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Synthesis and fluorescent study of 5-phenyl furocoumarin derivatives as vasodilatory agents

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ABSTRACT

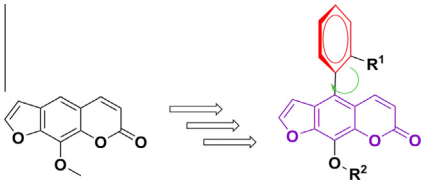
Two series of 5-phenyl furocoumarin derivatives were designed and prepared based on our previous research. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectra. Furthermore, they were screened for their vasodilatory activity on the mesenteric artery of Sprague-Dawley rats, and they all presented with moderate vasodilatory activity. Fluorescent properties of the target compounds were tested in methanol. The fluorescence variation of **4a** was investigated in different solvents, various pH and the migration time was determined. All results indicated that this type of fluorescent compound can be used as vasodilatory agents and probes simultaneously after further structural modifications.

Hypertension is increasing in prevalence worldwide due to aging of the population and rising rates of obesity.[1] Although novel agents and channelopathy for the treatment of hypertension have made substantial progress,[2–5] hypertension remains an incurable disease. Because vasodilatory capacity damnification is a significant hallmark of hypertension, vascular studies have become an interesting field for vasodilatory agents.

Furocoumarins form a large class of naturally occurring compounds, which possess surprising pharmacological activity, optical properties and promising therapeutic prospects.[6–14] During the search for novel furocoumarin-based potent antihypertensive agents, we developed a number of furocoumarin derivatives and screened them for potent vasodilatory activity, vascular remodeling effects and fluorescent activity.[15–19] Theoretical studies reveal that geometric structures of diphenyl–furocoumarin derivatives are altered following the change of the ortho-substituent of phenyl. The dihedral angle between furocoumarin and phenyl gradually increases with the change of F, Cl, Br, CF_3, which is consistent with their vasodilatory activity. The dihedral angle is almost 90° with the CF_3 substituent. This suggests that the dihedral angle between furocoumarin (marked in purple) and phenyl (marked in red) may effect the vasodilatory activity. Further theoretical studies show that the substituents of methoxycarbonyl and ethoxycarbonyl could afford a 90° dihedral angle. Moreover, introduction of an ester group to the phenyl could change the electron distribution, which may enhance the conjugation, contributing to the fluorescence of the molecule.[20,21]

Based on these observations, we developed two series of compounds (Scheme 1) to enhance the structural diversity and fluorescence potency. The docking results confirm our hypothesis of the geometric structure of the target compounds. Activity evaluation indicates all the target compounds possess favorable vasodilatory activity and optical properties.

The general methods for synthesis of compounds **4a**–**5c** are summarized in Scheme 2. The option of methoxycarbonyl and ethoxycarbonyl for R^1 was based on theoretical study. The R^2 were selected based on our previous studies in consideration of bioactivity and fluorescence. Compounds substituted with pyrrolidyl, morpholinyl and piperidyl possessed high bioactivity and fluorescence compared with other substituents, as previously reported. Compound **4d** was synthesized to investigate the substitution effect on bioactivity. The reaction were monitored by TLC under



Scheme 1. Design strategy of target compounds.

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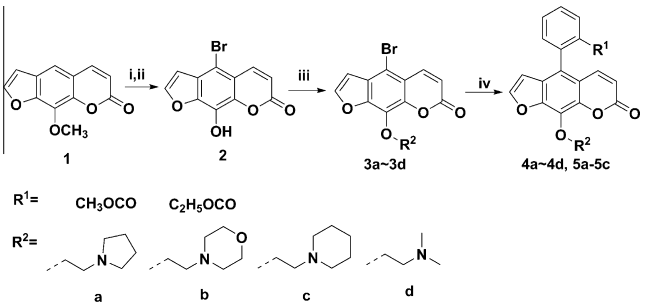
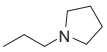
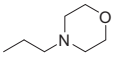
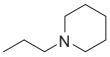
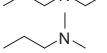
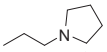
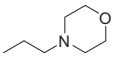
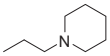


Scheme 2. Synthetic route of target compounds. Reagents and conditions: (i) Br_2, AcOH, 0 °C–rt; (ii) BBr_3, CH_2Cl_2, −5 °C to rt; (iii) K_2CO_3, acetone, reflux; (iv) Na_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O (v/v = 3:1).

365 nm because compounds **4a**–**5c** showed favorable primary fluorescence.

The vasodilator activities of the synthesized derivatives were evaluated on the in vitro rat mesenteric artery rings against a K^+-induced contractions model, and the results were summarized in Figure 1 and Table 1. Generally, all novel designed compounds were more effective than the parent scaffold. Compounds with an ethoxycarbonyl substituent had higher vasodilator activity than that of methoxycarbonyl, as shown in compound **4a** compared with **5a**, **4b** compared with **5b**, **4c** compared with **5c**, separately. This may be because the ethoxycarbonyl group contributes more electrons to the molecule, and the larger substituent favors the forming of a vertical dihedral angle. The result also supports our hypothesis. The pentacyclic pyrryl in **4a** was replace with a larger moiety piperidyl to yield **4c**, and the vasodilator activities were simultaneously improved. The same trend is observed in **5a** and **5c**. However, **4d** exhibited higher activity than **4a** and **5a**, which suggests that a flexible substituent is beneficial for activity. Altering the piperidyl of **4c** to an oxygen-contained isostere morpholinyl yielded the more effective compound **4b**, which was consistent with **5b**. This result may be because an oxygen atom in the morpholinyl is beneficial for forming a hydrogen bond with the target protein. In conclusion, the lipophilic substituent ethoxycarbonyl in the R^1 position enhances the bioactivity as well as the morpholinyl moiety in R^2 position. Compound **5b** with a pEC_{50} = 5.81 ± 0.13 was the most efficient agent.

Table 1
Structures and in vitro vasodilator activity of title compounds

Compd	R^1	R^2	pEC_{50} (μM) (n = 6)	E_{max} (%)
4a	CH_3OCO		4.71 ± 0.03	102.2 ± 2.22
4b	CH_3OCO		5.59 ± 0.06	100.1 ± 2.44
4c	CH_3OCO		5.35 ± 0.07	115.9 ± 3.04
4d	CH_3OCO		5.27 ± 0.01	101.5 ± 0.05
5a	C_2H_5OCO		5.15 ± 0.01	100.1 ± 0.10
5b	C_2H_5OCO		5.81 ± 0.13	113.3 ± 1.17
5c	C_2H_5OCO		5.38 ± 0.03	113.4 ± 6.45
Imperatorin	—	—	4.95 ± 0.14	85.6 ± 0.40
Verapamil	—	—	7.51 ± 0.09	95.8 ± 1.92

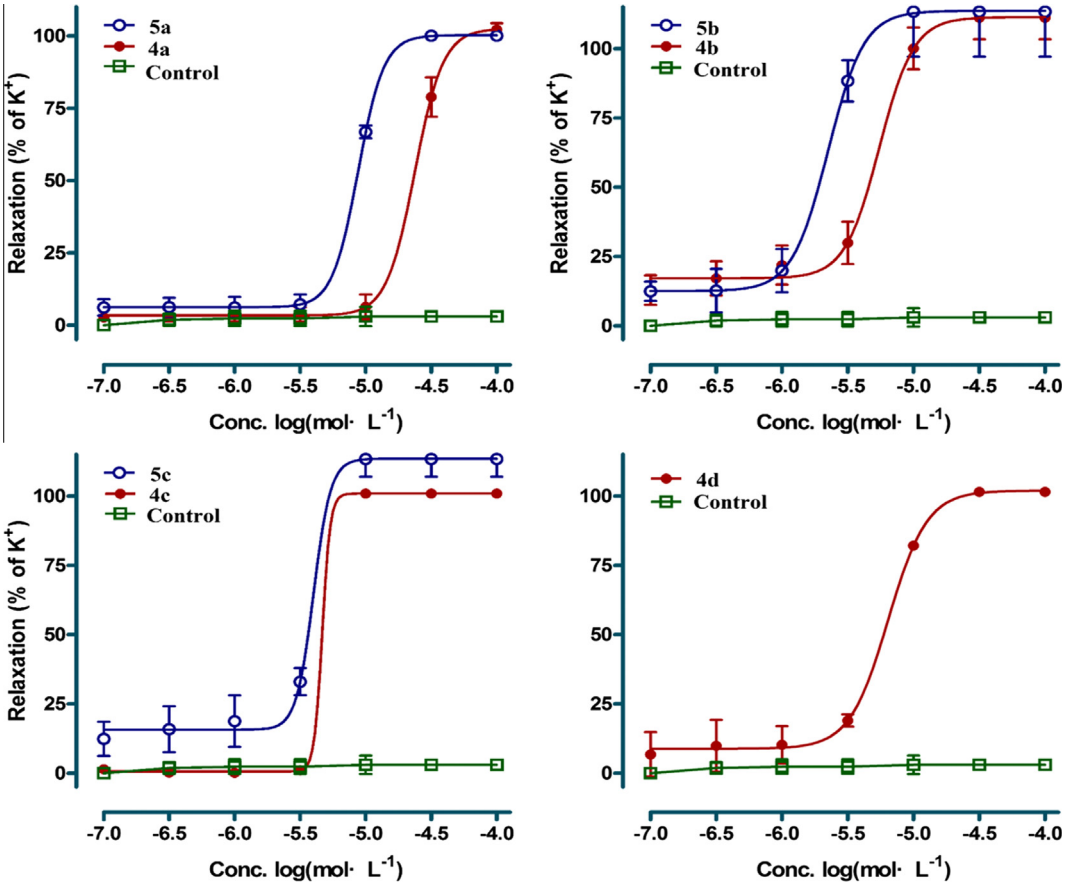


Figure 1. In vitro vasodilator activity induced by title compounds.