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Synthesis of sulfonyl curcumin mimics exerting a vasodilatation effect on the basilar artery of rabbits

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ABSTRACT

In order to discover novel small vasodilatory molecules for potential use in the treatment of vascular disease, we tested the vasodilatation effect of two types of synthetic curcumin mimics, amide type (**3**) and sulfonyl amide type (**4**), upon the basilar artery of rabbits. In general, the sulfonyl amide type mimic (**4**) is more potent than the amide type (**3**). Curcumin (**1**) and compounds **12** and **20** effectively dilated the basilar artery of white rabbits.

Curcumin, a chemopreventive and chemotherapeutic natural product (diferuloyl methane, **1**), isolated from the root of *Curcuma longa* L., suppresses, retards, or reverses carcinogenesis.[1] Curcumin also has antiinflammatory, antioxidant, antiviral, and anti-infectious activities and wound-healing properties.[2]

We have previously reported that pyridine- and thiophene-linked symmetrical bis-alkynyl curcumin derivatives (**2**) effectively inhibit the proliferation and tube formation of human umbilical vein endothelial cells (HUVECs).[3] We have also found that various curcumin mimics (**3**) with asymmetric units possessing the alkyl amide and the aryl amide functional groups have an antiangiogenesis effect[4] and a multidrug resistance (MDR) reversal activity.[5,6] The results of our researches on curcumin mimics to discover the diverse biological activities of curcumin indicate that it is a potential leading natural product for potential use in drugs (Fig. 1).

Recently, vascular diseases, including hypertension, stroke, subarachnoid hemorrhage, and Alzheimer's disease, have become public health challenges; hence, there is a very urgent need to develop modulators that control vascular tone in order to treat these diseases.[7,8] In particular, vasoconstriction of the basilar artery exerts a negative effect on the brain's blood supply and blood pressure in physiological and pathophysiological conditions.[9] Therefore, it is important to develop vasodilatory molecules with low toxicity profiles for clinical use.[10]

During our search for vasoactive molecules from a natural product with a low toxicity, we reported, for the first time, that the sargahydroquinoic acid purified from the brown alga *Sargassum micracanthum*, shows a selective 10-fold greater vasodilatation effect on the basilar artery than on the carotid artery of white rabbits.[11] Moreover, previous reports have stated that our promising lead compound, curcumin (**1**), showed a relaxant effect on porcine coronary arterial ring segments[12] and isolated rat aorta.[13]

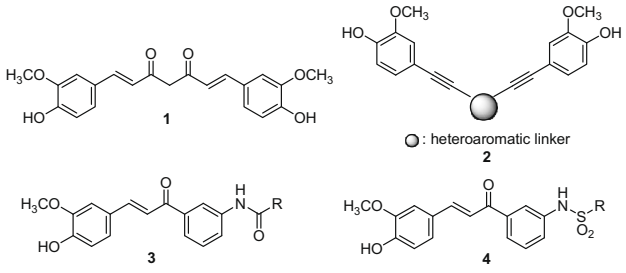

Figure 1.

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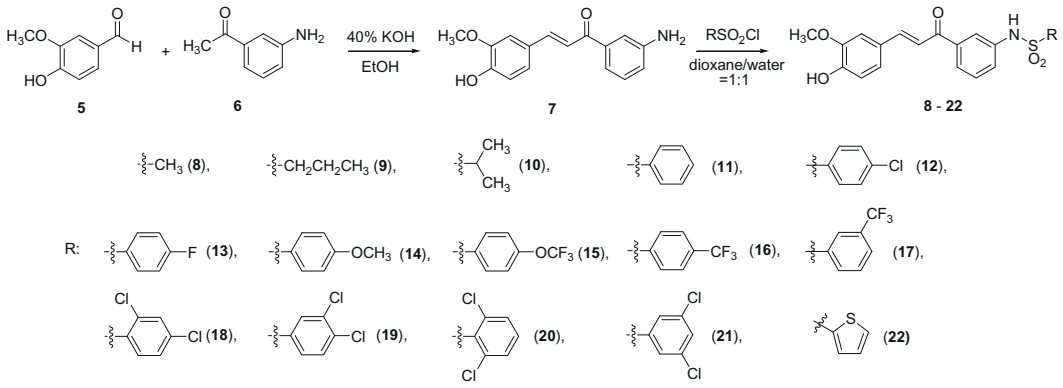

Scheme 1. Synthesis of novel curcumin mimics with the sulfonyl units including the various alkyl and aryl groups. Yield for **7**, 45%; **8**, 20%; **9**, 19%; **10**, 15%; **11**, 66%; **12**, 74%; **13**, 76%; **14**, 55%; **15**, 67%; **16**, 67%; **17**, 68%; **18**, 66%; **19**, 80%; **20**, 60%; **21**, 50%; **22**, 40%.

We assumed that the search for natural lead molecules using a specific screening system and the preparation of a synthetic library of such molecules are very effective methods for drug development. Hence, we tested the vasodilatation effect of previously described asymmetric alkyl or aryl amide curcumin mimics (**3**)[4] and newly synthesized sulfonyl curcumin mimics (**4**) upon the basilar artery of rabbits. We discovered that some asymmetric alkyl or aryl amide curcumin derivatives (**3**) show a vasodilatation effect, and that a novel type of curcumin mimics with various sulfonyl groups (**4**) dilate the basilar arteries of rabbits more effectively. In this report, we describe the method for synthesizing effective sulfonyl curcumin mimics and their vasodilatation effects.

The curcumin mimics with a substituted sulfonyl group were prepared as shown in Scheme 1. The reaction of 4-hydroxy-3-methoxybenzaldehyde (**5**) with 3-acetylaniline (**6**) in the presence of a basic catalyst (40% KOH) in ethanol at room temperature for 10 h produced 1-(3-aminophenyl)-3-(4-hydroxy-3-methoxyphenyl) propenone (**7**) through flash column chromatography ($CHCl_3/CH_3OH = 97/3$) on silica gel.[6,14] This amine (**7**) was dissolved in a 1:1 mixture solution of dioxane and H_2O, cooled to 0 °C (ice bath), and reacted with each of a variety of sulfonyl chlorides, with stirring, for 5–7 h at 0 °C. After the solvent was removed under reduced pressure, chromatography was performed ($CHCl_3/MeOH = 95/5$) on silica gel to afford the desired library of sulfonamides (**8**–**22**).[15] The yields of synthetic curcumin mimics with the alkyl sulfonyl group (**8**–**10**) were slightly low, but those of aromatic amide products (**11**–**22**) were moderate. The ^1H, ^{13}C NMR, and GC/MS spectra of all curcumin mimics (**8**–**22**) were identified to study the relationship between structural modification and the vasodilatation effect on the basilar arteries of the rabbits.[16]

In order to evaluate the vasodilatation effect on the basilar arteries of rabbits, we tested synthetic curcumin mimics in the organ bath system.[17–20] To begin with, to examine whether curcumin and our curcumin mimics exert a dilatation effect on the basilar arteries of white rabbits, we used a single concentration of 10 μM of the candidate compounds; the results are summarized in Table 1. When treated under high-K^+ concentrations (50 mM), the basilar arteries isometrically contracted by an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), and a steady state was reached within 20 min. First, when the natural lead compound, that is, curcumin (**1**), was applied to the pre-con-

Table 1
Vasodilatation potency of curcumin mimics, including types **3** and **4** on depolarization-induced constriction of rabbit basilar artery of the rabbit

Compound	Effective percentage (%) at 10 μM	Compound	Effective percentage (%) at 10 μM
1	58.4 (±6.4)[a]	**18**	4.2 (±2.2)
7	8.3 (±2.2)	**19**	30.2 (±4.8)
8	4.2 (±2.8)	**20**	99.4 (±0.4)
9	42.3 (±4.7)	**21**	37.3 (±6.4)
10	8.4 (±3.6)	**22**	36.1 (±3.3)
11	40.4 (±5.7)	**23**	20.6 (±3.7)
12	93.4 (±3.8)	**24**	32.3 (±4.2)
13	71.8 (±6.4)	**25**	22.5 (±4.6)
14	26.4 (±4.4)	**26**	27.9 (±2.7)
15	76.7 (±5.2)	**27**	41.7 (±5.2)
16	65.8 (±5.3)	**28**	27.1 (±4.6)
17	52.3 (±4.5)		

[a] Values are means of three experiments; standard deviation is shown within parentheses.

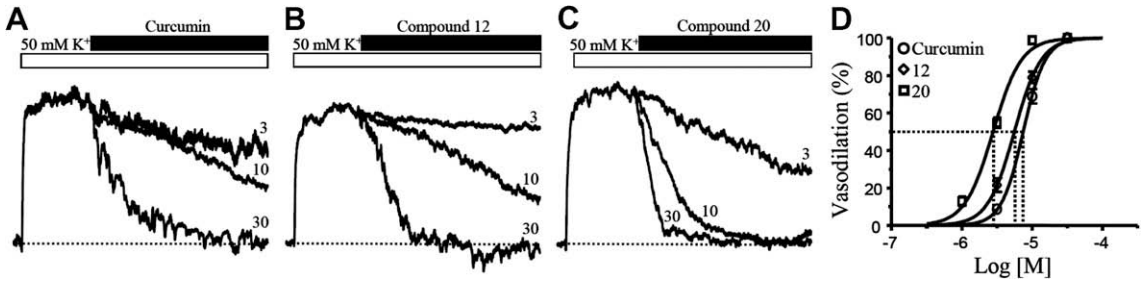

Figure 2. Vasodilatation effects of curcumin and synthetic curcumin mimics with an aromatic ring on depolarization-induced vasoconstriction of the rabbit basilar artery. Representative normalized traces were acquired by a single application of curcumin **1** (A) and compounds **12** (B) and **20** (C) 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 (20 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, $E = (1 + EC_{50}/[\text{compound}]^n)^{-1}$ (D). The estimated EC_{50} values of curcumin (**1**) and the other compounds (**12** and **20**) are 7.48 ± 0.28, 5.58 ± 0.64, and 2.78 ± 0.33 μM, respectively. Data are represented as mean ± SD ($n = 4$).

tracted with high-K^+ concentration (50 mM) of the basilar artery, the curcumin slightly dilated the basilar artery at the concentration of 10 μM. Although the effect was not sufficiently strong to consider the use of this compound as a vasodilatory drug, we could confirm that it is very useful to use curcumin mimics as the lead structure for the development of vasodilatative drugs. In the case of asymmetric alkyl or aryl amide curcumin mimics, the result was unsatisfactory, that is, only six compounds dilated the basilar artery slightly, by about 30%.[20] Finally, using the organ bath system, we discovered that some molecules of the curcumin mimics with various sulfonyl groups exhibited a strong vasodilatation effect on the basilar arteries of rabbits. In particular, compounds **12** and **20** caused efficient dilatation of the basilar artery by almost 100% at the concentration of 10 μM. Although the structure–activity relationship revealed by the preliminary results is more or less vague, curcumin mimics possessing the chlorobenzene sulfonyl group, such as **12** and **20,** have shown a strong dilatation effect.

The serial application of curcumin (**1**) and compounds **12** and **20** induced vasodilatation of the basilar arteries in a concentration-dependent manner. As shown in Figure 2, the curve fittings of the concentration–response relationship determined based on the Hill equation confirmed that the concentration required for half maximal dilatation (EC_{50}) of curcumin (**1**) and compounds **12** and **20** for the basilar artery were 7.48 ± 0.28, 5.58 ± 0.64, and 2.78 ± 0.33 μM ($n = 4$), respectively. These results indicated that curcumin mimics, especially compounds **12** and **20**, exerted a more effective and rapid dilatation effect on the basilar artery than curcumin at an equimolar concentration.

In conclusion, in order to discover efficient vasodilatory molecules for the treatment of vascular diseases, including hypertension, stroke, subarachnoid hemorrhage, and Alzheimer's disease, we synthesized a library of curcumin mimics by a simple aldol reaction and amide or sulfonyl amide addition, and then tested the library. Curcumin (**1**), a natural product, was found to exert a dilation effect on the basilar arteries of rabbits. In addition, curcumin mimics with various sulfonyl groups are more potent than those possessing amide groups. In particular, compounds **12** and **20** were found to be strong vasodilatory molecules and are now are being tested in an in vivo study for their potential use in the treatment of strokes.

Acknowledgments

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16. Selected instrumental data for highly active compounds. Compound **12**: mp 162–164 °C; TLC (ethyl acetate/*n*-hexane = 1/1) $R_f = 0.31$; ^1H 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; compound **13**: mp 163–165 °C; TLC (ethyl acetate/*n*-hexane = 1/1) $R_f = 0.29$; ^1H 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; compound **20**: mp 177–179 °C; TLC (chloroform/methanol = 95/5) $R_f = 0.50$; ^1H 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.
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19. *Experimental procedures*: After anesthetizing 20 male white rabbits weighing 2–2.5 kg by enflurane inhalation, basilar arteries were isolated quickly under sterile conditions and placed in a physiological salt solution (PSS) that contained 137 mM NaCl, 5.4 mM KCl, 1.5 mM $CaCl_2$, 1 mM $MgCl_2$, 23.8 mM $NaHCO_3$, and 5.5 mM glucose. Residual blood was rinsed from the lumen and adherent connective tissue, fat, and adventitia were carefully removed. Basilar arteries were cut into rings (3 mm) in a dissecting chamber filled with PSS saturated with a mixture containing 95% O_2 and 5% CO_2. Basilar rings were mounted using a pair of stainless steel hooks under a resting tension of 0.8 g in an organ bath containing 15 ml of PSS, which was maintained at 37 °C and aerated with a mixture containing 95% O_2 and 5% CO_2. One of the hooks was connected to a force transducer (MLT050; ADInstruments, Colorado Springs, CO, USA), and the vascular tone was recorded using a Powerlab/400 on a chart 5.0 (ADInstruments). After equilibration for 40 min, each ring specimen was repeatedly exposed to the high-K^+ solution (50 mM), which was prepared by replacing NaCl with an equimolar concentration of KCl in PSS, until the responses became stable.
20. Structure of asymmetric alkyl or aryl amide curcumin mimics with weak vasodilatation effect on the basilar artery of the rabbits.