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Synthesis of alkylsulfonyl and substituted benzenesulfonyl curcumin mimics as dual antagonist of L-type Ca^{2+} channel and endothelin A/B_2 receptor

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ABSTRACT

We synthesized a library of curcumin mimics with diverse alkylsulfonyl and substituted benzenesulfonyl modifications through a simple addition reaction of important intermediate, 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**), with various sulfonyl chloride reactants and then tested their vasodilatation effect on depolarization (50 mM K^+)- and endothelin-1 (ET-1)-induced basilar artery contraction. Generally, curcumin mimics with aromatic sulfonyl groups showed stronger vasodilation effect than alkyl sulfonylated curcumin mimics. Among the tested compounds, six curcumin mimics (**11g**, **11h**, **11i**, **11j**, **11l**, and **11s**) in a depolarization-induced vasoconstriction and seven compounds (**11g**, **11h**, **11i**, **11j**, **11l**, **11p**, and **11s**) in an ET-1-induced vasoconstriction showed strong vasodilation effect. Based on their biological properties, synthetic curcumin mimics can act as dual antagonist scaffold of L-type Ca^{2+} channel and endothelin A/B_2 receptor in vascular smooth muscle cells. In particular, compounds **11g** and **11s** are promising novel drug candidates to treat hypertension related to the overexpression of L-type Ca^{2+} channels and ET peptides/receptors-mediated cardiovascular diseases.

1. Introduction

Curcumin (**1**) isolated from the root of *Curcuma longa* L. has versatile and useful biological properties. It shows anti-inflammatory,[1] antioxidant,[2] antiviral,[3] chemopreventive,[4] anti-infective,[5] and wound-healing properties.[6] Based on its diverse and interesting biological properties, we previously reported the synthesis of a curcumin mimic library and described the novel biological properties of each member after first report by Bowen and co-workers.[7] For example, the alkyl or aryl amide-linked curcumin mimic library (**2**) was shown to inhibit angiogenesis[8] and multidrug resistance (MDR).[9,10] Substituted triazolyl curcumin mimics (**3** and **4**) synthesized through click reaction exhibited strong inhibitory activity against osteoclastogenesis induced by the receptor activator of NF-κB ligand (RANKL).[11] Recently, we have expanded the original structure of curcumin mimics to include a 4-diethylamino chalcone structure (**5**) by replacing the methoxy and hydroxyl groups of curcumin to increase bulkiness and the electronic effect. As a result, newly synthesized curcumin derivatives (**5**) show a sensitization effect to tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). These observations indicate that curcumin mimics having 4-diethylamino and substituted triazole groups are promising TRAIL-sensitizers with the potential for application in combination chemotherapy of brain tumors.[12,13] All members of the synthetic curcumin library reported in our laboratory show low cellular toxicity, whereas curcumin mimics with substituted benzimidazole groups (**6**) exhibited strong cytotoxicity against various cancer cells[14] and multidrug-resistant cancer cells.[15] Considering our previous reports on the structure–activity relationship of diverse curcumin mimic libraries, we conclude that their diverse biological properties mainly depend on the additional right-side functionalities. Although the biological properties of curcumin (**1**) are very impressive in the field of healthcare food

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supplements, its potency is actually inadequate for use as a clinical drug. Nevertheless, it is very promising to begin drug discovery from the structural modification of curcumin (**1**).

Several years ago, we synthesized an alkyl or aryl sulfonyl amide curcumin mimic library (**7**) and reported that library members exhibit a vasodilatation effect on the depolarization (50 mM K^+)-induced basilar arterial contraction ex vivo.[16] Therefore, it seems reasonable to conclude that the sulfonyl amide linked curcumin library (**7**) has a potential to control vascular tone. Considering this, we extended our research of the basic vasodilation property of curcumin mimics (**7**) in order to evaluate the clinical potential for treating vascular related diseases (Fig. 1).

Vascular tone is mainly dependent on intracellular Ca^{2+} ($[Ca^{2+}]_i$) concentration which is increased by L-type Ca^{2+} channels on the vascular smooth muscle cell (VSMC) membrane and inositol 1,4,5-trisphosphate (IP_3)-mediated Ca^{2+} release from sarcoplasmic reticulum (SR) through G protein-coupled receptor-induced phospholipase C (PLC) activation.[17,18] Physiologically, L-type Ca^{2+} channels are slowly inactivated during sustained depolarization, so that the Ca^{2+} influx is sufficient to mediate the pressure-induced constriction of resistance vessels and contribute to the dynamic autoregulation of the systemic and cerebral arteries.[19] Therefore, sustained Ca^{2+} influx via L-type Ca^{2+} channels maintains a tonic level of vascular contraction and provides an excitatory template for endogenously vasoactive substances.[20] However, in hypertension, the development of anomalous arterial tone is associated with increased expression of L-type Ca^{2+} channel α1C subunits, which play a critical role in increasing blood pressure and flow.[21] Therefore, L-type Ca^{2+} channel antagonists can be used as anti-hypertensive agents, but can be expected to act only as adjuvants because the overexpression of L-type Ca^{2+} channels is not limited to hypertension.[22]

More importantly, endothelial dysfunction is regarded to occur early during the development of cardiovascular diseases including severe hypertension, vascular complications associated with diabetes mellitus, atherosclerosis, and stroke.[23] Reduction in bioavailability of nitric oxide (NO) is considered the key factor of endothelial dysfunction that causes increased vascular tone, platelet aggregation, and inflammation.[24] Endothelial dysfunction also involves biological mediators, including increased endotheline-1 (ET-1) expression and altered expression of ET-1 receptors.[25] ET-1 is a vasoactive peptide of 21-amino acids originally isolated from endothelial cell-conditioned medium[26] and is well known as the most potent vasoconstrictor.[27,28] In physiological states, ET-1 is produced in small amounts predominantly in endothelial cells (ECs)[23] and acts as a vascular regulator, pro-inflammatory mediator, and mitogen mediated by endothelin receptor type A (ET_AR), type B1 ($ET_{B1}R$), and type B2 ($ET_{B2}R$) coupled with G proteins.[29,30] ET_AR and $ET_{B2}R$ primarily have vasoconstriction and cell-proliferation functions, whereas $ET_{B1}R$ mainly mediates vasodilatation, inhibition of growth, and inflammation via NO and prostaglandin I_2.[31] $ET_{B1}R$ is also involved in the clearance of ET-1 peptides from the circulation,[32] since its blockade increases the concentration of ET-1 peptide in plasma, whereas activation of this receptor on EC also exerts a negative feedback and inhibits ET-1 peptide synthesis.[33] Thus, the vasoactive effect of ET-1 depends mainly on the overall ET receptor profile, defined as the relative density of ET_AR and $ET_{B2}R$ on VSMCs compared to $ET_{B1}R$ on ECs.[34]

The pathological significance of ET-1 is well characterized in atherosclerosis, vascular complications associated with diabetes mellitus, chronic renal disease, and pulmonary hypertension.[23,35] In accordance with its multiple activities, ET-1 production has been shown to be modulated by several factors including hypoxia, glucose, insulin, cytokines, angiotensin II, growth factor, and vasoactive substances.[36–38] In particular, increasing ET-1 production results in atherosclerosis caused by inflammatory cytokines released from macrophages,[39,40] oxidative stress due to reactive oxygen species production from VSMCs,[41,42] lipid biosynthesis,[43] and hypercholesterolaemia.[44] Thus, the inhibitors of ET-1 synthesis or ET_A/ET_{B2} receptor antagonists are clinically important to treat or prevent cardiovascular diseases including atherosclerosis, essential hypertension, pulmonary arterial hypertension (PAH), peripheral (PAD) and coronary artery disease (CAD), stroke, and diabetic complications of the vasculature.[45–47] In the vascular wall, ET receptor type A (ET_AR) and type B_2 ($ET_{B2}R$) are localized in vascular smooth muscle cells and mediates the major part of the vasoconstrictor effect of ET-1, whereas the ET receptor type B_1 ($ET_{B1}R$) is localized to the endothelial cells and mediates vasodilatation via release of nitric oxide (NO).[23]

Therefore, when considering the clinical usefulness of the vasodilation effect depending on the mechanism-based vascular dilation activity, it is more important to discover novel vasodilation drug candidates affecting both depolarization- and ET-1-induced vascular constriction.

As shown in our previous research, the sulfonyl amide linked curcumin library (**7**) showed a vasodilation effect on the contraction of the basilar artery induced by depolarization. Subsequently, we conducted experiments to determine whether our sulfonyl curcumin mimics library (**7**) also dilated constricted vascular tone induced by ET-1. In this paper, we describe the synthesis of a sulfonyl amide linked curcumin library (**7**) including newly synthesized compounds and show their vasodilation effect on contracted rabbit basilar artery produced via depolarization (50 mM K^+) and ET-1, which means that they can be used as dual antagonist of L-type Ca^{2+} channel and $ET_{A/B2}R$.

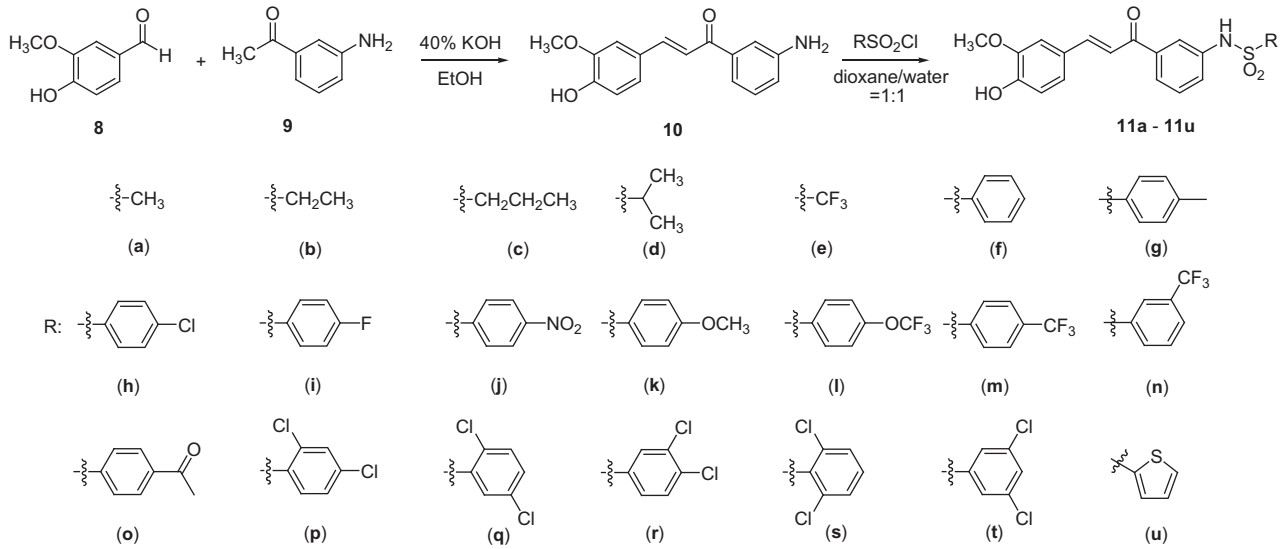
2. Results and discussion

2.1. Synthesis

In our previous report,[16] we synthesized 15 sulfonyl curcumin mimics; however, as shown in Scheme 1, we additionally produced six compounds to obtain a more detailed structure–activity relationship. Namely, the important synthetic intermediate, 1-(3-Aminophenyl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**10**), was produced from the aldol reaction of 4-hydroxy-3-methoxybenzaldehyde (**8**) with 3-acetylaniline (**9**) using basic catalyst (40% KOH) in ethanol at room temperature for 10 h. This amine intermediate (**10**) was reacted with a variety of sulfonyl chlorides in a solution of dioxane and water (1:1) while stirring for 5–7 h at 0 °C to yield alkyl- or aryl-substituted sulfonylamide curcumin derivatives (**11a–11u**). Newly synthesized compounds created for a more detailed structure–activity relationship included ethyl (**11b**), trifluoromethyl (**11e**), *p*-toluyl (**11g**), *p*-chlorophenyl (**11h**), and 2′,6′-dichlorophenyl (**11s**) sulfonylamide curcumin mimic derivatives. The double bond in the feruloyl structure was confirmed to the *trans* configuration because of a large coupling constant (approximately J = 15 Hz) between its two protons.[11] The structure of synthetic intermediate (**10**) and all sulfonylamide linked curcumin compounds (**11a–11u**) were identified by ^1H and ^{13}C NMR spectroscopy, and GC/MS analysis and were evaluated for vasodilation effect on rabbit basilar artery contracted with depolarization (50 mM K^+) and ET-1.

2.2. Vasodilatation effect of curcumin and synthetic curcumin mimics on depolarization-induced constriction of the rabbit basilar artery

We first evaluated the vasodilatation potency of curcumin and synthetic sulfonylamide-linked mimics on depolarization-induced constriction of rabbit basilar artery, a common cerebral artery,



Scheme 1. Synthesis of novel curcumin mimics with the sulfonyl units including the various alkyl and aryl groups. Yields for **10**, 45%; **11a**, 20%; **11b**, 20%; **11c**, 19%; **11d**, 15%; **11e**, 16%; **11f**, 66%; **11g**, 76%; **11h**, 74%; **11i**, 76%; **11j**, 75%; **11k**, 55%; **11l**, 67%; **11m**, 67%; **11n**, 68%; **11o**, 19%; **11p**, 66%; **11q**, 38%; **11r**, 80%; **11s**, 60%; **11t**, 50%; **11u**, 40%.

using an organ bath system. When treated with high K^+ (50 mM) as a hypothetical depolarizing condition, the basilar artery was isometrically contracted and reached a steady-state within 10 min. As summarized in Table 1, a single application of curcumin and sulfonyl curcuminoids at 10 μM induced vasodilatation of the basilar artery contracted with 50 mM K^+. Among the 22 compounds tested, including curcumin (**1**), eight compounds showed a stronger vasodilatation effect (⩾60%) in 10 μM concentration than curcumin (58.4% vasodilation activity at the same concentration). Interestingly, those compounds showing strong effect are curcumin mimics that have a functional group at the *para* position of benzene except for **11s**, which has 2′,6′-dichloro groups, and electron-withdrawing groups, except for **11g**, which has a methyl group. Conversely, five alkyl sulfonamide curcumin derivatives (**11a**–**11e**) exhibited a weak vascular dilation effect. However, the strongest three molecules (**11g**, **11h**, and **11s**) showing a greater than 90% vasodilation effect did not show any benzyl substituent tendency of the electronic property. Based on this SAR analysis, we can conclude that the change in vasodilation effect is caused by the addition of *para* benzene electron-withdrawing groups. Considering the previous SAR analysis, we confirm that a *para* electron-withdrawing group-substituted phenyl sulfonamide on the half curcumin structure plays an important role in increasing the vasodilation effect on depolarization-induced constriction of rabbit basilar artery.

The serial application of curcumin (**1**) and the strongest three molecules (**11g**, **11h**, and **11s**) at 3, 10, and 30 μM concentration yielded vasodilatation of the basilar arteries constricted by depolarization in a concentration-dependent manner. As shown in Figure 2, the curve fittings of the concentration–response relationship based on the Hill equation confirmed that the concentration required for half maximal dilatation (EC_{50}) of curcumin (**1**) and the three other compounds (**11g**, **11h**, and **11s**) were 7.48 ± 0.28, 3.67 ± 0.45, 5.58 ± 0.64, and 2.78 ± 0.33 μM ($n = 4$), respectively. These results indicated that curcumin mimics, especially compounds **11g**, **11h**, and **11s**, exerted a more potent vasodilatation effect on the basilar artery than curcumin at an equimolar concentration. When considering that vascular tone is mainly dependent on the increment of intracellular Ca^{2+} ($[Ca^{2+}]_i$) concentration by L-type Ca^{2+} channels on the vascular smooth muscle cell (VSMC) membrane, selected three compounds (**11g**, **11h**, and **11s**) can be acted as strong L-type Ca^{2+} channel blockers.

Table 1
Vasodilatation percentage of curcumin mimics in 10 μM concentration on depolarization-induced constriction of rabbit basilar artery

	Effective percentage (%) at 10 μM		Effective percentage (%) at 10 μM
11a	4.2 (±2.8)[a]	**11l**	**76.7** (±**5.5**)
11b	55.3 (±3.8)	**11m**	65.8 (±5.3)
11c	42.3 (±4.3)	**11n**	52.3 (±4.5)
11d	20.5 (±2.7)	**11o**	67.9 (±4.7)
11e	10.7 (±2.5)	**11p**	4.2 (±2.2)
11f	50.4 (±4.7)	**11q**	53.4 (±4.9)
11g	**98.7** (±**1.1**)	**11r**	30.2 (±4.8)
11h	**93.4** (±**3.8**)	**11s**	**99.4** (±**0.4**)
11i	**71.8** (±**6.4**)	**11t**	37.3 (±6.4)
11j	**70.7** (±**5.6**)	**11u**	32.4 (±3.6)
11k	26.4 (±4.4)	Curcumin	58.4 (±6.4)

[a] Data for observed effects represent means of five independent experiments; standard deviation is shown within parentheses.

2.3. Vasodilatation effect of curcumin and synthetic curcumin mimics on endothelin-1-induced vasoconstriction of rabbit basilar artery

Endothelin-1 (ET-1) is a potent vasoconstrictor, proinflammatory, and proliferative endothelial cell-derived peptide. ET-1 is pathophysiologically important in developing several cardiovascular diseases including atherosclerosis, diabetic retinopathy, nephropathy, and insulin resistance.[45] Therefore, antagonists of ET-1 actions or $ET_{A/B2}R$ might have potent therapeutic applications.[47] In this study, we investigated the vasodilatation potency of curcumin and synthetic curcumin mimics on a basilar artery contracted with ET-1 (3 nM). It is well known that ET-1 evokes vascular constriction via $[Ca^{2+}]_i$ increase through inositol-3-phosphate (IP_3)-mediated Ca^{2+} release from the sarcoplasmic reticulum (SR), extracellular Ca^{2+} entry by receptor-operated Ca^{2+} entry (ROCC), and L-type Ca^{2+} channels.[23] Consistent with this, when treated with ET-1 (3 nM), the basilar artery contracted and reached a stationary phase within 15 min.

The vasodilatation potencies of curcumin and synthetic curcumin mimics at 10 μM concentration are shown in Table 2. In this screening using ET-1 as a vascular constriction inducer, curcumin showed a weak vasodilation effect; 8.5 ± 2.4% and 48.5 ± 4.2 μM of EC_{50}, which are weaker than the vasodilation effect determined

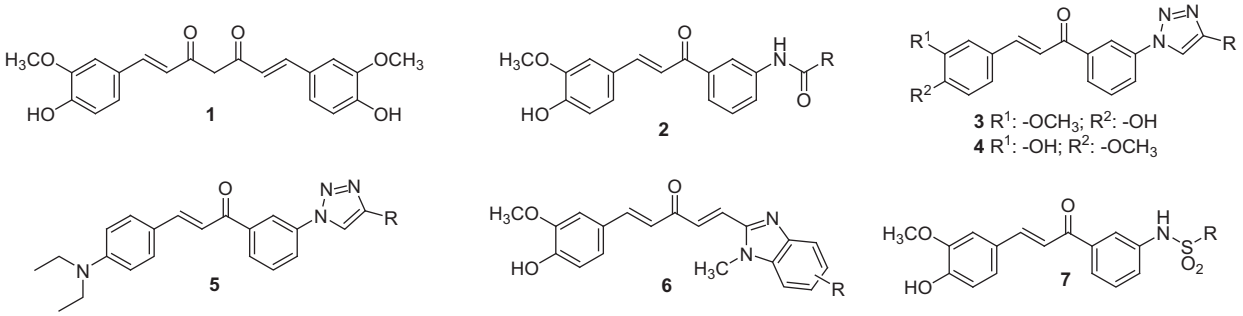


Figure 1. Structures of curcumin and synthetic curcumin mimic derivatives.

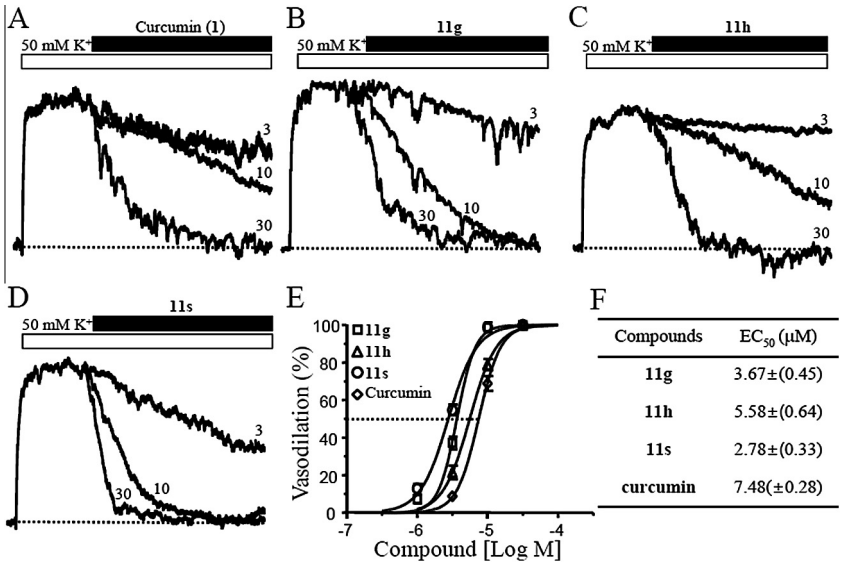


Figure 2. Concentration-dependent vasodilatation effect and their EC_{50} of curcumin and selected curcumin mimics on depolarization-induced vasoconstriction of the rabbit basilar artery. Representative normalized traces were acquired by a single application of curcumin **1** (A), **11g** (B), **11h** (C), and **11s** (D) in log scale concentration ($10^{-5.5}$, 10^{-5}, $10^{-4.5}$ M) for 40 min after pre-contraction with high K^+ (50 mM), and the effect reached a stationary phase (10 min). The vasodilatation efficacy was plotted as a function of the log scale concentration of curcumin (**1**) and the other compounds (**12** and **20**), and the curves were fitted using the Hill equation, $E = (1 + EC_{50}/[\text{compound}]^n)^{-1}$ (E). The estimated EC_{50} values of curcumin **1** (A), **11g** (B), **11h** (C), and **11s** (D) are 7.48 ± 0.28, 3.67 ± 0.45, 5.58 ± 0.64, and 2.78 ± 0.33 μM, respectively (F). Data are represented as mean ± SD ($n = 4$).

in the depolarization-induced system. Among the tested curcumin mimics, seven compounds (**11g**, **11h**, **11i**, **11j**, **11l**, **11p**, and **11s**) exhibited a strong vasodilatation effect greater than 70%. Simply comparing the vasodilatation efficacy between depolarization- and ET-1-induced basilar artery contraction, we found that six compounds (**11g**, **11h**, **11i**, **11j**, **11l**, and **11s**) showed similarly strong activity on both systems. Interestingly, **11p** having a 2,4-dichlorobenzene sulfonyl group showed weak vasodilation effect (only 4.2 ± 2.2% in 10 μM concentration) on the basilar artery contraction induced by high K^+ but strong potency (83.4 ± 6.2% in 10 μM concentration) on ET-1 induced contraction. When considering the vasodilation effect on both systems with two inducers, depolarization and ET-1, the tendencies of vasodilatation effect according to structure variation are consistent. Based on these results, we have potentially discovered a novel vasodilation agent created through structural modification.

To confirm dose-dependency and the effective concentration of half-maximal vasodilatation (EC_{50}) of the selected seven compounds (**11g**, **11h**, **11i**, **11j**, **11l**, **11p**, and **11s**) and curcumin, we monitored the basilar artery vasodilatation, and the resultant EC_{50} values are summarized in Table 2. Also, the curve fitting of concentration responses for **11g**, **11h**, **11j**, **11s**, and curcumin using the Hill equation are shown in Figure 3. The compounds induced potent vasodilatation of the basilar artery contracted with ET-1 in a concentration-dependent manner. Among them, the EC_{50} of compounds, **11s** and **11g**, were 1.8 ± 0.2 and 2.7 ± 0.2 μM, respectively, which represent the strongest vasodilatation agents for ET-1-induced basilar artery contraction. This result suggests that **11s** and **11g** can act as novel and potent $ET_{A/B2}R$ antagonist.

2.4. Structure-vasodilation effect relationship of curcumin and synthetic curcumin mimics on high K^+ induced and endothelin-1-induced vasoconstriction of rabbit basilar artery

When considering vasodilation effect on both inducer systems, depolarization and ET-1, the tendencies according to structure variation are very similar. The curcumin mimics showing strong vasodilation effect include six compounds (**11g**, **11h**, **11i**, **11j**, **11l**, and **11s**) for depolarization-induced and seven compounds (**11g**, **11h**, **11i**, **11j**, **11l**, **11p**, and **11s**) for ET-1-induced vasoconstriction. Except for **11p**, the other compounds simultaneously and strongly dilate the contracted rabbit basilar artery. Considering that structural modification only occurred in benzene groups via sufonyl linkage, the variation of vasodilation effect is quite large. However, we observe structural consistency when considering strongly active curcumin mimics; namely, most of them, except

Table 2
Vasodilatation potency of curcumin mimics on endothelin 1-induced constriction of rabbit basilar artery

	Effective percentage (%) at 10 μM	EC_{50} (μM)[a]		Effective percentage (%) at 10 μM	EC_{50} (μM)
11a	22.3 (±4.3)[b]	–[c]	**11l**	**81.4** (±**4.8**)	**6.1** (±**0.6**)
11b	19.7 (±5.1)	–	**11m**	46.1 (±6.8)	–
11c	30.8 (±2.9)	–	**11n**	36.5 (±4.4)	–
11d	31.2 (±3.3)	–	**11o**	68.7 (±3.7)	–
11e	34.6 (±4.2)	–	**11p**	**83.4** (±**6.2**)	**8.8** (±**0.3**)
11f	40.2 (±3.9)	–	**11q**	30.4 (±6.7)	–
11g	**99.6** (±**0.2**)	**2.7** (±**0.2**)	**11r**	41.8 (±5.6)	–
11h	**78.3** (±**4.5**)	**5.9** (±**0.4**)	**11s**	**99.8** (±**0.1**)	**1.8** (±**0.2**)
11i	**75.1** (±**5.3**)	**6.4** (±**0.3**)	**11t**	55.9 (±7.1)	–
11j	**98.9** (±**0.4**)	**3.9** (±**0.3**)	**11u**	39.1 (±6.6)	–
11k	56.8 (±5.5)	–	Curcumin	8.5 (±2.4)	48.5 (±4.2)

[a] Effective concentration of half maximal vasodilatation.
[b] Data for observed effects represent means of five independent experiments; standard deviation is shown within parentheses.
[c] Not determined because of low potency.

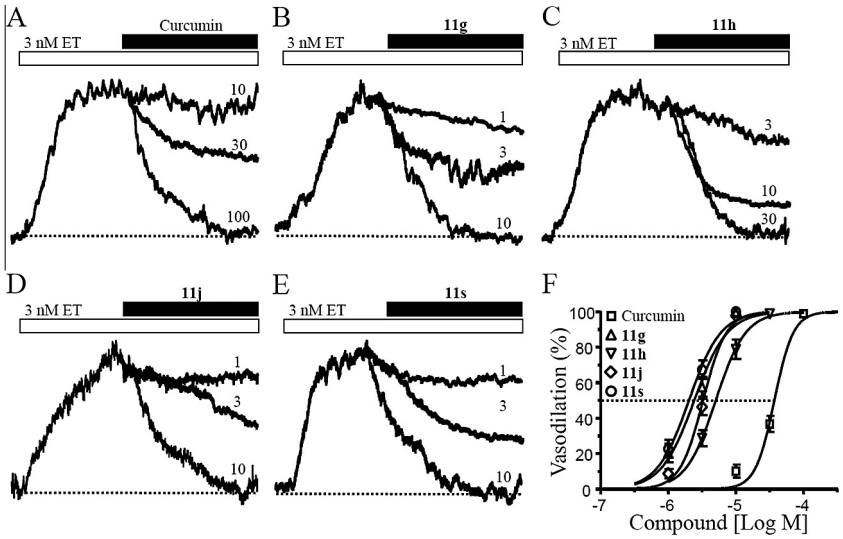


Figure 3. Vasodilatative effects of curcumin and synthetic curcumin mimics with aromatic ring on endothelin-1-induced vasoconstriction of rabbit basilar artery. Representative normalized traces were acquired by single application of curcumin (A), **11g** (B), **11h** (C), **11j** (D), and **11s** (E) in log scale concentration (10^{-6}–10^{-4} M range) for 20 min after pre-contracted with endothelin-1 (3 nM) reached a maximal contraction (15 min) on the basilar artery of white rabbits. The vasodilatation efficacy were plotted as a function of log scale concentration for compounds and the curves were fitted using Hill equation, $E = (1 + EC_{50}/[\text{compound}]^n)^{-1}$ (F). Data are represented as mean ± SD ($n = 4$).

11s, have a functional group in the *para* position of the benzene sulfonyl group, although their electronic properties do not perfectly coincide. Compound **11j** has a strong activating group, $–NO_2$, but the others (**11g**, **11h**, **11i**, **11l**, and **11p**) have moderate activating groups such as methyl, halogen (–F and –Cl), and $–OCF_3$, respectively. Only **11s** has a 2,6-dichloro group. Based on the structure–vasodilation effect relationship of the curcumin nature-mimetic library, half of the curcumin compounds with a benzenesulfonyl group having *para*-position functionality on benzene can be novel vasodilation candidates for contracted vasculature induced by both depolarization and ET-1.

3. Conclusion

In order to discover novel vasodilation agents for the treatment of cardiovascular diseases such as atherosclerosis, essential hypertension, PAH, coronary artery disease, stroke, and diabetic complications of vasculature, we synthesized a library of curcumin mimics with alkylsulfonyl group and variously substituted benzenesulfonyl linkages through a simple addition reaction of an important intermediate, 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**), with various sulfonyl chlorides, and tested their vasodilatation effect on depolarization- and ET-1-induced basilar artery contraction. Although curcumin (**1**), a natural compound in this mimetic library, disclosed a weak vasodilation effect on the contracted basilar arteries induced by both depolarization and ET-1, our synthetic curcumin mimics were more potent than curcumin (**1**). We found that six curcumin mimics (**11g**, **11h**, **11i**, **11j**, **11l**, and **11s**) in depolarization- and seven compounds (**11g**, **11h**, **11i**, **11j**, **11l**, **11p**, and **11s**) in ET-1-induced vasoconstriction system are promising as novel vasodilators. When considering their vasodilation effect on basilar arteries constricted by depolarization and ET-1, we can conclude that selected curcumin mimic vasodilators are novel dual antagonists of L-type Ca^{2+} channel and $ET_{A/B2}R$. In particular, compounds **11g** and **11s** are the strongest vasodilatation molecules among the tested curcumin mimics and are now being tested in an in vivo study for potential use in the treatment of vascular-related diseases.

4. Experimental

4.1. General

Melting points were determined on Electrothermal IA9200 apparatus and were not corrected. ^1H and ^{13}C NMR spectra

recorded on Bruker 400 MHz FT-NMR spectrometer at 400 MHz, respectively, in the indicated solvent using TMS as internal standard. Elemental analysis was carried out on CE instruments EA1110 elemental analyzer. Thin-layer chromatography (TLC) has been performed on precoated Merck silica gel 60 F254 plates. Column chromatography was performed over silica gel (230–400 mesh). All other reagents were commercially available.

Male New Zealand white rabbits weighing 2–2.5 kg were purchased from Orient BIO Inc. (Sungnam, Gyeonggi, Korea), and acclimated for 1 week at a temperature of 25 ± 1 °C and humidity of 50 ± 5%. All experiments were performed according to the Care and Use of Laboratory Animals published by the US National Institutes of Health and has been approved by the Committee for the Care and Use of Laboratory Animals in Catholic Kwandong University. NaCl, KCl, $CaCl_2$, $MgCl_2$, and $NaHCO_3$ were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

4.2. Synthesis

4.2.1. 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (10)

A mixture of 4-hydroxy-3-methoxybenzaldehyde (**8**, 1.5 g, 10.0 mmol) and 3′-aminoacetophenon (**9**, 1.4 g, 10.0 mmol) is dissolved in 15 mL of ethanol and allowed to stir for several min at 5 °C (ice bath). 10 mL of a 40% KOH solution in water is added dropwise to the flask over several min. The mixture is then allowed to stir at room temperature for approximately 10 h. After the reaction was complete, the reaction mixture was neutralized with a dilute HCl. The solution was extracted with anhydrous ether (3 × 10 mL). The organic layer was concentrated and purified by silica gel column chromatography (CH_2Cl_2/methanol = 94:6). Yield 45%; mp 154–155 °C; TLC (methylene chloride/methanol = 94:6) R_f = 0.39; ^{1}H NMR ($CDCl_3$): δ 3.82 (2H, s, NH_2), 3.97 (3H, s, OCH_3), 5.89 (1H, s, OH), 6.88–6.90 (1H, m, $NH_2C_6H_4$), 6.96 (1H, d, J = 8.21 Hz, $CH_3OC_6H_3$), 7.13 (1H, d, J = 1.76 Hz, $CH_3OC_6H_3$), 7.21 (1H, dd, J = 8.21 and 1.80 Hz, $CH_3OC_6H_3$), 7.28–7.39 (3H, m, $NH_2C_6H_4$), 7.33 (1H, d, J = 15.63 Hz, CH=C*H*Ar), 7.73 (1H, d, J = 15.63 Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$): δ 56.0, 110.2, 114.4, 115.1, 118.7, 119.2, 119.9, 123.4, 127.3, 129.4, 139.6, 145.0, 146.9, 147.1, 148.6, 190.9. MS (EI+) (m/z) 269 (M^+); Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.72; H, 5.66; N, 5.10.

4.2.2. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-methanesulfonamide (11a)

To a solution of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**1**) (0.1 g, 0.373 mmol) in 2.5 mL of dioxane/H_2O (50:50) was added methanesulfonyl chloride (0.043 g, 0.372 mmol) over a 20 min period at 0 °C followed by 5 h of vigorous stirring at room temperature. The solvent was removed in vacuo, and the resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 20%; mp 140–142 °C; TLC (chloroform/methanol = 95:5) R_f = 0.19; ^{1}H NMR ($CDCl_3$): δ 3.06 (3H, s, CH_3), 3.98 (3H, s, OCH_3), 5.99 (1H, s, O*H*), 6.97 (1H, d, J = 8.22 Hz, $CH_3OC_6H_3$), 7.02 (1H, s, N*H*), 7.16 (1H, d, J = 1.55 Hz, $CH_3OC_6H_3$), 7.25 (1H, dd, J = 7.48 and 1.62 Hz, $CH_3OC_6H_3$), 7.35 (1H, d, J = 15.58 Hz, CH=C*H*Ar), 7.52 (1H, t, J = 7.76 Hz, NHC_6H_4), 7.57 (1H, d, J = 7.77 Hz, NHC_6H_4), 7.82 (1H, s, NHC_6H_4), 7.76 (1H, d, J = 15.59 Hz, C*H*=CHAr), 7.87 (1H, d, J = 7.18 Hz, NHC_6H_4) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 50.6, 56.0, 110.4, 115.3, 119.4, 120.3, 123.6, 124.3, 124.4, 127.1, 129.7, 138.5, 139.8, 145.8, 147.3, 149.0, 190.0. MS (FAB+) (m/z) 347 (M^+); Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 59.78; H, 4.93; N, 4.03; S, 9.23. Found: C, 60.03; H, 5.06; N, 4.08; S, 9.28.

4.2.3. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-ethanesulfonamide (11b)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with ethanesulfonyl chloride (0.048 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 8:2). Yield 20%; mp 118–120 °C; TLC (ethyl acetate/*n*-hexane = 8:2) R_f = 0.52; ^{1}H NMR ($CDCl_3$): δ 2.80 (3H, t, J = 7.37 Hz, CH_2CH_3), 3.17 (2H, q, J = 7.40 Hz, CH_2CH_3), 3.98 (3H, s, OCH_3), 5.94 (1H, s, O*H*), 6.91 (1H, s, N*H*), 6.97 (1H, d, J = 8.27 Hz, $CH_3OC_6H_3$), 7.17 (1H, d, J = 1.26 Hz, $CH_3OC_6H_3$), 7.26 (1H, dd, J = 5.36 and 1.71 Hz, $CH_3OC_6H_3$), 7.35 (1H, d, J = 15.58 Hz, CH=C*H*Ar), 7.50 (1H, t, J = 7.85 Hz, NHC_6H_4), 7.58 (1H, d, J = 8.02 Hz, NHC_6H_4), 7.80 (1H, d, J = 7.63 Hz, NHC_6H_4), 7.84 (1H, d, J = 15.62 Hz, C*H*=CHAr), 7.89 (1H, s, NHC_6H_4) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 8.2, 46.0, 56.0, 110.4, 115.3, 119.4, 119.9, 123.6, 123.9, 124.1, 127.1, 129.7, 138.6, 139.8, 145.8, 147.3, 149.0, 190.1. MS (FAB+) (m/z) 361 (M^+); Anal. Calcd for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88; S, 8.87. Found: C, 59.95; H, 5.26; N, 3.83; S, 8.77.

4.2.4. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-propanesulfonamide (11c)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 1-propanesulfonyl chloride (0.053 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 19%; mp 117–119 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.23; ^{1}H NMR ($CDCl_3$): δ 1.03 (3H, t, J = 7.42 Hz, $CH_2CH_2CH_3$), 1.86–1.91 (2H, m, $CH_2CH_2CH_3$), 3.09–3.13 (2H, m, $CH_2CH_2CH_3$), 3.98 (3H, s, OCH_3), 5.96 (1H, s, O*H*), 6.87 (1H, s, N*H*), 6.97 (1H, d, J = 8.20 Hz, $CH_3OC_6H_3$), 7.16 (1H, d, J = 1.59 Hz, $CH_3OC_6H_3$), 7.26 (1H, dd, J = 7.57 and 1.65 Hz, $CH_3OC_6H_3$), 7.35 (1H, d, J = 15.58 Hz, CH=C*H*Ar), 7.50 (1H, t, J = 7.80 Hz, NHC_6H_4), 7.56 (1H, d, J = 8.33 Hz, NHC_6H_4), 7.80 (1H, d, J = 7.55 Hz, NHC_6H_4), 7.83 (1H, d, J = 15.73 Hz, C*H*=CHAr), 7.85 (1H, s, NHC_6H_4) ppm. ^{13}C NMR ($CDCl_3$): δ 12.9, 17.3, 53.7, 56.1, 110.5, 114.9, 118.7, 120.2, 123.7, 123.9, 124.7, 127.3, 129.9, 138.1, 139.7, 146.7, 146.8, 148.7, 189.9. MS (FAB+) (m/z) 375 (M^+); Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 61.21; H, 5.72; N, 3.79; S, 8.63.

4.2.5. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-isopropanesulfonamide (11d)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with isopropylsulfonyl chloride (0.053 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 15%; mp 124–126 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.21; ^{1}H NMR ($CDCl_3$): δ 1.42 (6H, d, J = 6.85 Hz, $CH(CH_3)_2$), 3.31–3.33 (1H, m, C*H*$(CH_3)_2$), 3.98 (3H, s, OCH_3), 5.98 (1H, s, O*H*), 6.80 (1H, s, N*H*), 6.97 (1H, d, J = 8.25 Hz, $CH_3OC_6H_3$), 7.16 (1H, d, J = 1.28 Hz, $CH_3OC_6H_3$), 7.25 (1H, dd, J = 11.41 and 1.58 Hz, $CH_3OC_6H_3$), 7.34 (1H, d, J = 15.62 Hz, CH=C*H*Ar), 7.48 (1H, t, J = 7.83 Hz, NHC_6H_4), 7.57 (1H, d, J = 8.06 Hz, NHC_6H_4), 7.78 (1H, d, J = 7.90 Hz, NHC_6H_4), 7.79 (1H, d, J = 16.99 Hz, C*H*=CHAr), 7.84 (1H, s, NHC_6H_4) ppm. ^{13}C NMR ($CDCl_3$): δ 16.6, 53.0, 56.1, 110.4, 114.9, 118.9, 120.0, 123.6, 123.8, 124.5, 127.3, 129.9, 138.3, 139.7, 146.6, 146.8, 148.6, 189.9. MS (FAB+) (m/z) 375 (M^+); Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 60.98; H, 5.71; N, 3.80; S, 8.61.

4.2.6. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-trifluoromethanesulfonamide (11e)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with trifluromethanesulfonyl chloride (0.063 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 16%; mp 120–122 °C; TLC (chloroform/methanol = 95:5) R_f = 0.19; ^{1}H NMR ($CDCl_3$): δ 3.98 (3H, s, OCH_3), 5.98 (1H, s, O*H*), 6.91 (1H, s, N*H*), 6.98 (1H, d, J = 8.20 Hz, $CH_3OC_6H_3$), 7.29 (1H, d, J = 1.62 Hz, $CH_3OC_6H_3$), 7.27 (1H, dd, J = 4.60 and 1.71 Hz, $CH_3OC_6H_3$), 7.34 (1H, d, J = 15.58 Hz, CH=C*H*Ar), 7.55 (1H, t, J = 7.87 Hz, NHC_6H_4), 7.63 (1H, d, J = 8.02 Hz, NHC_6H_4), 7.85 (1H, d, J = 15.35 Hz, C*H*=CHAr), 7.93 (1H, d, J = 7.69 Hz, NHC_6H_4), 8.01 (1H, s, NHC_6H_4) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 55.9, 110.7, 115.6, 119.0, 121.4, 122.1, 123.6, 125.8, 125.9, 126.6, 129.5, 136.0, 139.6, 146.1, 147.8, 149.7, 189.8. MS (FAB+) (m/z) 401 (M^+); Anal. Calcd for $C_{17}H_{14}F_3NO_5S$: C, 50.87; H, 3.52; N, 3.49; S, 7.99. Found: C, 49.75; H, 3.36; N, 3.36; S, 7.84.

4.2.7. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-benzenesulfonamide (11f)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with benzenesulfonyl chloride (0.066 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 66%; mp 165–167 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.28; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.95 (3H, s, OCH_3), 6.94 (1H, d, J = 7.92 Hz, $CH_3OC_6H_3$), 7.14–7.16 (2H, m, $CH_3OC_6H_3$), 7.25 (1H, d, J = 15.54 Hz, CH=C*H*Ar), 7.31–7.36 (1H, m, benzenesulfonyl-*H*), 7.39–7.41 (2H, m, benzenesulfonyl-*H*), 7.41–7.51 (2H, m, NHC_6H_4), 7.50 (1H, d, J = 7.40 Hz, NHC_6H_4), 7.62 (1H, s, O*H*), 7.68 (1H, d, J = 15.45 Hz, C*H*=CHAr), 7.77 (1H, s, NHC_6H_4), 7.83 (2H, m, benzenesulfonyl-*H*), 9.77 (1H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$): δ 56.0, 110.7, 115.5, 119.2, 120.5, 123.5, 124.1, 124.5, 127.0, 128.8, 128.9, 129.3, 132.7, 138.2, 139.4, 139.7, 145.7, 147.7, 149.4, 190.0. MS (FAB+) (m/z) 409 (M^+); Anal. Calcd for $C_{22}H_{19}NO_5S$: C, 64.53; H, 4.68; N, 3.42; S, 7.83. Found: C, 65.01; H, 4.74; N, 3.52; S, 7.91.

4.2.8. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-methylbenzenesulfonamide (11g)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-methylbenzenesulfonyl chloride (0.071 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 76%; mp 170–172 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.26; ^{1}H NMR ($CDCl_3$): δ 2.36 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 5.92 (1H, s, O*H*), 6.94 (1H, s, N*H*), 6.96 (1H, d, J = 8.27 Hz, $CH_3OC_6H_3$), 7.15 (1H, d, J = 1.75 Hz, $CH_3OC_6H_3$), 7.22 (2H, d, J = 10.63 Hz, 4-methylbenzenesulfonyl-*H*), 7.23 (1H, d, J = 8.19 Hz, $CH_3OC_6H_3$), 7.29 (1H, d, J = 15.65 Hz, CH=C*H*Ar), 7.38–7.42 (2H, m, NHC_6H_4), 7.68 (2H, d, J = 8.28 Hz, 4-methylbenzenesulfonyl-*H*), 7.70 (1H, s, NHC_6H_4), 7.74–7.76 (1H, m, NHC_6H_4), 7.80 (1H, d, J = 15.59 Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 21.5, 56.0, 110.6, 115.4, 119.3, 120.5, 123.5, 124.0, 124.4, 126.7, 127.1, 129.3, 129.6, 136.7, 138.3, 139.4, 143.4, 145.6, 147.6, 149.3, 190.1. MS (FAB+) (m/z) 423 (M^+); Anal. Calcd for $C_{23}H_{21}NO_5S$: C, 65.23; H, 5.00; N, 3.31; S, 7.57. Found: C, 66.17; H, 5.15; N, 3.40; S, 7.76.

4.2.9. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-chlorobenzenesulfonamide (11h)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-chlorobenzenesulfonyl chloride (0.079 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 74%; mp 162–164 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.31; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OCH_3), 5.92 (1H, s, O*H*), 6.97 (1H, d, J = 8.21 Hz, $CH_3OC_6H_3$), 7.00 (1H, s, N*H*), 7.15 (1H, d, J = 1.64 Hz, $CH_3OC_6H_3$), 7.24 (2H, dd, J = 10.12 and 1.72 Hz, $CH_3OC_6H_3$), 7.30 (1H, d, J = 15.61 Hz, CH=C*H*Ar), 7.41 (2H, d, J = 8.65 Hz, 4-chlorobenzenesulfonyl-*H*), 7.41–7.44 (2H, m, NHC_6H_4), 7.72 (2H, d, J = 8.55 Hz, 4-chlorobenzenesulfonyl-*H*), 7.73 (1H, s, NHC_6H_4), 7.77–7.80 (1H, m, NHC_6H_4), 7.82 (1H, d, J = 15.72 Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.5, 115.4, 119.3, 120.8, 124.5, 124.7, 128.5, 128.6, 129.1, 129.2, 129.4, 137.9, 138.2, 139.1, 139.5, 145.7, 147.4, 149.2, 190.0. MS (FAB+) (m/z) 443 (M^+); Anal. Calcd for $C_{22}H_{18}ClNO_5S$: C, 59.53; H, 4.09; N, 3.16; S, 7.22. Found: C, 59.29; H, 3.98; N, 3.09; S, 7.09.

4.2.10. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-fluorobenzenesulfonamide (11i)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-fluorobenzenesulfonyl chloride (0.072 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 76%; mp 163–165 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.29; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OCH_3), 5.92 (1H, s, O*H*), 6.93 (1H, s, N*H*), 6.97 (1H, d, J = 8.24 Hz, $CH_3OC_6H_3$), 7.10 (2H, d, J = 8.49 Hz, 4-fluorobenzenesulfonyl-*H*), 7.14 (1H, d, J = 2.94 Hz, $CH_3OC_6H_3$), 7.24 (1H, dd, J = 9.93 and 1.28 Hz, $CH_3OC_6H_3$), 7.29 (1H, d, J = 15.77 Hz, CH=C*H*Ar), 7.42–7.43 (2H, m, NHC_6H_4), 7.71 (1H, s, NHC_6H_4), 7.80 (2H, d, J = 8.92 Hz, 4-fluorobenzenesulfonyl-*H*), 7.81 (1H, d, J = 10.73 Hz, NHC_6H_4), 7.82 (1H, d, J = 15.71 Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.5, 115.4, 116.1, 116.3, 119.3, 120.8, 123.5, 124.4, 124.7, 127.0, 129.4, 129.8, 129.9, 138.0, 139.5, 145.7, 147.4, 149.2, 190.0. MS (FAB+) (m/z) 427 (M^+); Anal. Calcd for $C_{22}H_{18}FNO_5S$: C, 61.82; H, 4.24; N, 3.28; S, 7.50. Found: C, 59.98; H, 4.12; N, 3.22; S, 7.24.

4.2.11. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-nitrobenzenesulfonamide (11j)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-nitrobenzenesulfonyl chloride (0.082 g, 0.372 mmol) sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 75%; mp 140–142 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.26; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OCH_3), 5.94 (1H, s, O*H*), 6.97 (1H, d, J = 8.28 Hz, $CH_3OC_6H_3$), 7.17 (1H, d, J = 1.68 Hz, $CH_3OC_6H_3$), 7.27 (1H, dd, J = 8.78 and 1.76 Hz, $CH_3OC_6H_3$), 7.34 (1H, d, J = 15.55 Hz, CH=C*H*Ar), 7.47 (1H, t, J = 8.07 Hz, NHC_6H_4), 7.55 (1H, d, J = 8.49 Hz, NHC_6H_4), 7.63 (1H, s, N*H*), 7.82 (1H, s, NHC_6H_4), 7.83 (1H, d, J = 2.09 Hz, NHC_6H_4), 7.92 (1H, d, J = 15.55 Hz, C*H*=CHAr), 7.97 (2H, d, J = 8.87 Hz, 4-nitrobenzenesulfonyl-*H*), 8.27 (2H, d, J = 8.83 Hz, 4-notrobenzenesulfonyl-*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.7, 115.6, 119.0, 120.9, 123.5, 124.1, 124.8, 124.9, 126.7, 128.4, 129.5, 137.5, 139.6, 145.6, 145.9, 147.7, 149.6, 149.9,

189.8. MS (FAB+) (*m*/*z*) 454 (M^+); Anal. Calcd for $C_{22}H_{18}N_2O_7S$: C, 58.14; H, 3.99; N, 6.16; S, 7.06. Found: C, 60.22; H, 4.15; N, 6.53; S, 7.31.

4.2.12. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-methoxybenzenesulfonamide (11k)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-methoxybenzenesulfonyl chloride (0.077 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 8:2). Yield 55%; mp 189–191 °C; TLC (chloroform/methanol = 8:2) R_f = 0.71; ^{1}H NMR ($CDCl_3$): δ 3.81 (3H, s, 4-methoxylbenzenesulfonyl-OC*H*$_3$), 3.97 (3H, s, OC*H*$_3$), 5.99 (1H, s, O*H*), 6.89 (2H, d, *J* = 8.88 Hz, 4-methoxylbenzenesulfonyl-*H*), 6.95 (1H, s, N*H*), 6.96 (1H, d, *J* = 8.15 Hz, $CH_3OC_6H_3$), 7.14 (1H, d, *J* = 1.34 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, *J* = 8.28 and 1.42 Hz, $CH_3OC_6H_3$), 7.28 (1H, d, *J* = 15.55 Hz, CH=C*H*Ar), 7.39–7.41 (2H, m, NHC_6H_4), 7.67 (1H, s, NHC_6H_4), 7.72 (2H, d, *J* = 8.89 Hz, 4-methoxylbenzenesulfonyl-*H*), 7.75 (1H, d, *J* = 2.09 Hz, NHC_6H_4), 7.77 (1H, d, *J* = 15.50 Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 50.5, 56.0, 110.5, 114.1, 115.3, 119.4, 120.6, 123.5, 124.2, 124.6, 127.1, 129.3, 129.4, 131.2, 138.2, 139.4, 145.6, 147.4, 149.0, 162.9, 190.1. MS (FAB+) (*m*/*z*) 439 (M^+); Anal. Calcd for $C_{23}H_{21}NO_6S$: C, 62.86; H, 4.82; N, 3.19; S, 7.30. Found: C, 65.09; H, 5.01; N, 3.30; S, 7.55.

4.2.13. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-trifluoromethoxybenzenesulfonamide (11l)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-(trifluoromethoxy)benzenesulfonyl chloride (0.097 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 67%; mp 154–156 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.36; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OC*H*$_3$), 5.93 (1H, s, O*H*), 6.97 (1H, d, *J* = 8.20 Hz, $CH_3OC_6H_3$), 7.17 (1H, d, *J* = 1.57 Hz, $CH_3OC_6H_3$), 7.25 (1H, d, *J* = 8.28 Hz, $CH_3OC_6H_3$), 7.27 (2H, d, *J* = 8.88 Hz, 4-(trifluoromethoxy)benzenesulfonyl-*H*), 7.33 (1H, d, *J* = 15.57 Hz, CH=C*H*Ar), 7.41 (1H, s, N*H*), 7.44 (1H, t, *J* = 7.80 Hz, NHC_6H_4), 7.51 (1H, d, *J* = 8.57 Hz, NHC_6H_4), 7.80 (1H, d, *J* = 7.77 Hz, NHC_6H_4), 7.81 (1H, s, NHC_6H_4), 7.85 (2H, d, *J* = 8.89 Hz, 4-(trifluoromethoxy)benzenesulfonyl-*H*), 7.90 (1H, d, *J* = 15.59 Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.5, 115.3, 119.3, 120.7, 120.8, 123.5, 124.5, 124.6, 127.0, 129.2, 129.3, 129.4, 137.8, 138.1, 139.6, 145.8, 147.4, 149.1, 152.0, 190.0. MS (FAB+) (*m*/*z*) 493 (M^+); Anal. Calcd for $C_{23}H_{18}F_3NO_6S$: C, 55.98; H, 3.68; N, 2.84; S, 6.50. Found: C, 59.70; H, 3.96; N, 3.03; S, 6.94.

4.2.14. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-trifluoromethylbenzenesulfonamide (11m)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-(trifluoromethyl)benzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 67%; mp 157–159 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.29; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OC*H*$_3$), 5.93 (1H, s, O*H*), 6.97 (1H, d, *J* = 8.21 Hz, $CH_3OC_6H_3$), 7.17 (1H, d, *J* = 1.13 Hz, $CH_3OC_6H_3$), 7.27 (1H, d, *J* = 6.33 Hz, $CH_3OC_6H_3$), 7.33 (1H, d, *J* = 15.56 Hz, CH=C*H*Ar), 7.45 (1H, t, *J* = 7.82 Hz, NHC_6H_4), 7.49 (1H, s, N*H*), 7.52 (1H, d, *J* = 7.71 Hz, NHC_6H_4), 7.70 (2H, d, *J* = 8.29 Hz, 4-(trifluoromethyl)benzenesulfonyl-*H*), 7.81 (1H, d, *J* = 12.12 Hz, C*H*=CHAr), 7.82 (1H, d, *J* = 4.22 Hz, NHC_6H_4), 7.88 (1H, s, NHC_6H_4), 7.93 (2H, d, *J* = 7.78 Hz, 4-(trifluoromethyl)benzenesulfonyl-*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.5, 115.4, 119.2, 120.9, 123.5, 124.6, 124.7, 126.0, 126.1, 126.2, 127.0, 127.7, 129.5, 137.7, 139.6, 143.4, 145.8, 147.4, 149.2, 189.9. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{23}H_{18}F_3NO_5S$: C, 57.86; H, 3.80; N, 2.93; S, 6.72. Found: C, 56.82; H, 3.79; N, 2.88; S, 6.60.

4.2.15. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-3-trifluoromethylbenzenesulfonamide (11n)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 3-(trifluoromethyl)benzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 68%; mp 158–160 °C; TLC (ethyl acetate/*n*-hexane = 1:1) R_f = 0.32; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OC*H*$_3$), 5.93 (1H, s, O*H*), 6.97 (1H, d, *J* = 8.24 Hz, $CH_3OC_6H_3$), 7.16 (1H, d, *J* = 1.57 Hz, $CH_3OC_6H_3$), 7.25 (1H, dd, *J* = 7.10 and 1.53 Hz, $CH_3OC_6H_3$), 7.31 (1H, d, *J* = 15.55 Hz, CH=C*H*Ar), 7.32 (1H, s, N*H*), 7.45 (1H, t, *J* = 7.77 Hz, NHC_6H_4), 7.51 (1H, d, *J* = 7.77 Hz, NHC_6H_4), 7.58 (1H, t, *J* = 7.85 Hz, 3-(trifluoromethyl)benzenesulfonyl-*H*), 7.75 (1H, s, NHC_6H_4), 7.79 (1H, d, *J* = 9.70 Hz, 3-(trifluoromethyl)benzenesulfonyl-*H*), 7.81 (1H, d, *J* = 7.62 Hz, NHC_6H_4), 7.87 (1H, d, *J* = 15.57 Hz, C*H*=CHAr), 7.95 (1H, d, *J* = 7.96 Hz, 3-(trifluoromethyl)benzenesulfonyl-*H*), 8.05 (1H, s, 3-(trifluoromethyl) benzenesulfonyl-*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.7, 115.6, 119.0, 121.0, 121.9, 123.5, 124.1, 124.2 124.6, 124.9, 126.6, 129.2, 129.4, 129.7, 130.3, 137.7, 139.5, 140.9, 145.8, 147.8, 149.6, 189.8. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{23}H_{18}F_3NO_5S$: C, 57.86; H, 3.80; N, 2.93; S, 6.72. Found: C, 57.08; H, 3.78; N, 2.88; S, 6.69.

4.2.16. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-4-acetylbenzenesulfonamide (11o)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 4-acetylbenzenesulfonyl chloride (0.081 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 19%; mp 155–157 °C; TLC (chloroform/methanol = 95:5) R_f = 0.07; ^{1}H NMR ($CDCl_3$): δ 2.60 (3H, s, acetyl-*H*), 3.97 (3H, s, OC*H*$_3$), 5.94 (1H, s, O*H*), 6.93 (1H, s, N*H*), 6.96 (1H, d, *J* = 8.25 Hz, $CH_3OC_6H_3$), 7.13 (1H, d, *J* = 1.59 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, *J* = 8.27 and 1.85 Hz, $CH_3OC_6H_3$), 7.28 (1H, d, *J* = 15.54 Hz, CH=C*H*Ar), 7.41–7.43 (2H, m, NHC_6H_4), 7.68 (1H, s, NHC_6H_4), 7.77–7.79 (1H, m, NHC_6H_4), 7.78 (1H, d, *J* = 15.63 Hz, C*H*=CHAr), 7.88 (2H, d, *J* = 8.47 Hz, 4-acetylbenzenesulfonyl-*H*), 8.00 (2H, d, *J* = 8.43 Hz, 4-acetylbenzenesulfonyl-*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 26.8, 56.0, 110.4, 115.3, 119.3, 120.9, 123.5, 124.6, 124.8, 127.0, 127.5, 128.8, 129.5, 137.7, 139.5, 139.9, 143.6, 145.7, 147.3, 149.0, 189.9, 196.8. MS (FAB+) (*m*/*z*) 451 (M^+); Anal. Calcd for $C_{24}H_{21}NO_6S$: C, 63.85; H, 4.69; N, 3.10; S, 7.10. Found: C, 63.67; H, 4.72; N, 3.12; S, 7.06.

4.2.17. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-2,4-dichlorobenzenesulfonamide (11p)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 2,4-dichlorobenzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 66%; mp 169–171 °C; TLC (chloroform/methanol = 95:5) R_f = 0.38; ^{1}H NMR

($CDCl_3$): δ 3.97 (3H, s, OCH_3), 5.96 (1H, s, O*H*), 6.97 (1H, d, *J* = 8.20 Hz, $CH_3OC_6H_3$), 7.14 (1H, s, $CH_3OC_6H_3$), 7.23 (1H, d, *J* = 8.14 Hz, $CH_3OC_6H_3$), 7.28 (1H, d, *J* = 15.17 Hz, CH=C*H*Ar), 7.32 (1H, d, *J* = 8.94 Hz, 2,4-dichlorobenzenesulfonyl-*H*), 7.38 (1H, t, *J* = 7.47 Hz, NHC_6H_4), 7.40 (1H, s, N*H*), 7.50 (1H, d, *J* = 4.08 Hz, NHC_6H_4), 7.59 (1H, s, 2,4-dichlorobenzenesulfonyl-*H*), 7.74 (1H, d, *J* = 6.06 Hz, NHC_6H_4), 7.79 (1H, d, *J* = 15.57 Hz, C*H*=CHAr), 7.80 (1H, s, NHC_6H_4), 7.99 (1H, d, *J* = 8.53 Hz, 2,4-dichlorobenzenesulfonyl-*H*) ppm. ^{13}C NMR ($CDCl_3$): δ 56.1, 110.3, 114.9, 118.9, 121.1, 123.6, 124.7, 125.6, 127.2, 127.7, 129.8, 131.6, 132.4, 132.9, 134.7, 136.3, 139.7, 140.3, 146.4, 146.8, 148.6, 189.6. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{22}H_{17}Cl_2NO_5S$: C, 55.24; H, 3.58; N, 2.93; S, 6.70. Found: C, 56.26; H, 3.68; N, 2.98; S, 6.82.

4.2.18. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-2,5-dichlorobenzenesulfonamide (11q)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 2,5-dichlorobenzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 38%; mp 153–155 °C; TLC (chloroform/methanol = 95:5) R_f = 0.45; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.96 (3H, s, OCH_3), 6.94 (1H, d, *J* = 7.94 Hz, $CH_3OC_6H_3$), 7.15 (1H, s, $CH_3OC_6H_3$), 7.15––7.17 (1H, m, $CH_3OC_6H_3$), 7.25 (1H, d, *J* = 15.72 Hz, CH=C*H*Ar), 7.34–7.41 (2H, m, NHC_6H_4), 7.37–7.41 (2H, m, 2,5-dichlorobenzenesulfonyl-*H*), 7.67 (1H, d, *J* = 7.40 Hz, NHC_6H_4), 7.69 (1H, d, *J* = 15.52 Hz, C*H*=CHAr), 7.79 (1H, s, NHC_6H_4), 8.09 (1H, s, 2,5-dichlorobenzenesulfonyl-*H*), 8.09 (1H, s, O*H*), 10.07 (1H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.7, 115.6, 119.1, 120.2, 123.5, 124.0, 124.4, 126.7. 129.5, 130.1, 131.5, 132.9, 133.1, 133.8, 137.1, 138.3, 139.5, 145.8, 147.7, 149.5, 189.9. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{22}H_{17}Cl_2NO_5S$: C, 55.24; H, 3.58; N, 2.93; S, 6.70. Found: C, 57.82; H, 3.78; N, 3.08; S, 6.99.

4.2.19. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-3,4-dichlorobenzenesulfonamide (11r)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 3,4-dichlorobenzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 80%; mp 159–161 °C; TLC (chloroform/methanol = 95:5) R_f = 0.37; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.94 (3H, s, OCH_3), 6.94 (1H, d, *J* = 8.39 Hz, $CH_3OC_6H_3$), 7.14 (1H, s, $CH_3OC_6H_3$), 7.14–7.19 (1H, m, $CH_3OC_6H_3$), 7.28 (1H, d, *J* = 15.57 Hz, CH=C*H*Ar), 7.37 (1H, t, *J* = 7.65 Hz, NHC_6H_4), 7.40 (1H, d, *J* = 7.50 Hz, NHC_6H_4), 7.50 (1H, d, *J* = 8.44 Hz, 3,4-dichlorobenzenesulfonyl-*H*), 7.64 (1H, d, *J* = 8.42 Hz, 3,4-dichlorobenzenesulfonyl-*H*), 7.70 (1H, d, *J* = 15.30 Hz, C*H*=CHAr), 7.71 (1H, d, *J* = 7.40 Hz, NHC_6H_4), 7.79 (1H, s, 3,4-dichlorobenzenesulfonyl-*H*), 7.95 (1H, s, NHC_6H_4), 8.36 (1H, s, O*H*), 10.15 (1H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.7, 115.6, 119.0, 120.8, 123.5, 124.6, 124.7, 126.3, 126.6, 129.0, 129.5, 130.9, 133.3, 137.2, 137.6, 139.5, 139.6, 145.9, 147.7, 149.5, 189.8. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{22}H_{17}Cl_2NO_5S$: C, 55.24; H, 3.58; N, 2.93; S, 6.70. Found: C, 56.32; H, 3.74; N, 3.01; S, 6.86.

4.2.20. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-2,6-dichlorobenzenesulfonamide (11s)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 2,6-dichlorobenzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 60%; mp 177–179 °C; TLC (chloroform/methanol = 95:5) R_f = 0.50; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.95 (3H, s, OCH_3), 6.94 (1H, d, *J* = 8.58 Hz, $CH_3OC_6H_3$), 7.15 (1H, s, $CH_3OC_6H_3$), 7.15–7.16 (1H, m, $CH_3OC_6H_3$), 7.30 (1H, d, *J* = 15.58 Hz, CH=C*H*Ar), 7.31 (1H, d, *J* = 6.83 Hz, 2,6-dichlorobenzenesulfonyl-*H*), 7.37 (1H, t, *J* = 7.86 Hz, NHC_6H_4), 7.41–7.42 (1H, m, NHC_6H_4), 7.41–7.42 (2H, m, 2,6-dichlorobenzenesulfonyl-*H*), 7.67 (1H, d, *J* = 7.54 Hz, NHC_6H_4), 7.70 (1H, d, *J* = 15.59 Hz, C*H*=CHAr), 7.87 (1H, s, NHC_6H_4), 8.21 (1H, s, O*H*), 10.14 (1H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.3, 111.0, 115.9, 119.2, 119.3, 123.4, 123.9, 124.3, 127.1, 129.9, 131.9, 133.2, 134.7, 135.9, 137.7, 139.8, 146.1, 148.0, 149.8, 190.2. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{22}H_{17}Cl_2NO_5S$: C, 55.24; H, 3.58; N, 2.93; S, 6.70. Found: C, 57.52; H, 3.73; N, 3.06; S, 6.96.

4.2.21. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-3,5-dichlorobenzenesulfonamide (11t)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 3,5-dichlorobenzenesulfonyl chloride (0.091 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 50%; mp 187–189 °C; TLC (chloroform/methanol = 95:5) R_f = 0.24; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.94 (3H, s, OCH_3), 6.93 (1H, d, *J* = 8.68 Hz, $CH_3OC_6H_3$), 7.14–7.16 (2H, m, $CH_3OC_6H_3$), 7.28 (1H, d, *J* = 15.52 Hz, CH=C*H*Ar), 7.39–7.41 (1H, m, NHC_6H_4), 7.45–7.46 (1H, m, NHC_6H_4), 7.47–7.48 (1H, m, 3,5-dichlorobenzenesulfonyl-*H*), 7.65–7.69 (1H, m, NHC_6H_4), 7.70 (1H, d, *J* = 15.59 Hz, C*H*=CHAr), 7.72–7.73 (2H, m, 3,5-dichlorobenzenesulfonyl-*H*), 7.78 (1H, s, NHC_6H_4), 8.64 (1H, s, O*H*), 10.26 (1H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.8, 115.7, 118.9, 120.9, 123.5, 124.7, 124.8, 125.4, 125.5, 129.5, 132.5, 135.6, 137.5, 139.5, 142.6, 145.8, 147.8, 149.7, 189.7. MS (FAB+) (*m*/*z*) 477 (M^+); Anal. Calcd for $C_{22}H_{17}Cl_2NO_5S$: C, 55.24; H, 3.58; N, 2.93; S, 6.70. Found: C, 55.14; H, 3.50; N, 2.87; S, 6.58.

4.2.22. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-thiophene-2-sulfonamide (11u)

The same procedure described above was employed for the preparation of **11a** by addition reaction of 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**10**) with 2-thiophenesulfonyl chloride (0.068 g, 0.372 mmol) as sulfonylation agent. The resulting solid was purified by silica gel column chromatography ($CHCl_3$/methanol = 95:5). Yield 40%; mp 164–166 °C; TLC (chloroform/methanol = 95:5) R_f = 0.28; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.96 (3H, s, OCH_3), 6.95 (1H, d, *J* = 8.10 Hz, $CH_3OC_6H_3$), 6.99 (1H, m, thiophene-*H*), 7.15 (1H, s, $CH_3OC_6H_3$), 7.17 (1H, dd, *J* = 9.12 and 1.86 Hz, $CH_3OC_6H_3$), 7.28 (1H, d, *J* = 15.59 Hz, CH=C*H*Ar), 7.36 (1H, t, *J* = 7.73 Hz, NHC_6H_4), 7.44–7.47 (1H, m, NHC_6H_4), 7.49–7.53 (2H, m, thiophene-*H*), 7.59–7.62 (1H, m, NHC_6H_4), 7.71 (1H, d, *J* = 15.48 Hz, C*H*=CHAr), 7.73 (1H, s, NHC_6H_4), 7.84 (1H, s, O*H*), 9.68 (1H, s, N*H*) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.8, 115.7, 118.9, 120.5, 123.5, 124.3, 124.6, 126.5, 126.9, 127.2, 128.7, 129.3, 131.9, 132.1, 138.0, 139.3, 145.6, 147.9, 149.8, 189.7. MS (FAB+) (*m*/*z*) 415 (M^+); Anal. Calcd for $C_{20}H_{17}NO_5S_2$: C, 57.82; H, 4.12; N, 3.37; S, 15.44. Found: C, 61.18; H, 4.41; N, 3.57; S, 16.39.

4.3. Measurements of vascular tension

Male New Zealand white rabbits weighing 2–2.5 kg were anesthetized by inhaling enflurane. The basilar artery was rapidly isolated under sterile conditions and placed in a Ca^{2+}-free

physiological salt solution (PSS) that contained the following components (in mM): 135 NaCl, 5 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$, 5.5 glucose, and 23.8 $NaHCO_3$ (pH 7.4, adjusted with a 95% O_2 and 5% CO_2). Residual blood was rinsed from the lumen and adherent connective tissue, fat, and adventitia were carefully removed. The basilar artery was cut into rings (3 mm) in a dissecting chamber filled with a Ca^{2+}-free PSS saturated with a 95% O_2 and 5% CO_2 mixture. The basilar ring was mounted using a pair of stainless steel hooks under a resting tension of 0.8 g in organ baths containing 15 mL of PSS, which was maintained 37 °C and bubbled with a 95% O_2 and 5% CO_2 mixture. One of the hooks was connected to a force displacement transducer (MLT050; ADInstruments, Colorado Springs, CO, USA) and the tension was recorded with chart 5 on a Powerlab/400 (ADInstruments). After an equilibration was performed for 30 min, each ring specimen was repeatedly exposed to the high K^+ solution (50 mM K^+), which was prepared by replacing NaCl with an equimolar concentration of KCl, until the responses became stable. Functional endothelial cells were confirmed by the ability of acetylcholine (1 μM) to induce relaxation. Concentration–response relationships were obtained by a single application of compounds in a log scale concentration after pre-contraction induced by endothelin-1 (3 nM) reached a steady state on the basilar artery.

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