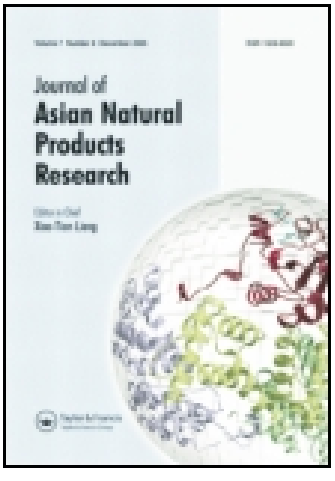

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ganp20

Design, synthesis and evaluation of 9-hydroxy-7H-furo[3,2-g]chromen-7-one derivatives as new potential vasodilatory agents

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Published online: 08 Jan 2014.

To cite this article: Cheng Wang, Tao Wang, Nan Zhou, Xiao-Yan Pan & Huai-Zhen He (2014) Design, synthesis and evaluation of 9-hydroxy-7H-furo[3,2-g]chromen-7-one derivatives as new potential vasodilatory agents, Journal of Asian Natural Products Research, 16:3, 304-311, DOI: 10.1080/10286020.2013.874345

To link to this article: http://dx.doi.org/10.1080/10286020.2013.874345

Journal of Asian Natural Products Research, 2014
Vol. 16, No. 3, 304–311, http://dx.doi.org/10.1080/10286020.2013.874345

Design, synthesis and evaluation of 9-hydroxy-7H-*furo*[3,2-g]chromen-7-one derivatives as new potential vasodilatory agents

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(*Received 7 October 2013; final version received 8 December 2013*)

Two new 9-hydroxy-7H-*furo*[3,2-g]chromen-7-one derivatives were designed, synthesized and evaluated for their *in vitro* vasodilatory activity. The structures of two compounds were elucidated by infrared, ^{1}H NMR, and mass spectral data. The *in vitro* pharmacological evaluation indicated that both of them possessed well vasodilatory activity compared with imperatorin. The molecule docking also showed two target compounds docked well with L-calcium channel (PDB code: 3G43). The result suggested that they would be potential vasodilatory agents for hypertension.

Keywords: 9-hydroxy-7H-*furo*[3,2-g]chromen-7-one; vasodilatory activity; synthesis; molecule docking

1. Introduction

Hypertension is the most common chronic disease, as well as the main risk factor for cardio-cerebrovascular diseases. There are five major categories of hypertension drugs [1], including diuretics [2], β adrenergic receptor blocker [3], calcium channel blockers [4], angiotensin-converting enzyme inhibitors, and vascular angiotensin II receptor blockers [5]. Thereinto, calcium channel blockers are a very important class of antihypertensive drugs [6,7]. The prototypical agents of this group are diltiazem, nifedipine, and verapamil. The properties of these drugs and the mechanisms by which they function have been extensively reviewed during the past 30 years.

Imperatorin is a furocoumarin isolated from traditional Chinese herbs such as *Cnidium monnieri* Cuss or *Angelica dahurica* [8]. Its medical effects have been studied, such as anticonvulsant, anti-inflammatory, antitumor, antibacterial, and anticoagulant activities [9,10]. In our previous studies, we found that the mechanism of its vasodilatation activity was possibly involved with regulating the influx and release of calcium ions by inhibiting voltage-dependent calcium channel [11]. Homology modeling and docking studies indicated that imperatorin occupied the active binding site of L-type calcium channel [12]. However, the use of imperatorin was limited by its low activity and poor solubility [13,14]. Poor solubility is a major problem in the biological testing of compounds, which has made a challenge for *in vivo* studies of efficacy and pharmacokinetics [15]. Structure optimization of imperatorin by incorporating a nitrogen group in its molecule could improve the solubility and drug-like properties [16].

2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-amino-pentanenitrile (compound **5**) and 2-(3,4-dimethoxyphenyl)-2-isopropyl-5-methylamino-pentanenitrile (compound **6**) are two metabolites of verapamil [17]. Some studies indicated that they exhibited some activities [18]. Nitrogen atom was also contained in the two molecules.

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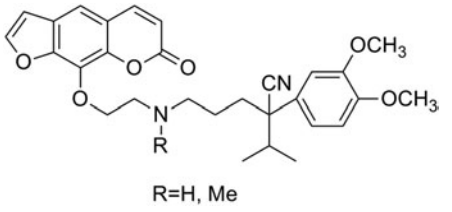


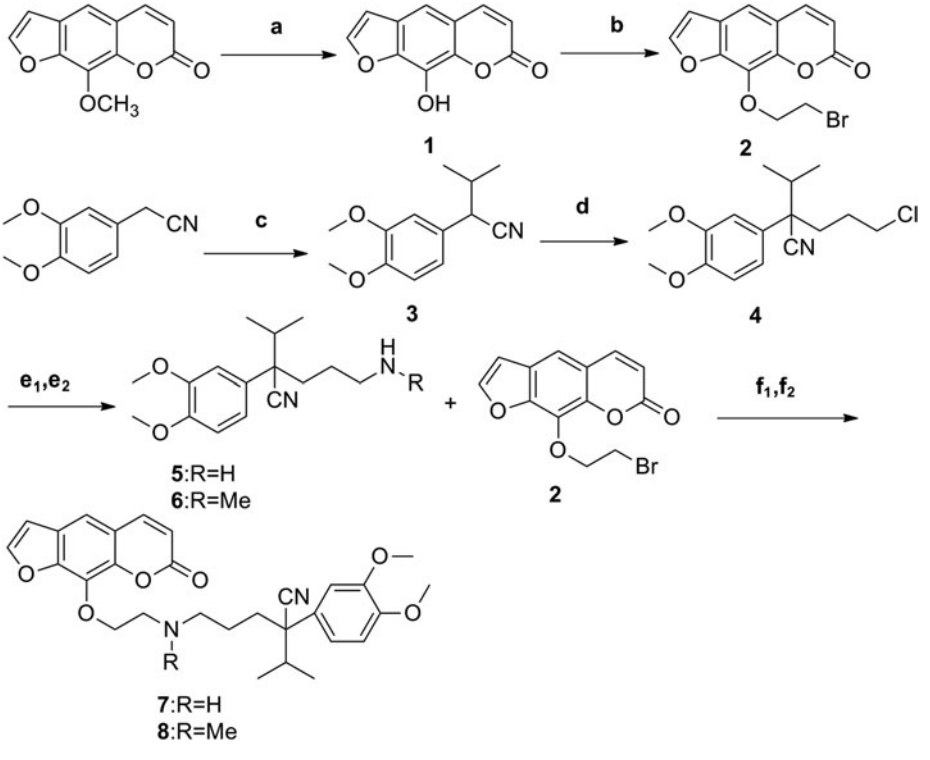
Scheme 1. Structures of target compounds.

We suppose that the combination of two compounds with 9-hydroxy-7H-*furo* [3,2-g]chromen-7-one will improve activity and solubility. Therefore, in this paper, we designed and synthesized two novel derivatives (Scheme 1). Their vasodilatory activity was evaluated by using three kinds of vascular models: renal artery (RA), brain artery (BA), and mesenteric artery (MA).

2. Results and discussion

2.1 Chemistry

The synthesis route being utilized in the preparation of the imperatorin derivatives is shown in Scheme 2. Compound **1** was obtained by demethylation of xanthotoxin with boron tribromide at low temperature. The key intermediate compound **2** can be prepared by alkylation of compound **1** with 1,2-dibromoethane. For alkylation of 2-(3,4-dimethoxyphenyl) acetonitrile with 2-bromopropane using dimethyl sulfoxide (DMSO) as solvent, enough solvent could promote the reaction accomplishment. Compound **4** was also got by alkylation of compound **3**. The amination of compound **4** with aqueous ammonia afforded compound **5**. During the reaction, aqueous ammonia was re-added in order to get more targeted



Scheme 2. Synthesis route of target compounds. Reagents and conditions: (a) CH_2Cl_2, BF_3, $-5°C \sim 0°C$, 4 h; (b) K_2CO_3, $BrCH_2CH_2Br$, CH_3COCH_3, reflux, 12 h; (c) NaOH, 2-bromopropane, DMSO, Rt, 2 days; (d) $NaNH_2$, 1-bromo-3-chloropropane, toluene, reflux, 2 days; (e_1) $NH_3{\cdot}H_2O$, KI, EtOH, H_2O, 50°C, 5 days; (e_2) NH_2Me, KI, EtOH, H_2O, 50°C, 3 days; (f_1) K_2CO_3, MeCN, reflux, 3 days; (f_2) K_2CO_3, MeCN, reflux, 3 days.

compound. The higher temperature (70°C) could increase the rate of reaction. During preparation of compound **7**, KI was added to increase the rate and productivity of reaction. We supposed that the iodine atom would substitute the chlorine atom. As a result, the reactivity was improved. The syntheses of compound **6** and compound **8** similar to those of compound **5** and compound **7**, respectively, but they showed higher rate and yield. The reason mainly was the secondary amine showed higher reactivity compared with the primary amine.

Before we designed this pathway, we had explored another way. Compound **2** reacted separately with aqueous ammonia and methylamine. The reaction products reacted with compound **4** will gain the targets, but the productivity of this pathway was lower than the latter one.

2.2 Pharmacology

Vasodilatory activities of imperatorin derivatives were evaluated in three kinds of vascular model, RA, BA, and MA. Imperatorin was used as the positive control. All the tested compounds promoted relaxation in a dose-dependent manner and their maximal effects were observed at 100 μM. The vasodilatory activity of imperatorin and its derivatives are shown in Table 1 and Figure 1.

According to the results, we found that these compounds exhibited stronger vasorelaxant activity, respectively, than that of imperatorin in the three kinds of vascular model, especially in the RA and MA, comparing compounds **7** ($pEC_{50} = 5.76$, 6.42) and **8** ($pEC_{50} = 5.99$, 6.01) with imperatorin ($pEC_{50} = 4.95$, 5.20). The target compounds exhibited much higher activity.

Although they gained obviously improved activity than imperatorin, they still showed lower activity compared with the positive drug, verapamil [19]. But a further study of structural optimization has commenced in our team to gain more derivatives which would be more effective on vasodilatory activity.

2.3 Docking

Our previous studies indicated that the mechanism of antihypertensive effect of imperatorin possibly was involved in regulating Ca^{2+} influx and release by inhibiting voltage-dependent calcium channel. Molecule docking study was performed to investigate the binding mode of these compounds with L-calcium channel (PDB code: 3G43) [20]. Molecular docking was carried out using the Sulflex-Dock Mode of Sybyl-X program package (New Tripos International, St. Louis, USA). The small molecules and the X-ray crystal structure of L-calcium channel (PDB code: 3G43) were imported.

Compounds **7** and **8** were used to perform docking, and the docking results are shown in Figure 2. Figure 2(A) shows that compound **7** docked well with 3G43. Oxygen atom in furan nucleus forms two hydrogen bonds, respectively, with SER^{81} and LYS^{94} residues, and the bond lengths are 2.13 and 2.30 Å, respectively. Figure 2 (B) shows that compound **8** docked better with 3G43 than compound **7**. Oxygen atom in furan nucleus and oxygen atom

Table 1. Vasodilatory activity in RA, BA, and MA.

		RA		BA		MA	
Compounds	*n*	pEC_{50}	E_{max} (%)	EC_{50} (μM)	pEC_{50} (%)	E_{max} (%)	EC_{50} (μM, %)
Imperatorin	6	4.95 ± 0.14	85.6 ± 4.0	5.26 ± 0.15	65.0 ± 4.2	5.20 ± 0.09	96.0 ± 1.0
Compound **7**	6	5.76 ± 0.01	98.3 ± 2.4	5.52 ± 0.43	92.1 ± 3.2	6.42 ± 0.10	98.5 ± 2.6
Compound **8**	6	5.99 ± 0.10	117 ± 4.6	5.94 ± 0.11	98.3 ± 4.8	6.01 ± 0.16	104 ± 2.0

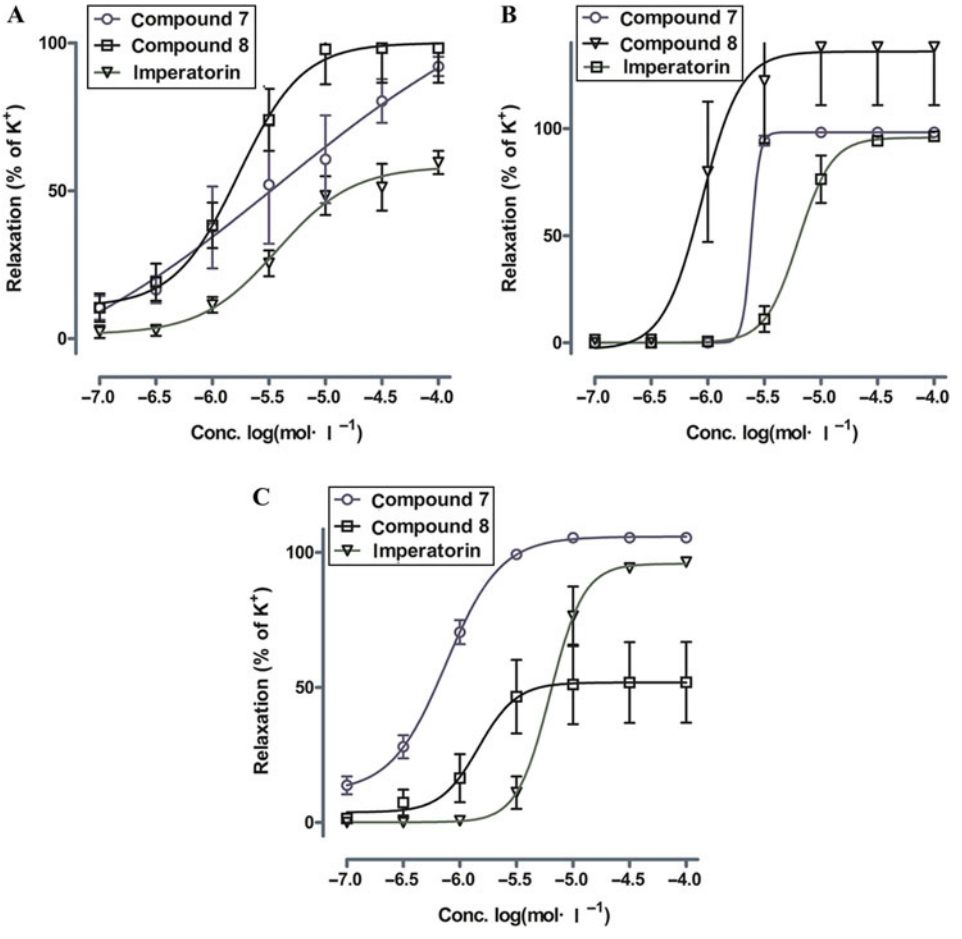


Figure 1. Vasodilatory activity in RA (A), BA (B), and MA (C).

connected to benzene ring form two hydrogen bonds, respectively, with LYS^{94} residue, and the bond lengths were 2.06 and 1.96 Å, respectively. Oxygen atom in lactone ring and oxygen atom connected to benzene ring form two hydrogen bonds, respectively, with HIS^{107} residue, and the bond lengths were 2.09 and 2.51 Å. Oxygen atom of carbonyl formed a hydrogen bond with THR^{110} residue, and the bond length was 2.54 Å. Oxygen atom of methoxyl formed a hydrogen bond with LYS^{77} residue, and the bond length was 1.94 Å.

The molecular modeling study of imperatorin is shown in Figure 2(C). The result obviously indicated that the mode of imperatorin with amino acid residues was similar to compound **8**. The bond lengths were separately 2.00, 1.93, 2.05, 2.45, and 2.34 Å. These observations, together with experimental results, provided a good explanation for their vasodilatory activity.

3. Experimental

3.1 General experimental procedures

Melting points were determined on a Beijing micro-melting point apparatus (Dongfang Annuo Co., Ltd., Beijing, China). The infrared (IR) spectra were recorded on a Shimadzu FT-IR 440 spectrometer in the 4000–500 cm^{-1} range (Shimadzu, Tokyo, Japan). ^1H NMR

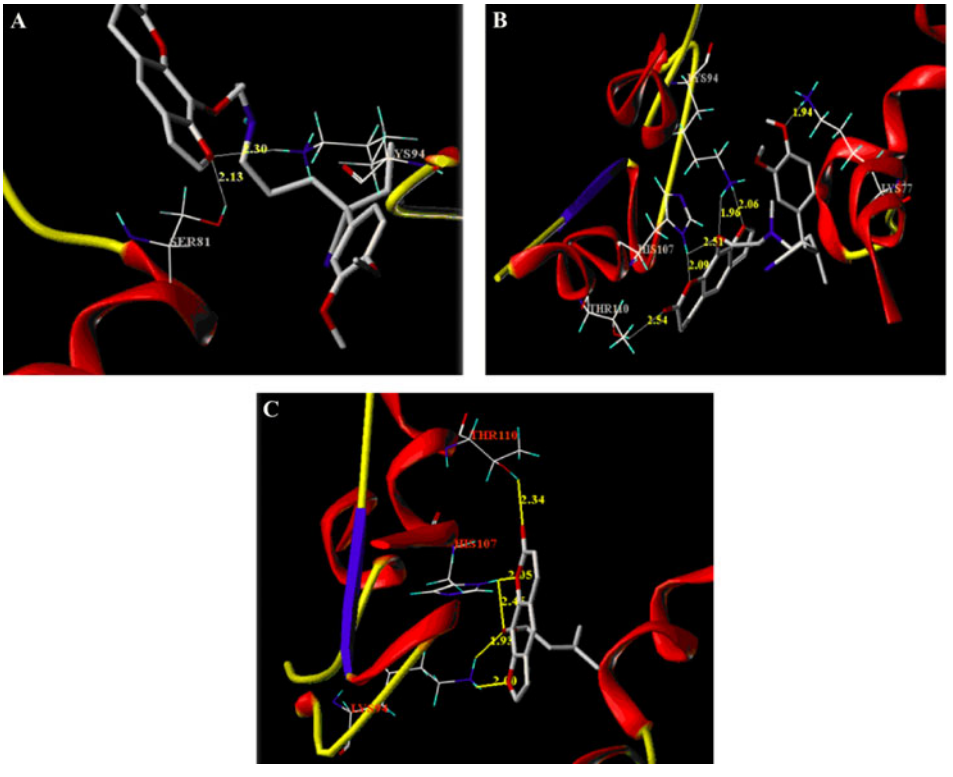


Figure 2. Binding mode of compounds (A: **7**), (B: **8**), and (C: imperatorin) to L-calcium channel (PDB code: 3G43).

spectra were recorded on a Bruker AVANCF 400 MHz instrument in $CDCl_3$ solution with TMS as internal standard (Bruker, Zurich, Switzerland). Mass spectra were performed on a Shimadzu GC-MS-QP2010 instrument (Shimadzu). The HR-ESI-MS data were obtained on a Bruker micrOTOF-Q II spectrometer (Bruker, Karlsruhe, Germany). All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Solvents were purified before use according to standard procedures. All reactions were monitored by thin layer chromatography on 0.25-mm silica gel plates (GF-254) and visualized with UV light. All other reagents were commercially available and used as received. The syntheses of compounds **1**, **3**, and **4** were based on the references [21–23].

3.2 9-Hydroxy-7H-furo[3,2-g] chromen-7-one (1)

Xanthotoxin (1.00 g, 4.50 mmol) was dissolved in dry dichloromethane (20 ml) and stirred for 15 min under the ice–salt bath. A solution of boron tribromide (2 ml) in dichloromethane (20 ml) was dropped in the mixture. After stirring for 4 h under nitrogen at 0°C, the mixture was poured slowly into saturated sodium bicarbonate solution under stirring. After stirred for 1 h, the product was obtained by filtering, which was washed with H_2O and dried. Yield: 0.85 g (91%). M.p.: 249–251°C [21]; IR (KBr): ν_{max} 3294 (O–H), 1697 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, $J = 9.6$ Hz, 1H), 8.04 (d, $J = 2.4$ Hz, 1H), 7.42 (s, 1H), 7.01 (d, $J = 2.4$ Hz, 1H), 6.35 (d, $J = 9.6$ Hz, 1H). MS: *m/z* 201.9 $[M]^+$.

3.3 9-(2-Bromoethyl)-7H-furo[3,2-g] chromen-7-one (2)

Anhydrous kalium carbonicum (3.04 g, 22 mmol) was added to a solution of xanthotoxol (2.02 g, 10 mmol) in dry acetone (240 ml). After stirring for 30 min, 1,2-dibromoethane was added. The reaction mixture was heated at reflux temperature for 12 h. After cooling, the product was obtained by filtering, then washed with H_2O and dried. Yield: 2.78 g (91%). M.p.: 148–149°C; IR (KBr): ν_{max} 1697 (C═O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, $J = 9.6$ Hz, 1H), 7.72 (s, 1H), 7.41 (s, 1H), 6.84 (s, 1H), 6.39 (d, $J = 9.2$ Hz, 1H), 4.76 (t, $J = 6.4$ Hz, 2H), 3.75 (t, $J = 6.4$ Hz, 2H). MS: *m/z* 307.9 $[M]^+$.

3.4 2-(3,4-Dimethoxyphenyl)-3-methyl-butanenitrile (3)

Sodium hydroxide aqueous solution (50%, 80 ml) and 2-bromopropane (2.83 ml, 29.89 mmol) were added into a solution of 3,4-dimethoxyphenyl acetonitrile (3.54 g, 20.00 mmol) in DMSO (20 ml). After stirring for 2 days at ambient temperature, ethyl acetate (100 ml) was added. The organic layer was washed with brine (2 × 50 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/ether (1:2). Yield: 3.63 g (83%), white solid. M.p.: 48–50°C; IR (KBr): ν_{max} 2964 (C–H), 1456 (C–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, $J = 0.8$ Hz, 2H), 6.81 (s, 1H), 3.94 (s, 6H), 3.62 (d, $J = 6.8$ Hz, 1H), 2.08–2.16 (m, 1H), 1.06 (d, $J = 6.8$ Hz, 6H). MS: *m/z* 219.2 $[M]^+$.

3.5 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-chloro-pentanenitrile (4)

A solution of compound **3** (3.63 g) in toluene (100 ml) was dropped in the mixture of sodium amide (2.95 g) and toluene (50 ml) at reflux temperature under N_2. After stirring for 2 h, 1-bromo-3-chloropropane was added at 50°C. The reaction mixture was heated at reflux for 2 days. After cooling, H_2O (20 ml) was added and aqueous phase was extracted with toluene (10 ml). The combined organic phase was washed with brine (2 × 50 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/ether (1:3). Yield: 4.89 g (81%), yellow liquid. IR (KBr): ν_{max} 2916 (C–H), 1463 (C–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.83 (d, $J = 3.6$ Hz, 2H), 3.86 (s, 6H), 2.86–2.92 (m, 2H), 2.55–2.61 (m, 2H), 2.12 (t, $J = 6.8$ Hz, 1H), 2.08–2.10 (m, 2H), 1.16 (d, $J = 6.8$ Hz, 6H); MS: *m/z* 295.1 $[M^+]$.

3.6 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-amino-pentanenitrile (5)

Aqueous ammonia (100 ml) was added three times into a mixture of compound **4** (13.9 g), ethanol (100 ml), and potassium iodide (9.24 g). The reaction mixture was heated at 50°C for 5 days. After cooling, the mixture was evaporated *in vacuo* and extracted with ethyl acetate (50 ml). The organic phase was washed with H_2O (4 × 50 ml) and the combined organic phase was evaporated *in vacuo*. Ethyl acetate was added to the residue, and after stirred for 4 h, the product was obtained by filtering and dried. Yield: 6.54 g (50%), white solid. M.p.: 175–179°C; IR (KBr): ν_{max} 3384 (N–H), 1673 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.05 (s, 2H), 2.05–2.15 (m, 2H), 1.83 (s, 2H), 1.48 (s, 1H), 1.20 (d, $J = 6.0$ Hz, 3H), 0.79 (d, $J = 6.4$ Hz, 3H). MS: *m/z* 276.1 $[M]^+$.

3.7 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-methylamino-pentanenitrile (6)

After stirring at 70°C for 3 days, the reaction mixture of methylamine water

solution (10 ml), compound **4** (3.67 g), and ethanol (100 ml) was evaporated *in vacuo*. Ethyl acetate was added to the residue. After stirred for 4 h, the product was obtained by filtering and dried. Yield: 2.63 g (73%), white solid. M.p.: 157–158°C; IR (KBr): ν_{max} 3421 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 2.89 (s, 2H), 2.53 (d, $J = 4.8$ Hz, 3H), 2.08–2.14 (m, 2H), 1.83 (s, 2H), 1.48 (s, 1H), 1.22 (d, $J = 6.8$ Hz, 3H), 0.79 (d, $J = 6.8$ Hz, 3H). MS: *m/z* 290.3 $[M]^+$.

3.8 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-((2-((7-oxo-7H-furo[3,2-g]chromen-9-yl)oxy)ethyl)amino) pentanenitrile (7)

After stirring for 0.5 h, potassium carbonate (13.6 g) was added to the mixture of compound **5** (7.41 g), compound **2** (8.1 g), and acetonitrile (450 ml), then the reaction mixture was stirred under reflux for 3 days. After cooling, the mixture was evaporated *in vacuo*. H_2O (100 ml) and ethyl acetate (100 ml) were added. The aqueous phase was extracted with ethyl acetate (4 × 50 ml), and the combined organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/-ether (2:1) and EtOAc/methanol (5:1). Yield: 4.13 g (31%), white solid. M.p.: 81–84°C. IR (KBr): ν_{max} 3531 (N–H), 1259 (C–O–C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, $J = 9.6$ Hz, 1H), 7.68 (s, 1H), 7.40 (s, 1H), 6.95–6.99 (m, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 6.83–6.84 (m, 1H), 6.37 (d, $J = 9.6$ Hz, 1H), 4.60–4.62 (m, 2H), 3.89 (s, 6H), 3.09 (s, 2H), 2.87 (s, 2H), 2.07–2.11 (m, 2H), 1.98 (s, 2H), 1.35–1.37 (m, 1H), 1.20 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H). MS: *m/z* 503.95 $[M]^+$; HR-ESI-MS: *m/z* 505.2349 $[M + H]^+$ (calcd for $C_{29}H_{33}N_2O_6$, 505.2333).

3.9 2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-(methyl-(2-((7-oxo-7H-furo[3,2-g]chromen-9-yl)oxy)ethyl)amino) pentanenitrile (8)

After stirring for 0.5 h, potassium carbonate (3.25 g) was added to the mixture of compound **6** (1.58 g), compound **2** (1.53 g), and acetonitrile (200 ml) and then the reaction mixture was stirred under reflux for 3 days. After cooling, the mixture was evaporated *in vacuo*. H_2O (100 ml) and ethyl acetate (100 ml) were added. The aqueous phase was extracted with ethyl acetate (4 × 50 ml), and the combined organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/ether (2:1) and EtOAc/chloroform (3:2). Yield: 1.50 g (57%), white solid. M.p.: 127–128°C. IR (KBr): ν_{max} 1149 (C–N), 1103 (C–N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, $J = 9.6$ Hz, 1H), 7.70 (s, 1H), 7.44 (s, 1H), 6.98 (d, $J = 11.6$ Hz, 1H), 6.93 (s, 1H), 6.87 (d, $J = 11.2$ Hz, 1H), 6.84 (s, 1H), 6.38 (d, $J = 9.6$ Hz, 1H), 4.74 (s 2H), 3.92 (s, 3H), 3.89 (s, 3H), 2.51 (s, 3H), 2.32–2.35 (m, 2H), 2.12–2.16 (m, 2H), 1.86 (s, 2H), 1.67 (s, 2H), 1.44–1.48 (m, 1H), 1.20 (d, $J = 6.0$ Hz, 3H), 0.78 (d, $J = 6.0$ Hz, 3H). MS: *m/z* 518.2 $[M]^+$; HR-ESI-MS: *m/z* 519.2518 $[M + H]^+$ (calcd for $C_{30}H_{35}N_2O_6$, 519.2490).

3.10 Pharmacological evaluation

Vascular model was prepared from RA, BA, and MA of male Sprague–Dawley rats. The contraction studies were performed following the general procedure described in the literature [24]. Isometric contractions induced by phenylephrine (PE) (3 μM) were obtained after an equilibration period of 2 h. Cumulatively, increasing concentrations of the tested compounds were added to the bath at 15–20 min intervals when contraction of the tissue in response to this vasoconstrictor

agent had stabilized. Control tissues were simultaneously subjected to the same procedures with adding the vehicle without the compounds. The imperatorin-induced maximal relaxation (E_{max}) in artery rings was calculated as a percentage of the contraction in response to PE (3 μM) [25]. All data were expressed as mean ± SEM. The half-maximum effective concentration (EC_{50}) was defined as the concentration of the imperatorin that induced 50% of maximum relaxation from the contraction elicited by PE and was calculated from the concentration–response curve by nonlinear regression (curve fit) using GraphPad Prism.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Nos 81202494, 30730110) and the Intramural Research Foundation of Xi'an Jiaotong University (Grant No. xjj2012048).

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