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Synthesis and biological evaluation of flavonoids as vasorelaxant agents

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Abstract—Several 5,7-dihydroxyflavone and quercetin 3-*O*-glycosides have been synthesized and evaluated for vasorelaxant activity. A log *P*–activity relationship amongst flavonoids was suggested.

Flavonoids are a group of polyphenolic compounds diverse in chemical structure and characteristic, they occur naturally in fruit, vegetables, nuts, seeds, flowers, and bark and are an integral part of the human diet. They have been reported to exhibit a wide range of biological effects, including antibacterial, antiviral, anti-inflammatory, antiallergic, and vasodilatory actions. In addition, flavonoids inhibit lipid peroxidation (LPO) platelet aggregation, capillary permeability, and fragility, and the activity of enzyme systems including *cyclo*-oxygenase and lipoxygenase.[1] There has been a great deal of interest due to flavonoids beneficial cardiovascular effects in humans.[2] Among them, quercetin **10** and rutin **5** have been shown to cause endothelium-dependent relaxation in the rat aorta,[3,4] but the synthesis and modification of which are surprisingly rarely reported however.[5,6] Our research approach is to use quercetin and rutin as lead compounds and modify the structure of these compounds to find more potent vasorelaxant agents. Herein, we described the synthesis of quercetin derivatives (or analogs) and their vasorelaxant actions in the isolated rat thoracic aorta rings.

The structures of the compounds utilized in this study are indicated in Table 1. Compounds **5**–**10** were purchased from commercial sources. Compound **11** was prepared as previously described.[7] The synthesis of compounds **1**–**4** is shown in Scheme 1. Ketal **17** was obtained through selective protection of quercetin with dichlorodiphenylmethane. Glycosylation of ketal took place completely at the position 3 using 1 equiv of K_2CO_3 as base in DMF that led to **18a**–**d**.[8] Cleavage of diphenylmethylene group was performed with hydrogenolysis catalyzed by 10% Pd/C. Compound **1** was afforded by removing the acetyl protecting group using CH_3OH and CH_3ONa. Compounds **2**, **3**, **4** were obtained according to the same procedure as described above. The large proton coupling (compound **1**, **2**, **3**, **4** $J_{1,2} = 7.2$, 7.7, 7.3, 5.2 Hz, respectively) of the anomeric proton demonstrated that target products **1**–**4** had β,β,β,β-configuration.

Compounds **12**–**16** were prepared from phloroglucinol (Scheme 2). Condensation of phloroglucinol with acetonitrile catalyzed by $ZnCl_2$ and followed by treatment with HCl gas provided 2,4,6-trihydroxyacetophenone **19**. Compound **19** reacted with an excess of aroyl chlorides **20a**–**e** in the biphasic system under tetrabutylammonium bromide to get the diarylpropane-1,3-diones **21a**–**e**. The cyclization of **21a**–**e** was carried out in refluxing 5% aqueous potassium carbonate in 6 h then treated with acetic acid leading to the expected compounds **12**–**16** in 57–69% yield.[9]

All compounds were evaluated for their vasorelaxant activities in the rat thoracic aorta rings against PE-induced contractions model.[4] After 10^{-6} mol/L phenylephrine (PE) induced steady contraction in endothelium-intact rings, flavonoids (36 μmol/L) were added. The tension was recorded, and the maximal relaxation (with standard error, SE) was calculated. Octanol–water partition coefficients (log *P*) were

Keywords: 5,7-Dihydroxyflavone; Quercetin 3-*O*-glycosides; Vasorelaxant activity.
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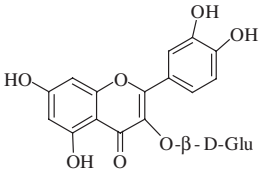
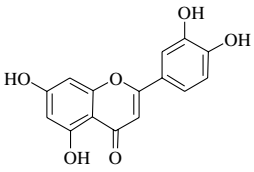
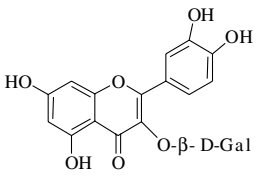
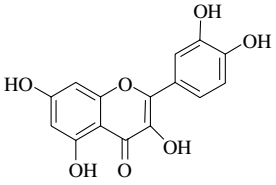
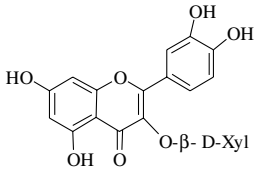
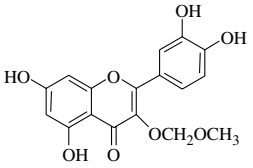
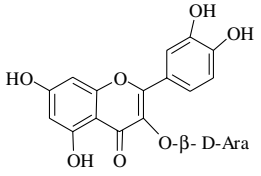
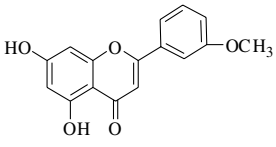
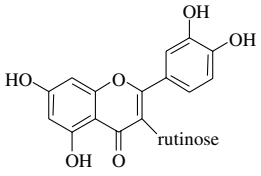
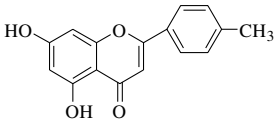
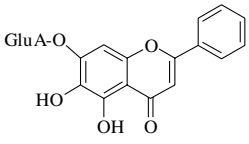
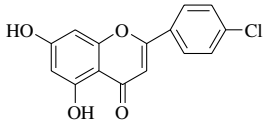
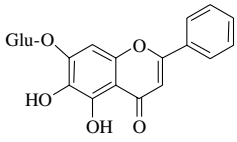
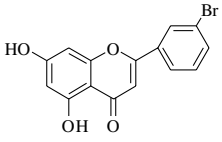
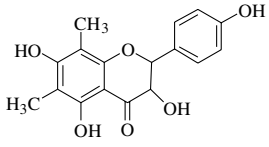
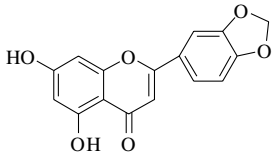
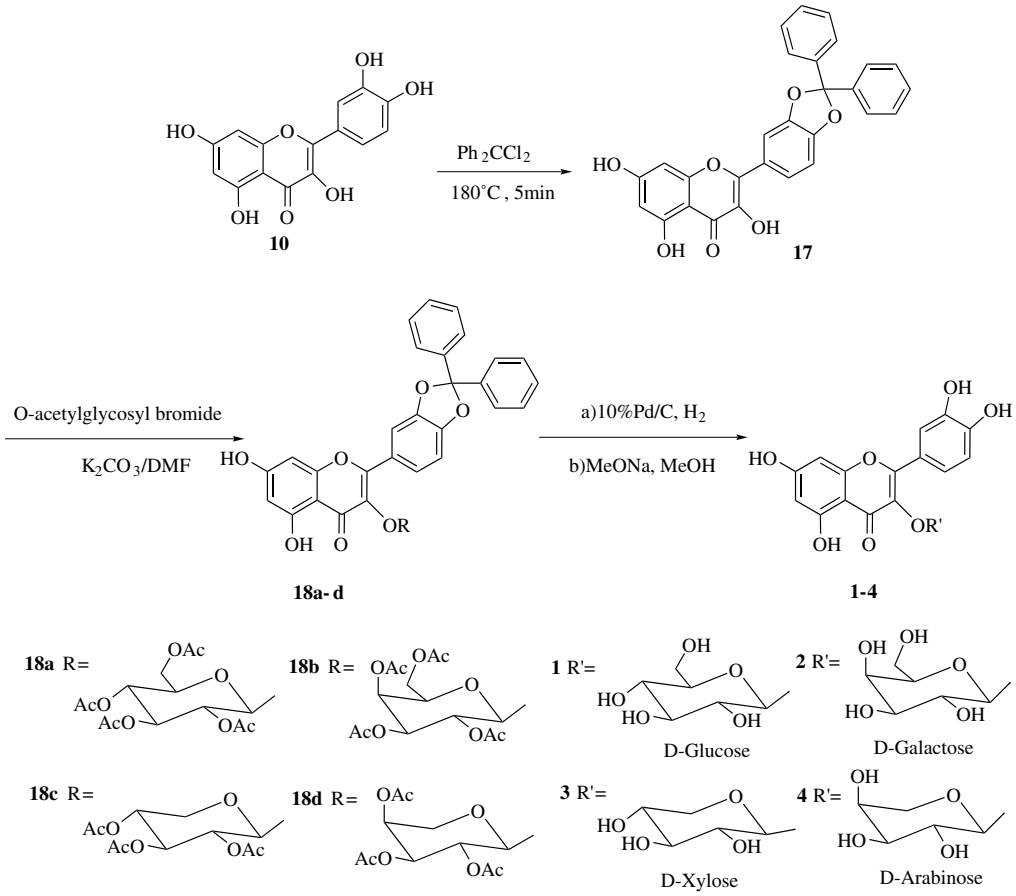
Table 1. Vasorelaxant effects for compounds **1**–**16** against PE-induced contractions in rat aortic rings

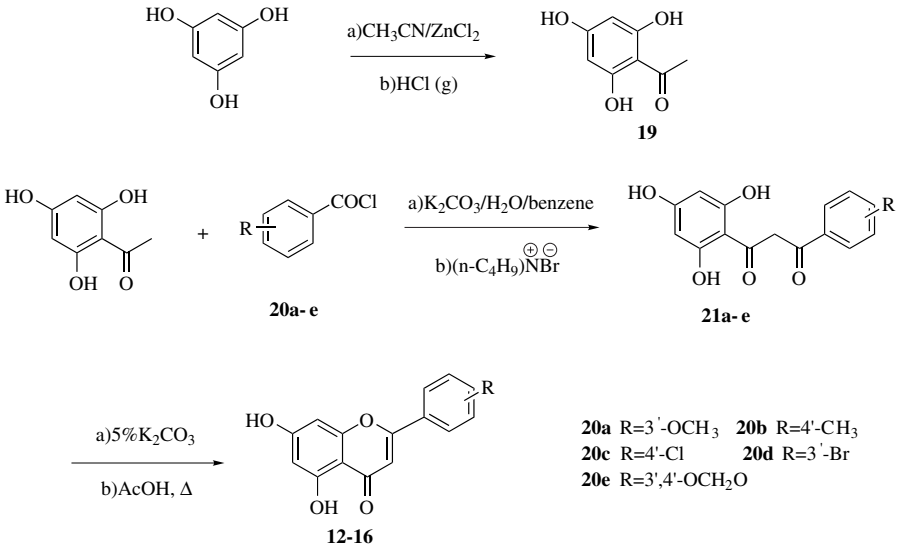
Compound	Structure	Maximal relaxation (%)	log *P*	Compound	Structure	Maximal relaxation (%)	log *P*
1		48.6 ± 2.9	1.28	**9**		70.2 ± 2.3	2.30
2		34.0 ± 4.7	1.26	**10**		45.9 ± 2.9	2.10
3		35.1 ± 3.2	1.44	**11**		71.6 ± 7.0	2.42
4		24.7 ± 4.3	1.45	**12**		80.8 ± 5.6	3.53
5		24.7 ± 2.7	1.18	**13**		77.2 ± 5.9	3.81
6		20.1 ± 2.3	1.74	**14**		92.7 ± 4.1	3.90
7		36.2 ± 3.0	1.50	**15**		95.0 ± 2.9	4.03
8		64.4 ± 3.5	2.99	**16**		91.3 ± 3.4	3.36

Values are expressed as mean ± SE ($n = 8$) $c = 36\,\mu mol/L$.

measured using a reversed-phase HPLC method.[10] The results are listed in Table 1. We found that **8**–**16** showed stronger vasorelaxant activity than **2**–**7**. Compound **15**, which has the maximal log *P* value, was identified as the most potent vasodilator activity. Although general structure–activity relationship of those compounds was not evident, from the data in Table 1, the following points were noteworthy: (1) The vasorelation actions of these compounds depended on log *P* values. In general, compounds had stronger activity with the augment of log *P* values. (2) Glycosylation of quercetin reduced the vasodilator activity. For example, compound **10** had stronger activity than **2**–**5**. (3) Comparing **10** with **11**, we found that 3-alkoxy substituted product **11** increased the vasodilator potency. (4) The lesser vasorelaxant activity of **10** in comparison to **9**, **12**–**15** suggested that the



Scheme 1.



Scheme 2.

presence of the –OH group in position 3 attenuated the vasorelaxant activity of the flavonoids.

In summary, we have designed and synthesized a series of quercetin derivatives or analogs.[11] These compounds exert vasodilatory effects that are related to the log *P* values. The presence of a sugar substitution reduces the vasorelaxant actions of these compounds.

References and notes

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11. Selected data for these compounds. Compound **4**, IR ν_{max} (cm^{-1}, KBr): 3382, 1656, 1604, 1507, 1499, 1442, 1358, 1300, 1199, 1166, 1069, 1016; ^1H NMR (400 MHz, DMSO-d_6): 3.77–3.20 (m, 5H, sugar-H), 4.55 (1H, s, sugar-OH), 4.68 (1H, s, sugar-OH), 5.22 (1H, s, sugar-OH), 5.27 (1H, d, $J = 5.2$ Hz, 1″-H), 6.19 (1H, d, $J = 2.0$ Hz, 6-H), 6.40 (1H, d, $J = 2.0$ Hz, 8-H), 6.84 (1H, d, $J = 8.4$ Hz, 5′-H), 7.50 (1H, d, $J = 2.2$ Hz, 2′-H), 7.66 (1H, dd, $J = 8.4$, 2.2 Hz, 6′-H), 9.16 (1H, s, 3′-OH), 9.74 (1H, s, 4′-OH), 10.88 (1H, s, 7-OH), 12.65 (1H, s, 5-OH); ^{13}C NMR (400 MHz, DMSO-d_6): 64.23 (5″-C), 66.01 (4″-C), 70.66 (3″-C), 71.58 (2″-C), 93.47 (8-C), 98.62 (6-C), 101.35 (1″-C), 103.82 (10-C), 115.23 (2′-C), 115.70 (5′-C), 120.82 (1′-C), 121.95 (6′-C), 133.66 (3-C), 144.89 (3′-C), 148.52 (4′-C), 156.20 (2, 9-C), 161.12 (5-C), 164.15 (7-C), 177.43 (4-C); MS-ESI: 434.1 (M^+-1). **15**, mp 269–271 °C; IR ν_{max} (cm^{-1}, KBr): 3443, 1658, 1618, 1569, 1500, 1426, 1356, 1168, 641; ^1H NMR (400 MHz, DMSO-d_6): 6.23 (1H, d, $J = 2.0$ Hz, 6-H), 6.56 (1H, d, $J = 2.0$ Hz, 8-H), 7.07 (1H, s, 3-H), 7.51–7.55 (1H, m, 5′-H), 7.80 (1H, d, $J = 8.8$ Hz, 6′-H), 8.08 (1H, d, $J = 8.0$ Hz, 4′-H), 8.27 (1H, s, 2′-H), 10.95 (1H, s, 7-OH), 12.76 (1H, s, 5-OH); MS (EI, 70 ev) m/z: 332 (M^+).