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Discovery of novel 3-benzylquinazolin-4(3*H*)-ones as potent vasodilative agents

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ABSTRACT

In the present study, a series of 3-benzylquinazolin-4(3*H*)-ones were synthesized and characterized. Their vasodilative effects were evaluated by wire myograph on isolated rat mesenteric arterial ring induced contraction with 60 mM KCl. The SAR of target compounds was discussed preliminarily. Among these compounds, **2a** and **2c** displayed potent vasodilatation action and could compete significantly the rat mesenteric arterial rings induced contraction with phenylephrine. Compounds **2a** and **2c** were further tested for their antihypertensive effects in SHR by oral administration. The results indicated that **2a** and **2c** could reduce significantly both diastolic and systolic blood pressure. Moreover, **2c** displayed antihypertensive effect in a dose dependent manner, and could maintain the effects for 6 h at a dosage of 4.0 mg/kg. These findings suggest that the title compounds are novel vasodilative agents, representing a novel series of promising antihypertensive agents.

The chemistry and biological study of quinazoline derivatives have been an interesting field in medicinal chemistry for a long time. Quinazoline and quinazolin-4(3*H*)-one have been regarded as two important drug scaffolds in drug discovery. The compounds derived from quinazoline or quinazolin-4(3*H*)-one exhibit a broad spectrum of biological activities, such as antitumor, antimicrobial, antifungal, anti-inflammatory, anticonvulsant and antidiabetic activities. Several 4-arylaminoquinazoline derivatives, including gefitinib, erlotinib and lapatinib, were studied as EGFR-TK inhibitors and launched successfully to treat cancer clinically.[1,2] 4,6-Disubstituted quinazoline derivatives were identified as PI3K inhibitors and anticancer agents.[3] The progress on the biological activities of quinazoline and quinazolin-4(3*H*)-one derivatives have been reviewed, respectively.[4–7]

In recent two years, the novel quinazoline and quinazolin-4(3*H*)-one derivatives were reported and their new activities were described. Russu reported that 2-phenyl-6-substituted quinazoline derivatives could inhibit NF-κB function, and the growth of cancer cells.[8] Mowafy described the design, synthesis and antiproliferative activity of 4,6-quinazolinediamines as potent EGFR-TK inhibitors.[9] de Esch discovered that 4-amino-2-(4-methylpiperazin-1-yl)quinazoline is a highly potent 5-HT_3 receptor ligand.[10] Huggan identified that 3-substituted quinazoline-2,4-diones are potent inhibitors of African trypanosomiasis.[11] Sasmal discovered that 2,4,6-trisubstituted quinazolines are melanin concentrating hormone receptor 1 (MCHR1) antagonists and discussed the SAR in detail.[12] Compared with quinazoline derivatives, the research on quinazolin-4(3*H*)-one is relatively less active. Some quinazolin-4(3*H*)-one derivatives display better activity than saturated drugs and could become new drugs in future. Balzarini reported that 3-(2-hydroxybenzylideneamino)-2-(4-chlorophenyl)-quinazoline-4(3*H*)-one is antiviral agent.[13] Saravanan discovered that 2-methyl-3- substituted-quinazolin-4(3*H*)-one displays analgesic activity.[14] Wang discovered that (*E*)-3-[2-arylideneaminoethyl]-2-[4-(trifluoromethoxy)-anilino]quinazoline-4(3*H*)-one derivatives exhibit potent antifungal activities.[15] Similarly, the quinazolin-4(3*H*)-one attached a triazole fragment at 3-position exhibited broad-spectrum antifungal activity against resistant and emerging pathogens.[16,17] Ahmed reported that 6,8-dibromo-4(3*H*)quinazolinone derivatives show strong antiproliferative activity against MCF-7.[18] Zayed described that the design, synthesis, and biological evaluation studies of 3-substituted 6,8-diiodo-2-methylquinazolin-4(3*H*)-ones as anticonvulsant agents.[19] The compounds derived from quinazoline-2,4(1*H*,3*H*)-diones also exhibit a wealth of biologic activities.[20,21] Lately, Leivers discovered that 2-amino-4,6-disubstituted-4(3*H*)quinazolinones are extremely selective PI4KIIIα inhibitors and anti HCV agents.[22] Hucke discovered that 1,6-disubstituted-4(3*H*)quinazolinones are allosteric HCV NS5B

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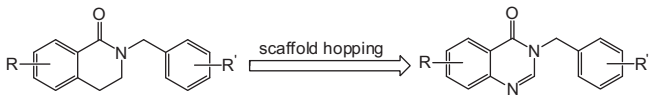


Figure 1. The design idea of the research subject.

polymerase thumb pocket 2 inhibitor with picomolar cellular replicon potency.[23] Chern identified that (*E*)-3-(2-ethyl-7-fluoro-4-oxo-3-phenethyl-3,4-dihydroquinazolin-6-yl)-*N*-hydroxy-acrylamide is a potent selective HDAC6 inhibitor.[24]

In search for novel antihypertensive agents, some derivatives from quinazoline or quinazolin-4(3*H*)-one were discovered. For example, prazosin and terazosin, derived from 4-amino-2-piperazinylquinazolines, were identified as α_1 adrenergic blockers using clinically to treat hypertension.[25,26] Recently, Abou El Ella discovered that 2-methyl-3-arylpiperazinylaminoquinazolin-4(3*H*)-one derivatives are also α_1-adrenoreceptor antagonists and show hypotensive effects in vivo.[27] Although, a few studies provide the diversity of quinazolin-4(3*H*)-one derivatives on activity and structure, additional studies for discovering the novel activities of quinazolin-4(3*H*)-one derivatives are still called for.

In our previous work, we reported a new approach to the synthesis of 2-benzyl-3,4-dihydro-1(2*H*)-isoquinolinones and discovered that these compounds exhibit the vasodilative effects.[28,29] The detail results indicate that 2-benzyl-5-hydroxy-6-methoxy-3,4-dihydro-1(2*H*)-isoquinolinone induces vasodilation by inhibiting the VDCC and ROCC, and receptor-mediated Ca^{2+} influx and release. In order to seek a novel scaffold of antihypertensive agents, we assume that 3-benzylquinazolin-4(3*H*)-ones possess the similar configuration as 2-benzyl-3,4-dihydro-1(2*H*)-isoquinolinone on basis of scaffold hopping. The similar characteristic in structure reveals that 3-benzylquinazolin-4(3*H*)-ones may be a novel scaffold of vasodilative agents and antihypertensive drugs (see Fig. 1). Herein, we describe the synthesis, vasodilative and antihypertensive effect of 3-benzylquinazolin-4(3*H*)-ones.[30]

The synthetic route for the title compounds **1a**–**1o** is outlined in Scheme 1. The mixture of substituted 2-aminobenzoic acid, triethyl orthoformate and substituted benzylamine in ethanol was refluxed for 2–8 h to produce the title compounds **1a**–**1o**.[31]

4-Methoxyaniline was used as starting material to synthesize compound **1p** to compare the vasodilative action of 3-phenylquinazolin-4(3*H*)-one with **1h** (Scheme 2).

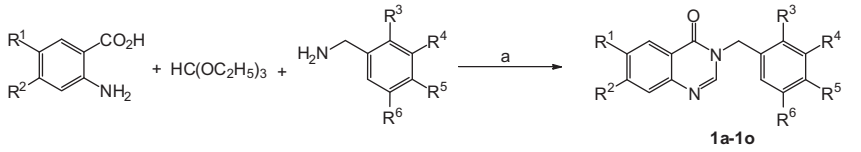
To expand the structural diversity of the substituted group at 3-position, we synthesized compound **2** with a benzyloxy group attached to the phenyl ring of 3-benzyl group (Scheme 3).

The reaction of the commercial available hydroxyl benzaldehyde with benzyl bromide produced compound **3**. The latter was reduced with sodium borohydride to produce the corresponding benzyl alcohol **4**, which was then converted to benzyl chloride **5** by the reaction with thionyl chloride. Benzyl amine **6** was prepared by employing the Gabriel reaction of **5** with phthalimide. Compounds **2a**–**2h** were synthesized by the same reaction with preparation of compound **1**.

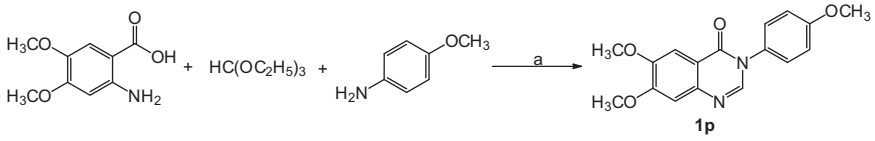
Compounds **2j**–**2l** can also be synthesized from compound **2a**, 6,7-dimethoxy-3-(4-(benzyloxy)-3-methoxyphenylmethyl) quinazolin-4(3*H*)-one. The *O*-benzyl in **2a** was removed by catalytic hydrogenolysis with Pd-C in H_2 atmosphere to produce compound **2i**. The subsequent nucleophilic substitution reaction produced the compounds **2j**–**2l** (Scheme 4). The catalytic amount of silver carbonate was added to accelerate the reaction.

The isolated rat mesenteric arterial rings induced contraction with 60 mM KCl MOPS solution were used in the screening experiment. The vasodilative effects of title compounds were evaluated by wire myograph with the concentrations ranged from 10^{-10} M to 10^{-4} M. The results of title compounds **1** and **2** are listed in Table 1 and Table 2, respectively.

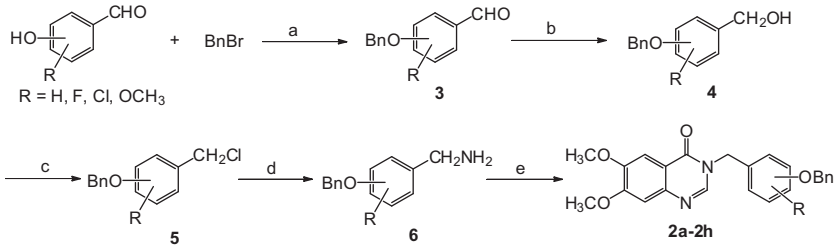
As we expected, all compounds exhibited significantly vasodilative effects. The maximal vasodilative effect (E_{max}) range from 78.3%



Scheme 1. Reagent and condition: (a) C_2H_5OH, reflux, 2–8 h.



Scheme 2. Reagent and condition: (a) C_2H_5OH, reflux, 6 h.



Scheme 3. Reagents and conditions: (a) K_2CO_3, CH_3COCH_3, reflux, 3–4 h. (b) $NaBH_4$, MeOH, rt, 3 h. (c) $SOCl_2$, DMF, rt, 1 h. (d) i: phthalimide, K_2CO_3, DMF, 120 °C, 6 h; ii: hydrazine hydrate, EtOH, reflux, 4 h. (e) 2-amino-4,5-dimethoxybenzoic acid, $CH(OEt)_3$, EtOH, reflux, 4 h.

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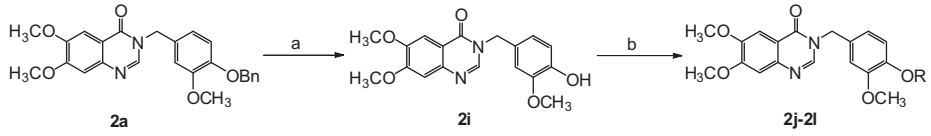
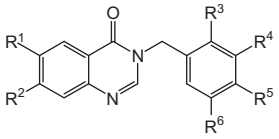


Scheme 4. Reagents and conditions: (a) H_2, Pd–C, THF, rt, overnight. (b) Substituted benzyl chloride, Cs_2CO_3, Ag_2CO_3, DMF, 120 °C, 6 h.

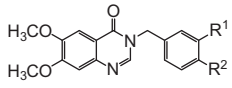
Table 1
Vasodilative effects of compounds **1a–1p** on rat mesenteric arterial rings ($n = 8$)



Compd	R^1	R^2	R^3	R^4	R^5	R^6	pEC_{50}	E_{max} (%)
DMSO							0	0
1a	H	F	H	H	F	H	4.0 ± 0.1	78.3 ± 3
1b	Br	H	H	H	F	H	4.3 ± 0.1	96.4 ± 4
1c	H	Cl	H	H	F	H	4.2 ± 0.2	101.2 ± 3
1d	H	Cl	H	H	OMe	H	4.3 ± 0.2	97.0 ± 5
1e	H	F	H	H	OMe	H	4.1 ± 0.1	87.7 ± 2
1f	OMe	OMe	H	H	H	H	4.4 ± 0.1	98.2 ± 2
1g	OMe	OMe	H	H	F	H	4.6 ± 0.1	97.8 ± 3
1h	OMe	OMe	H	H	OMe	H	4.6 ± 0.2	100.2 ± 3
1i	OMe	OMe	Cl	H	H	H	4.4 ± 0.1	98.3 ± 4
1j	OMe	OMe	Me	H	H	H	4.5 ± 0.1	97.3 ± 2
1k	OMe	OMe	H	H	NO_2	H	4.2 ± 0.2	86.2 ± 1
1l	OMe	OMe	H	H	CN	H	4.3 ± 0.1	85.6 ± 2
1m	OCH_2O		H	H	OMe	H	4.7 ± 0.1	100.6 ± 3
1n	OMe	OMe	H	OMe	OMe	OMe	6.3 ± 0.1	103.8 ± 4
1o	OMe	OMe	H	OCH_2O			5.1 ± 0.2	98.6 ± 4
1p							4.2 ± 0.1	96.3 ± 3
Nitren							8.4 ± 0.2	103.5 ± 4

$pEC_{50} = -\log EC_{50}$; E_{max}: maximal vasodilative effects; Nitren: nitrendipine.

Table 2
Vasodilative effects of compounds **2a–2l** on rat mesenteric arterial rings ($n = 8$)



Compd	R^1	R^2	pEC_{50}	E_{max} (%)
DMSO			0	0
2a	OMe	OBn	6.4 ± 0.1	102.8 ± 4
2b	OBn	OMe	4.5 ± 0.1	95.0 ± 3
2c	OMe	OCH_2Ph-4-F	6.6 ± 0.2	103.4 ± 4
2d	OMe	OCH_2Ph-3-F	6.0 ± 0.1	99.6 ± 2
2e	OMe	OCH_2Ph-3,4-diOMe	5.5 ± 0.1	99.7 ± 3
2f	H	OCH_2Ph-4-F	4.0 ± 0.1	50.3 ± 2
2g	Cl	OCH_2Ph-4-F	5.0 ± 0.1	98.9 ± 4
2h	F	OCH_2Ph-4-F	5.1 ± 0.1	99.1 ± 3
2i	OMe	OH	4.5 ± 0.2	87.6 ± 2
2j	OMe	OCH_2Py-4	4.7 ± 0.1	93.5 ± 3
2k	OMe	OCH_2Py-3	6.2 ± 0.1	98.4 ± 2
2l	OMe	OCH_2Ph-2,4-diCl	4.9 ± 0.2	97.8 ± 3
Nitren			8.4 ± 0.2	103.5 ± 3

$pEC_{50} = -\log EC_{50}$; E_{max}: maximal vasodilative effects; Nitren: nitrendipine.

to 103.8%. In order to investigate structure–activity relationship (SAR) of 3-benzylquinazolin-4(3*H*)-ones on vasodilative effects, the two structural fragments of the target compound, quinazolinone ring and phenyl ring in benzyl, were modified with different substituted groups. The fact that compounds **1g** ($pEC_{50} = 4.6$, $E_{max} = 97.8\%$) and **1f** ($pEC_{50} = 4.4$, $E_{max} = 98.2\%$) were more potent than compounds **1a** ($pEC_{50} = 4.0$, $E_{max} = 78.3\%$) and **1b** ($pEC_{50} = 4.3$, $E_{max} = 96.4\%$) indicates that the compounds with 6,7-dimethoxy may improve the vasodilative effects. Compound **1h** ($pEC_{50} = 4.6$) exhibited a little stronger vasodilative effect than that of compounds **1k** ($pEC_{50} = 4.2$) and **1l** ($pEC_{50} = 4.3$), which suggests that a substituent with electron-donating property at R^5 position may contribute the vasodilative effects. Meanwhile, we find that the activities of title compounds are improved as the number of methoxy substituent increasing by comparing the vasodilative effect of compounds **1h** ($pEC_{50} = 4.6$, $E_{max} = 100.2\%$), **1o** ($pEC_{50} = 5.1$, $E_{max} = 98.6\%$) and **1n** ($pEC_{50} = 6.3$, $E_{max} = 103.8\%$) with compound **1f** ($pEC_{50} = 4.4$, $E_{max} = 98.2$). Compound **1p** ($pEC_{50} = 4.2$) with a 3-phenyl at the 3-position of quinazolinone ring displayed weaker activity than compound **1h** ($pEC_{50} = 4.6$), which supports our design assumption.

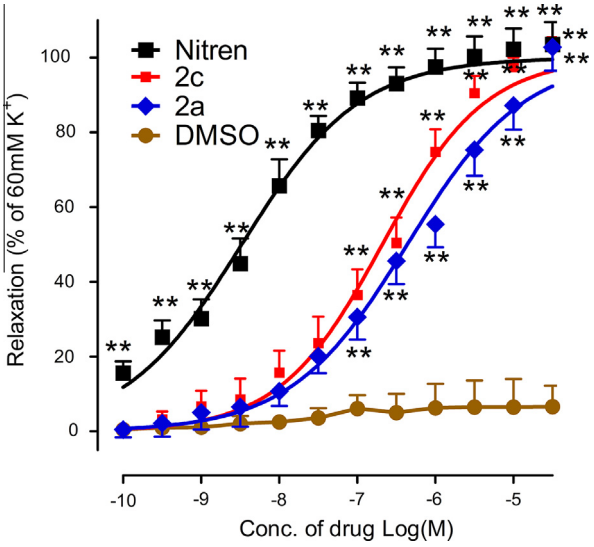


Figure 2. The vasorelaxant effect of **2a** and **2c** on rat mesenteric artery induced contraction with the 60 mM K^+. Data were shown as mean ± SEM, $n = 8$ for each group. $^{**}p < 0.01$ **2a**, **2c** and nitrendipine groups versus DMSO group.

The data in Table 1 indicate that the substituted groups at the phenyl of benzyl contribute significantly the vasodilative effects of title compounds. Thus, we intend to change the substituted groups linked to the phenyl in benzyl to improve the activity. Benzyloxy, substituted benzyloxy, fluoride or chloride were attached to the phenyl in 3-benzyl to synthesize compound **2**.

The vasodilative data summarized in Table 2 indicate that (1) benzyloxy group at R^2 is beneficial for the vasodilative activity (compound **2a**, $pEC_{50} = 6.4$, $E_{max} = 102.8\%$). However, when benzyloxy group is attached at R^1, the vasodilative activity dropped dramatically (compound **2b**, $pEC_{50} = 4.5$, $E_{max} = 95.0\%$); (2) the vasodilative effect declined when R^1 changes from methoxy group to halogens or hydrogen (compared compound **2c** with **2f–2h**); (3) the compound with a 3-pyridinylmethoxy group at R^2 displayed better activity than that of the compound with a 4-pyridinylmethoxy group; (4) the compound with a methoxy at R^1 position and a

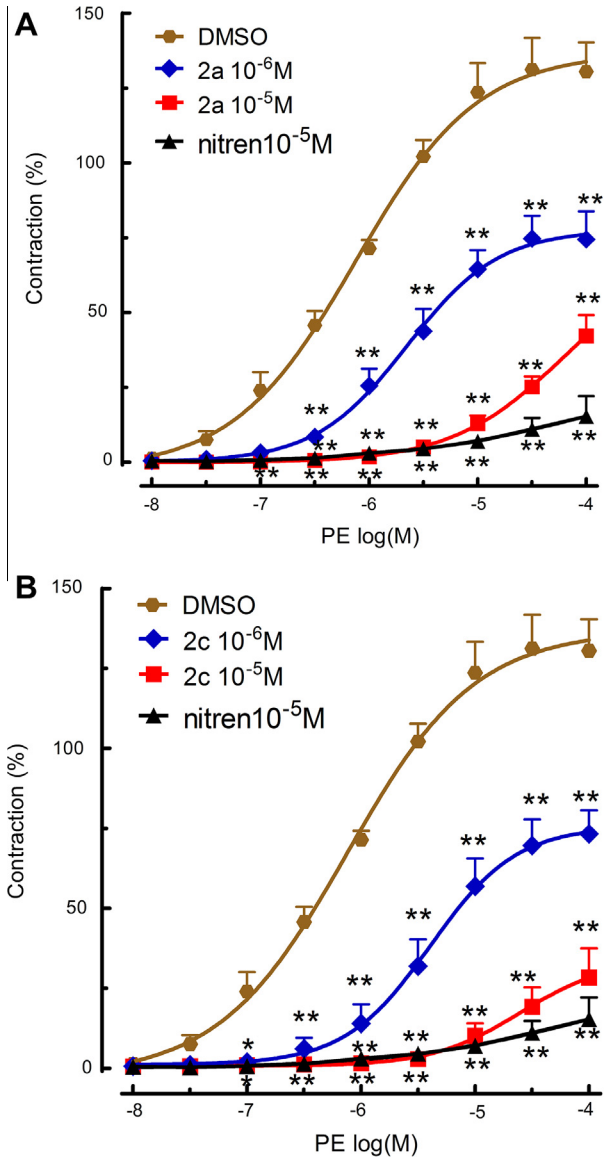


Figure 3. Inhibitory effects of **2a** (A) and **2c** (B) on artery contraction induced by phenylephrine. Data were shown as mean ± SEM, $n = 8$ for each group. $^{*}p < 0.05$, $^{**}p < 0.01$ versus DMSO group.

4-fluorobenzyloxy group at R^2 position exhibited the best vasodilative effect among the evaluated compounds (compound **2c**, $pEC_{50} = 6.6$, $E_{max} = 103.4\%$); (5) the activity of compound **2i** ($pEC_{50} = 4.2$, $E_{max} = 70.3$), removed *O*-benzyl at R^2, dropped dramatically.

The title compounds displayed the characteristics of working slowly and maintaining a long time on vasodilative effect. The dose–effect curves of compounds **2a** and **2c** are shown in Figure 2.

Compounds **2a** and **2c** can relax significantly the isolated rat mesenteric arterial rings induced contraction with 60 mM KCl MOPS solution. Whether compounds **2a** and **2c** can compete the contraction induced with phenylephrine (PE) on rat mesenteric arterial rings. The mesenteric artery segments were pretreated with the compounds **2a** or **2c** at the concentration of 10^{-5} M or 10^{-6} M for 30 min, respectively. Then, the PE at 10^{-8} M to 10^{-4} M was cumulatively added to baths. The obtained concentration- response curves are shown in Figure 3, respectively.

The curves in Figure 3 indicated that compounds **2a** and **2c** can decrease significantly the contraction induced with PE on rat mesenteric arterial rings. As our previous work demonstrated,[29] the title compounds may play the role of inducing vasodilative effect through multiple approaches.

Compounds **2a** and **2c** displayed potent vasodilative effect. Therefore, compounds **2a** and **2c** were further investigated.

Next, the antihypertensive effects of compounds **2a** and **2c** were evaluated by oral administration in spontaneously hypertensive rats (SHR). Nitrendipine was chosen as positive drug. The blood pressure was measured before (0 h) and after (1 h) drug administration. The results are summarized in Table 3. The data in Table 3 indicate that compound **2a** and **2c** exhibit significantly antihypertensive effects in SHR. The effects of compound **2c** are more potent than that of compound **2a**. This may be associated with a fluoro-substituted in compound **2c**. The effects of compound **2a** at the dosage of 4 mg/kg are weaker than that of nitrendipine at the dosage of 2 mg/kg. The effects of compound **2c** at the dosage of 4 mg/kg are in close proximity to that of nitrendipine at the dosage of 2 mg/kg.

Thus, **2c** was further evaluated for its hypotensive dose–effect relationship and time–effect relationship. The data are listed in Tables 4 and 5, respectively. The compound **2c** was tested at the dosage of 0.5, 1.0, 2.0 4.0 and 8.0 mg/kg. The data in Table 4 showed that the antihypertensive effect of compound **2c** was dose dependent.

The data in Table 5 indicated that the solvent did not affect both DBP and SBP in SHR. Meanwhile, compound **2c** can maintain the antihypertensive effect for 6 h at a dosage of 4.0 mg/kg.

In the present study, we assumed that the 3-benzylquinazolin-4(3*H*)-ones may exhibit vasodilative effects and antihypertensive effects. A series of 3-benzylquinazolin-4(3*H*)-ones were synthesized and characterized. Their vasodilative effects were evaluated by wire myograph on isolated rat mesenteric arterial ring induced contraction with KCl (60 mM). The SAR of target compounds was discussed preliminarily. The compounds **2a** and **2c** displayed potent vasodilatation action and can significantly compete the rat mesenteric arterial rings induced contraction with PE. The antihypertensive effects of **2a** and **2c** were evaluated by oral administration with SHR model. Compounds **2a** and **2c** can significantly reduce both diastolic and systolic blood pressure.

Table 3
Effects of compounds **2a** and **2c** on SBP and SDP in SHR at 1 h (mmHg, $\bar{x} \pm s$, $n = 8$)

Drug	Dose (mg/kg)	DBP (0 h)	DBP (1 h)	Reduced value	SDP (0 h)	SBP (1 h)	Reduced value
Solvent[a]	0	134 ± 7	136 ± 3	−2	182 ± 3	181 ± 7	1
2a	4.0	127 ± 7	108 ± 11	19	178 ± 7	130 ± 9	48
2c	4.0	131 ± 6	97 ± 3	34	184 ± 3	124 ± 5	60
Nitrendipine	2.0	130 ± 7	100 ± 6	30	180 ± 4	129 ± 4	51

[a] NMP/PEG400/H_2O = 1:7:2 (5 ml/kg).

Table 4
The hypotensive dose–effect relationship of **2c** in SHR (mmHg, $\bar{x} \pm s$, $n = 8$)

Drug	Dose (mg/kg)	DBP (0 h)	DBP (1 h)	Reduced value	SDP (0 h)	SBP (1 h)	Reduced value
Solvent[a]	0	134 ± 7	134 ± 9	−2	182 ± 3	181 ± 7	1
2c	0.5	133 ± 3	124 ± 1	9	183 ± 1	171 ± 4	12
	1.0	133 ± 6	118 ± 6	15	181 ± 4	153 ± 8	28
	2.0	128 ± 3	101 ± 10	18	182 ± 3	141 ± 4	41
	4.0	131 ± 6	97 ± 3	34	178 ± 7	124 ± 5	60
	8.0	137 ± 4	94 ± 4	43	184 ± 3	120 ± 5	64
Nitrendipine	2.0	130 ± 7	100 ± 6	30	180 ± 4	129 ± 4	51

[a] NMP/PEG400/H_2O = 1:7:2 (5 ml/kg).

Table 5
The hypotensive time–effect relationship of **2c** in SHR (mmHg, $\bar{x} \pm s$, $n = 8$)

Time (h)	Solvent[a]		**2c** (4 mg/kg)			
	DBP	SBP	DBP	Reduced DBP	SBP	Reduced SBP
0	134 ± 7	182 ± 3	131 ± 6		184 ± 3	
0.5	134 ± 9	180 ± 4	101 ± 3	20	138 ± 4	46
1	136 ± 3	181 ± 7	97 ± 3	34	124 ± 5	60
2	135 ± 3	178 ± 2	108 ± 3	23	142 ± 6	42
4	135 ± 3	180 ± 2	114 ± 5	17	148 ± 4	36
6	134 ± 2	181 ± 2	121 ± 5	10	163 ± 5	21
8	137 ± 4	184 ± 2	137 ± 4		182 ± 4	2

[a] NMP/PEG400/H_2O = 1:7:2 (5 ml/kg).

The antihypertensive effect of compound **2c** was dose dependent, and can maintain 6 h at 4.0 mg/kg. These findings suggest that the title compounds are novel vasodilative agents and compound **2c** is a novel potent antihypertensive agent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.10.092.

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