E*)-styryl-2-hydroxyphenyl sulfone (11). A mixture of 2-hydroxyphenyl sulfonyl acetic acid (**10**) (4.6 mmol), aromatic aldehydes (5.1 mmol), benzoic acid (0.7 mmol), and piperidine (0.6 mmol) in toluene (20 mL) was refluxed for 4 h with continuous removal of water using a Dean–Stark water separator. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution (20 mL), water (30 mL), and the organic phase was separated, and dried (Na_2SO_4). The solvent was removed in vacuo. Chromatography on silica gel (chloroform) gave the desired product **11**.

5.2.11.1. (*E*)-Styryl-2-hydroxyphenyl sulfone (11a). This product was obtained as a white solid (56% yield) by reaction of **10** with benzaldehyde. Mp126–128 °C; ^{1}H NMR ($CDCl_3$): δ 6.78 (d, J = 15.2 Hz, 1H), 6.91–7.77 (m, 8H), 7.52 (d, J = 15.4 Hz, 1H), 8.92 (br s, OH).

5.2.11.2. (*E*)-4-Chlorostyryl-2-hydroxyphenyl sulfone (11b). This product was obtained as a white solid (63% yield) by reaction of **10** with 4-chlorobenzaldehyde. Mp 132–134 °C; ^{1}H NMR ($CDCl_3$): δ 6.88 (d, J = 15.0 Hz,1H), 6.95–7.87 (m, 8H), 7.62 (d, J = 15.5 Hz, 1H), 8.97 (br s, OH).

5.2.11.3. (*E*)-4-Bromostyryl-2-hydroxyphenyl sulfone (11c). This product was obtained as a white solid (59% yield) by reaction of **10** with 4-bromobenzaldehyde. Mp 145–147 °C; ^{1}H NMR ($CDCl_3$): δ 6.82 (d, J = 15.4 Hz, 1H), 6.95–7.61 (m, 8H), 7.52 (d, J = 15.4 Hz, 1H), 8.86 (br s, OH).

5.2.11.4. (*E*)-2,4,6-Trimethoxystyryl-2-hydroxyphenyl sulfone (11d). This product was obtained as a white solid (63% yield) by reaction of **10** with 2,4-6-trimethoxybenzaldehyde. Mp 132–134 °C; ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 9H, OCH_3), 6.02 (s, 2H, Ar–H), 6.82 (d, J = 15.4 Hz, 1H), 6.95–7.61 (m, 6H), 7.52 (d, J = 15.4 Hz,1H), 8.78 (br s, OH).

5.2.12. General procedure for the synthesis of (*E*)-styryl-2-acetoxyphenyl sulfone (8). A reaction mixture containing (*E*)-styryl hydroxyphenyl sulfone (3 mmol), dry pyridine (3.2 mmol), and acetic anhydride (3.2 mmol) in 5 mL dry methylene chloride was stirred at room temperature for 6 h. Water was added to the reaction mixture, and the aqueous solution was extracted with methylene chloride (2×10 mL). The combined organic phase was washed with water, dried (Na_2SO_4), and filtered, and the solvent was concentrated in vacuo. Chromatography on silica gel (EtOAc/hexanes, 4:96) gave the desired acetate **8**.

5.2.12.1. (*E*)-Styryl-2-acetoxyphenyl sulfone (8a). This product was obtained as a solid (81% yield) by reaction of acetylation with **11a**. Mp 114–116 °C; ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, $COCH_3$), 6.83 (d, J = 15.4 Hz, 1H), 6.79–7.97 (m, 9H), 7.59 (d, J = 15.4 Hz, 1H).

5.2.12.2. (*E*)-4-Chlorostyryl-2-acetoxyphenyl sulfone (8b). This product was obtained as a white solid (86% yield) by reaction of acetylation with **11b**. Mp 120–122 °C; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, $COCH_3$), 6.93 (d, J = 15.4 Hz, 1H), 7.03–8.06 (m, 8H), 7.62 (d, J = 15.4 Hz, 1H).

5.2.12.3. (*E*)-4-Bromostyryl-2-acetoxyphenyl sulfone (8c). This product was obtained as a white solid (85% yield) by reaction of acetylation with **11c**. Mp 138–140 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, $COCH_3$), 6.97 (d, J = 15.5 Hz, 1H), 7.23–8.07 (m, 8H), 7.63 (d, J = 15.0 Hz, 1H).

5.2.12.4. (*E*)-2,4,6-Trimethoxystyryl-2-acetoxyphenyl sulfone (8d). This product was obtained as a white solid (83% yield) by reaction of acetylation with **11d**. Mp 122–124 °C; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, $COCH_3$), 3.89 (s, 9H, OCH_3), 6.02 (s, 2H, Ar–H), 6.82 (d, J = 15.4 Hz, 1H), 6.95–7.61 (m, 6H), 7.52 (d, J = 15.4 Hz, 1H).

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References and notes

1. Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 899.
2. Fu, J. Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. *J. Biol. Chem.* **1990**, *265*, 16737.
3. (a) Smith, W. L.; DeWitt, D. L. *Adv. Immunol.* **1996**, *62*, 167; (b) Herschman, H. R. *Biochem. Biophys. Acta* **1996**, *125*, 1299.
4. Meade, E. A.; Smith, W. L.; DeWitt, D. L. *J. Biol. Chem.* **1993**, *268*, 6610.
5. Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russell, R. I. G. *N. Engl. J. Med.* **1992**, *327*, 749.
6. Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. I. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1977**, *40*, 1347.
7. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
8. Nicoll-Griffith, D. A.; Yergey, J. A.; Trimble, L. A.; Silva, J. M.; Li, C.; Chauret, N.; Gauthier, J. Y.; Grimm, E.; Leger, S.; Roy, P.; Therien, M.; Wang, Z.; Prasit, P.; Zamboni, R.; Young, R. N.; Brideau, C.; Chan, C. C.; Mancini, J.; Riendeau, D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2683.
9. Gierse, J. K.; McDonald, J. J.; Hauser, S. D.; Rangwala, S. H.; Koboldt, C. M.; Seibert, K. *J. Biol. Chem.* **1996**, *271*, 15810.
10. Fabiola, G. F.; Pattabhi, V.; Nagarajan, K. *Bioorg. Med. Chem.* **1998**, *6*, 2337.
11. Rahim, M. A.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2753.
12. Roth, G. J.; Stanford, N.; Majerus, P. W. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 3073.
13. Vane, J. R. *Nat. New Biol.* **1971**, *231*, 232.
14. Smith, J. B.; Willis, A. L. *Nature* **1971**, *231*, 235.
15. Cheng, Y.; Austin, S. C.; Rocca, B.; Koller, B. H.; Coffman, T. M.; Grosser, T.; Lawson, J. A.; FitzGerald, G. A. *Science* **2002**, *296*, 539.
16. Vane, J. R. *Science* **2002**, *296*, 474.
17. Kalgutkar, A. S.; Crews, B. C.; Rowlinson, S. W.; Garner, C.; Seibert, K.; Marnett, L. J. *Science* **1998**, *280*, 1268.
18. Kalgutkar, A. S.; Kozak, K. R.; Crews, B. C.; Hochgesang, G. P.; Marnett, L. J. *J. Med. Chem.* **1998**, *41*, 4800.
19. Janine, C. *Ann. Chim.* **1948**, *12*, 393.
20. Reddy, M. V. R.; Reddy, S. *Synthesis* **1983**, 322.
21. Reddy, M. V. R.; Reddy, S. *Acta. Chim. Hung.* **1984**, *115*, 269.
22. Nguyen, V.; Nishino, H.; Kajikawa, S.; Kurosawa, K. *Tetrahedron* **1998**, *54*, 11445.
23. Reddy, M. V. R.; Vijayalakshmi, S.; Reddy, D. B.; Reddy, P. V. R. *Phosphorus, Sulfur, Silicon* **1991**, *60*, 209.
24. Reddy, D. B.; Reddy, N. S.; Reddy, S.; Reddy, M. V. R.; Balasubramanyam, S. *Org. Prep. Proc. Int.* **1988**, *20*, 205.
25. Gierse, J. K.; Koboldt, C. M.; Walker, M. C.; Seibert, K.; Isakson, P. C. *Biochem. J.* **1999**, *339*, 607.
26. (a) Wells, I.; Marnettt, L. J. *Biochemistry* **1992**, *31*, 9520; (b) Picot, D.; Loll, P. J.; Garavito, R. M. *Nature* **1994**, *367*, 243; (c) Loll, P. J.; Picot, D.; Garavito, R. M. *Nat. Struct. Biol.* **1995**, *2*, 637.
27. Vane, J. R.; Botting, R. M. *Thromb. Res.* **2003**, *110*, 255.
28. Triggle, D. J. *Drug Discovery Today* **1997**, *2*, 138.