Full Paper

Synthesis and Biological Activity of Some 1,3-Dihydro-2*H*-3-benzazepin-2-ones with a Piperazine Moiety as Bradycardic Agents

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A series of 1,3-dihydro-2*H*-3-benzazepin-2-ones with a piperazine moiety were designed and synthesized by treating the common intermediate of 1,3-dihydro-7,8-dimethoxy-3-[3-(1-piperazinyl)-propyl]-2*H*-3-benzazepin-2-ones with a variety of *N*-aryl-2-chloroacetamides and acyl chlorides. Their structures have been characterized by ^{1}H-NMR, MS, and elemental analysis. The title compounds were evaluated for their bradycardic activity *in vitro*. Most of the synthesized compounds exhibited some vasorelaxant activity and heart-rate-reducing activity with bradycardic potency.

Keywords: Bradycardic activity / 1,3-Dihydro-2*H*-3-benzazepin-2-one / Heart-rate reduction / Vasorelaxant activity

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Introduction

Stable angina pectoris is very common nowadays in elderly. Treatment for angina includes reducing heart rate with agents such as β-adrenergic blockers and some calcium-channel antagonists. However, these agents also exert other unwanted activities such as negative inotropic and hypotensive effects which could have serious consequences [1, 2]. The reduction of sinus heart rate (HR) is one of major interests in the treatment of cardiac ischemia. Myocardial ischemia results from an imbalance between oxygen supply and demand. HR reduction can correct this balance by improving myocardial perfusion and reducing myocardial oxygen demand. Lowering the heart rate is therefore one of the most important therapeutic approaches in the treatment of stable angina pectoris. Heart rate is determined by spontaneous electrical pacemaker activity in the sinoatrial node controlled by the I_f current. Thus, the search for novel heart-rate-reducing compounds without unwanted inotropic effects was initiated [3–5]. Hence, over the past few years, there have been significant research activities towards selective I_f inhibitors. A series of novel benzazepin-2-ones and related derivatives were developed for clinical trail [6–11], such as Zatebradine [9], Cilobradine [12], and Ivabradine [13].

Ivabradine (**I**) (Procoralan®, Servier) is the potent bradycardic agent which has been approved by the European agency for the evaluation of medicinal products for the treatment of ischemic heart disease, congestive heart failure, and angina pectoris. It is the first representative of a new class of selective agents for reducing heart rate which inhibit the I_f current in the sinoatrial node [6, 13].

Ranolazine (**II**) is a selective inhibitor of the late sodium current relative to the peak sodium channel current; it may decrease the sodium-dependent intracellular calcium overload during ischemia and reperfusion. This mechanism contributes to a reduction in intracellular sodium and intracellular calcium, and leads to reduce ischemic injury [14, 15]. Based on the results of these trials, Ranolazine was recently approved by the United States Food and Drug Administration (FDA) for treatment of patients with chronic stable angina (Scheme 1).

In view of the outstanding pharmacological profiles of Ivabradine and Ranolazine and taking into account the benzazepin-2-one backbone of the Ivabradine unit and

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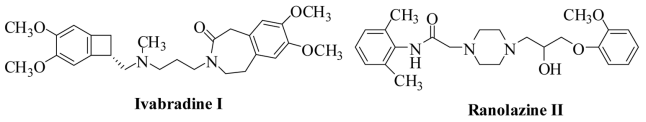
Abbreviation: sinus heart rate (HR)



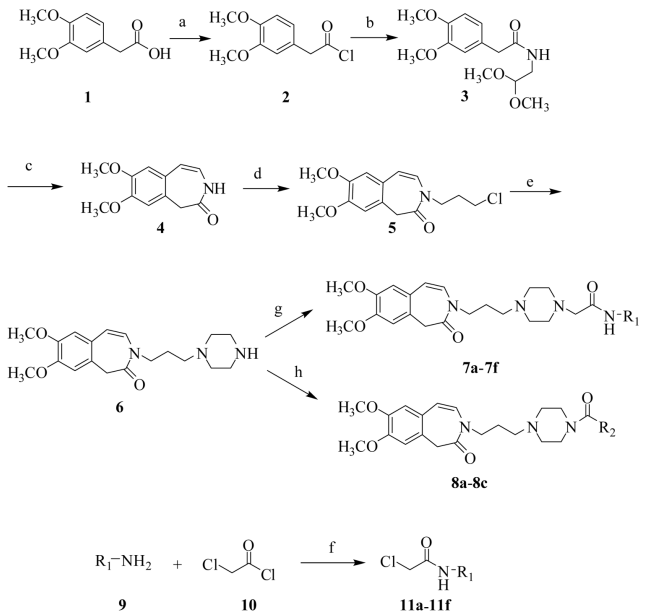
Scheme 1. The structures of Ivabradine and Ranolazine.

the acylpiperazine of the Ranolazine unit, as well as a tether length of a propyl group and a double bond in the benzazepinone ring for a good antimyocardial ischemia activity [6, 11], we have designed and synthesized a series of new propyl-linked 1,3-dihydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one-Ranolazine hybrid-related derivatives based on Ivabaradine and Ranolazine. As a continuation of our ongoing efforts towards the development and identification of new molecules for antimyocardial ischemia drugs [16, 17], we now present the synthesis and bradycardic activity of a series of 1,3-dihydro-7,8-dimethoxy-2*H*-3-benzazepin-2-ones with a piperazine moiety.

Results and discussion

The synthetic route depicted in Scheme 2 outlines the chemistry part of the present work. Though a series of synthetic procedures were developed for sythesis the benzazepin-2-one derivatives, including ring-closing olefin metathesis and Azido–Schmidt reaction [18–26], a facile synthesis was used in the preparation of the title compounds [6, 25, 26]. The key intermediate, 7,8-dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-one **4**, was obtained by treating 3,4-dimethoxyphenylacetic acid **1** with thionyl chloride in dichloromethane to give 3,4-dimethoxyphenylacetyl chloride **2**, which was acylated with aminoacetaldehyde dimethyl acetal to afford the *N*-(2,2-dimethoxyethyl)-3,4-dimethoxyphenylacetamide **3** as a white solid. Compound **3**, in the presence of hydrochloride acid and acetic acid, perfomed the ring-closing reaction to yield the desired intermediate **4** with an overall yield of 55% for three steps.

Having compound **4** in hands, it was treated with 1-bromo-3-chloropropane in the presence of sodium hydride in DMF at 0°C to give 1-(7,8-dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-on-3-yl)-3-chloropropane **5** in 66% yield [8]. After recrystallization from ethanol, the reaction of compound **5** with piperazine was carried out using ethanol as solvent in the presence of potassium carbonate to provide 1,3-dihydro-7,8-dimethoxy-3-[3-(1-piperazinyl)propyl]-2*H*-3-benzazepin-2-one **6**. In order to obtain more monosubstituted piperazine derivative **6**, an overdose of piperazine was used in this reaction. The long duration of the reaction might have been required due to



7a, 11a: $R_1 = C_6H_5$
7b, 11b: $R_1 = p\text{-}CH_3OC_6H_4$
7c, 11c: R_1 = 2-Cl-6-$CH_3C_6H_3$
7d, 11d: $R_1 = p\text{-}FC_6H_4$
7e, 11e: $R_1 = p\text{-}NO_2C_6H_4$
7f, 11f: R_1 = 2-thiazolyl

8a: $R_2 = p\text{-}ClC_6H_4$;
8b: $R_2 = p\text{-}OCH_3C_6H_4$
8c: $R_2 = p\text{-}NO_2C_6H_4$

Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, r.t., 8 h; (b) $NH_2CH_2CH(OCH_3)_2$, $N(C_2H_5)_3$, CH_2Cl_2, r.t., 5 h; (c) 37% HCl, AcOH, 6 h; (d) $BrCH_2CH_2CH_2Cl$, NaH, DMF, 0°C, 10 h; (e) piperazine, K_2CO_3, EtOH, reflux, 24 h; $N(C_2H_5)_3$, toluene, 80°C, 12 h; (g) acyl chloride; $N(C_2H_5)_3$, r.t., 6 h.; (f) THF, $N(C_2H_5)_3$, r.t., 6 h; (h) *N*-aryl-2-chloroacetamide **11e-11f**.

Scheme 2. Synthetic route to compounds **7a–7f**, **8a–8c**, and **11e–11f**.

the weak electrophilicity of compound **5**. The formation of compound **6** was confirmed by the presence of piperazine in the ^{1}H-NMR spectrum of compound **6**. Two broad peaks at δ = 2.60 ppm and 3.12 ppm were observed for the signal of four CH_2 groups on the piperazine ring. Data from the elemental analyses and molecular ion recorded in the mass spectrum further comfirmed the assigned structure.

The target compounds, 1,3-dihydro-7,8-dimethoxy-3-[3-1-(piperazinylpropyl)]-2*H*-3-benzazepin-2-ones **7** were obtained by alkylation of compound **6** with the corresponding *N*-aryl-2-chloroacetamides **11a–11f** [27, 28]. Acylation of compound **6** with acyl chlorides in THF provided compounds **8**. The formation of the title products is indicated by the presence of peaks of *N*-aryl-2-chloroacetamides and the acyl group in IR and ^{1}H-NMR spectra of all the target compounds. Two broad peaks around δ = 2.40 and 2.65 ppm were observed for the signal of four CH_2 groups on the disubstituted piperazine ring. The mass spectra of the title compounds are in conformity with

Table 1. Vasorelaxant activity of tested benzezapin-2-ones.

Compound	Vasorelaxant (% over control at 10 μM)[a]	Compound	Vasorelaxant (% over control at 10 μM)
7a	20.9%	**7b**	43.6%
7c	24.5%	**7d**	28.8%
7e	18.3%	**7f**	35.2%
8a	39.8%	**8b**	47.6%
8c	31.2%	Ivabradine	24.6%

[a] Vasorelaxant effects of benzazepin-2-ones on aortic rings with endothelium pre-contracted with KCl (80 mM) and $CaCl_2$ (2 mM). The results based on three determinations are given.

Table 2. Heart-rate reduction effect of tested benzazepin-2-ones.

Compound	Heart rate reduction (% over control at 10 μM)[a]	Compound	Heart rate reduction (% over control at 10 μM)
7a	−18.5%	**7b**	−28.3%
7c	−15.5%	**7d**	−8.8%
7e	−12.2%	**7f**	−21.2%
8a	−16.6%	**8b**	−24.8%
8c	−10.2%	Ivabradine	−30.5%

[a] The results based on three determinations are given.

the assigned structure. The mass spectra of these compounds showed molecular ion peaks corresponding to their molecular formula. Elemental analyses satisfactorily confirmed the elemental composition and purity of the synthesized compounds.

The biological evaluation for bradycardic activity was part of this paper. The vasorelaxant activity of synthesized 2*H*-3-benzazepin-2-ones was evaluated in the rat thoracic aorta rings with endothelium against a KCl- (80 mM) and $CaCl_2$- (2 mM) induced contraction model. The heart-rate reducion in rats was also assayed using Ivabradine as positive control. The effects of the title compounds on contraction of rat aortic strip are shown in Table 1. The results indicated that some of the test compounds exhibited significant vasorelexant activity. The activities of compounds **8a–8c** are stronger than those of compounds **7a–7f**, especially the inhibition of compounds **7b** and **8b** is 43.6% and 47.6%, respectively, given a concentration of 10 μM. The heart-rate-reducing activity data are shown in Table 2. The biological evaluation suggested the target compounds showed different reduction on the heart rate in rats on the concentration of 10 μM. Heart rate reduction of compound **7b** is −28.3%. It exhibited equipotent heart-rate-reducing activity when compared to the reference standard Ivabradine. These compounds displayed vasorelaxant activities in rat thoracic aorta and were lowering heart rate on guinea pig. These dual activities revealed that these compounds can serve as new antimyocardial ischemia agents.

With regards to the possible SAR, our preliminary assumption was to synthesize the compounds by introducing a piperazine moiety in order to enhance the ability of the molecules to induce vascular relaxation and keep the heart rat reduced. The phenyl group as a electron donor can favor the bradycardic activity. Further biological evaluation and structural modification are under way. The results will be presented in another paper.

Conclusion

A series of 1,3-dihydro-7,8-dimethoxy-3-[3-(1-piperazinyl) propyl]-2*H*-3-benzazepin-2-one derivatives were synthesized and evaluated for their vasorelaxant activity and heart-rate-reducing activity. Most of the tested compounds showed potent bradycardic activity. On the basis of pharmacological properties and preliminary structure-activity relationships (SAR), the target compounds represent a novel lead for the development of specific bradycardic agents. Futher studies of compounds **7b** are in progress in order to clarify the possible mechanism of its vasorelaxant and heart-rate-reducing activity.

Experimental

Chemistry

Melting points were taken in open capillaries on a B-shape melting point apparatus and were uncorrected. IR spectra were recorded in potassium bromide disks on a Nicolet 3080 spectrometer (Nicolet, Madison, WI, USA) in the range of 4000–400 cm^{-1}. The ^{1}H-NMR spectra were recorded on a Bruker AV 400 MHz NMR spectrometer (Bruker Bioscience, USA). The chemical shifts were reported as parts per million (δ, ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra (EI) were obtained on a QP-2010 instrument (Shimadzu Scientific Instruments, Japan). The progress of the reaction was monitored on ready-made silica gel plates using chloroform/methanol as a solvent system. Spectral data (IR, ^{1}H-NMR, and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. All chemicals and reagents were purchased from known commercial suppliers and were used without further purification. 7,8-Dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-one **4** [6, 25] and *N*-aryl-2-chloroacetamides **11a–11f** [27, 28] were synthesized according to the literature procedures with minor changes. The yields were not optimized.

3-(3-Chloropropyl)-1,3-dihydro-7,8-dimethoxy-2H-3-benzazepin-2-one ***5***

1,3-Dihydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one **4** (2.8 g, 13 mmol) was dissolved in DMF (25 mL), and then sodium hydride (0.60 g, 15 mmol) was added in batches with stirring for 30 min. To this solution, the mixture of 1-bromo-3-chloropropane (1.60 mL, 16 mmol) and DMF (8 mL) was added dropwise for 30 min at room temperature. The stirring was continued for 10 h, the reaction mixture was then poured into ice water. The solid obtained was filtered, washed, dried, and recrystallized from ethanol to give 2.56 g (66.5%) of compound **5** as yellow needle crystals. M.p.: 100–102°C (lit. [6]: m.p.: 101–103°C); ^{1}H-NMR($CDCl_3$, 40 MHz) δ: 1.89–1.95 (m, 2H, CH_2), 3.35–3.38 (m, 4H, 2 CH_2), 3.64 (t, *J* = 6.8 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.16 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.29 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.66 (s, 1H, Ar-H), 6.72 (s, 1H, Ar-H).

1,3-Dihydro-7,8-dimethoxy-3-[3-(1-piperazinyl)propyl]-2H-3-benzazepin-2-one ***6***

To a solution of compound **5** (6.0 g, 20.3 mmol) in ethanol (50 mL), a little potassium iodide was added and heated to reflux for 30 min, then cooled to the room temperature. This solution was droped into a mixture of piperazine (9.5 g, 0.11 mol), potassium carbonate (14.1 g, 0.10 mol), and ethanol (100 mL); the reaction was stirred at reflux for 24 h. After the solvent was removed in vacuum, the residue was diluted with water (100 mL), and the product was extracted with dichloromethane (3 × 100 mL). The organic layer was washed with water (2 × 100 mL), and dried over $MgSO_4$. The solvent was removed and purified by flash column chromatography (dichloromethane/methanol; 15:1, v/v) to give 5.54 g (79%) of compound **6** as yellow solid. M.p.: 86–89°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.64–1.71 (m, 2H, CH_2), 2.32 (t, *J* = 6.8 Hz, 2H, CH_2), 2.60 (brs, 4H, 2 CH_2), 3.12 (brs, 4H, 2 CH_2), 3.42–3.46 (m, 2H, CH_2), 3.58 (t, *J* = 6.8 Hz, 2H, CH_2), 3.88 (s, 6H, 2 OCH_3), 6.18 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.33 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72 (s, 1H, Ar-H), 6.78 (s, 1H, Ar-H); MS *m/z* (EI): 345 [M$^+$]. Anal. calcd. for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16. Found: C, 66.31; H, 7.58; N, 12.48.

General procedure for preparation of compounds ***7a–7f***

A mixture of compound **6** (5 mmol), triethylamine (3 mL), toluene (20 mL), and *N*-aryl-2-chloroacetamide (6.0 mmol) was refluxed for 12 h. The reaction mixture was washed with 10% Na_2CO_3 solution (2 × 20 mL) and water (2 × 15 mL). The organic layer was dried over $NaSO_4$. The solvent was removed and purified by flash column chromatography (dichloromethane/methanol; 20:1, v/v) to give compounds **7a–7f** as white solid. The physical and spectral data of the compounds **7a–7f** are as follows:

N-Phenyl-2-[4-[3-(7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl]piperazinyl]acetamide ***7a***

Yield: 48%; m.p.: 140–142°C; IR (KBr) ν cm^{-1}: 3286, 2920, 2850, 1686, 1663, 1518, 1460, 1401, 1377, 1269, 1238; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.67–1.73 (m, 2H, CH_2), 2.26–2.31 (m, 2H, CH_2), 2.45 (brs, 4H, 2 CH_2), 2.61 (brs, 4H, 2 CH_2), 3.11 (s, 2H, CH_2), 3.43 (s, 2H, CH_2), 3.59 (t, *J* = 6.8 Hz, 2H, CH_2), 3.88 (s, 6H, 2 OCH_3), 6.21 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.33 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72 (s, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 7.10–7.12 (m, 1H, Ar-H), 7.26–7.35 (m, 2H, Ar-H), 7.54–7.56 (m, 2H, Ar-H), 9.08 (s, 1H, Ar-NH-C=O); MS *m/z* (EI): 478 [M$^+$]. Anal. calcd. for $C_{27}H_{34}N_4O_4$: C, 67.76; H, 7.16; N, 11.71. Found: C, 67.48; H, 7.32; N, 11.92.

N-(4-Methoxyphenyl)-2-[4-[3-(7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl] piperazinyl]acetamide ***7b***

Yield: 56%; m.p.: 100–102°C; IR(KBr) ν cm^{-1}: 3286, 2928, 1660, 1613, 1554, 1508, 1409, 1274, 1255; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.69–1.72 (m, 2H, CH_2), 2.29–2.33 (m, 2H, CH_2), 2.45 (brs, 4H, 2 CH_2), 2.61 (brs, 4H, 2 CH_2), 3.10 (s, 2H, CH_2), 3.48 (s, 2H, CH_2), 3.60 (t, *J* = 6.8 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.88 (s, 6H, 2 OCH_3), 6.22 (d, *J* = 9.2 Hz,1H, Ar-CH=CH-), 6.34 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72 (s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 6.87 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.96 (s, 1H, Ar-NH-C=O); MS *m/z* (EI): 508 [M$^+$]. Anal. calcd. for $C_{28}H_{36}N_4O_5$: C, 66.12; H, 7.13; N, 11.02. Found: C, 66.59; H, 7.41; N, 10.96.

N-(2-Chloro-6-methylphenyl)-2-[4-[3-(7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl] piperazinyl]acetamide ***7c***

Yield: 41%; m. p.: 90–92°C; IR (KBr) ν cm^{-1}: 3312, 2936, 2817, 1655, 1511, 1458, 1401,1377, 1275, 1236; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.69–1.73 (m, 2H, CH_2), 2.18–2.29 (m, 5H, CH_2, CH_3), 2.48 (brs, 4H, 2 CH_2), 2.72 (brs, 4H, 2 CH_2), 3.18 (s, 2H, CH_2), 3.43 (s, 2H, CH_2), 3.61 (t, *J* = 6.8 Hz, 2H, CH_2), 3.88 (s, 6H, 2 OCH_3), 6.23 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.34 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.73 (s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 7.11–7.15 (m, 2H, Ar-H), 7.27 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.90 (s, 1H, Ar-NH-C=O); MS *m/z* (EI): 526 [M$^+$]. Anal. calcd. for $C_{28}H_{35}ClN_4O_4$: C, 63.81; H, 6.69; N, 10.63. Found: C, 63.50; H, 6.71; N, 11.13.

N-(4-Fluorophenyl)-2-[4-[3-(7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl] piperazinyl]acetamide ***7d***

Yield: 43%; m.p.: 108–110°C; IR(KBr) ν cm^{-1}: 3448, 2920, 2850, 1690, 1649, 1509, 1460, 1404, 1236; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.69–1.72 (m, 2H, CH_2), 2.28–2.34 (m, 2H, CH_2), 2.45 (brs, 4H, 2 CH_2), 2.61 (brs, 4H, 2 CH_2), 3.11 (s, 2H, CH_2), 3.43 (s, 2H, CH_2), 3.59 (t, *J* = 6.8 Hz, 2H, CH_2), 3.88 (s, 6H, 2 OCH_3), 6.22 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.34 (d, 1H, *J* = 9.2 Hz, Ar-CH=CH-), 6.72 (s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 7.00 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.07 (s, 1H, Ar-NH-C=O); MS *m/z* (EI): 496 [M$^+$]. Anal. calcd. for $C_{27}H_{33}FN_4O_4$: C, 65.31; H, 6.70; N, 11.28. Found: C, 65.16; H, 6.82; N, 11.17.

N-(4-Nitrophenyl)-2-[4-[3-(7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl]piperazinyl]acetamide ***7e***

Yield: 57%; m.p.: 167–168°C; IR(KBr) ν cm^{-1}: 3448, 2927, 1697, 1636, 1531, 1504, 1458, 1403, 1345, 1272, 1257; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.66–1.72 (m, 2H, CH_2), 2.32–2.37 (m, 2H, CH_2), 2.48 (brs, 4H, 2 CH_2), 2.64 (brs, 4H, 2 CH_2), 3.16 (s, 2H, CH_2), 3.49 (s, 2H, CH_2), 3.60 (t, *J* = 6.8 Hz, 2H, CH_2), 3.89 (s, 6H, 2 OCH_3), 6.21 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.34 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72 (s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 7.74 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.22 (d, *J* = 8.2 Hz, 2H, Ar-H), 9.47 (s, 1H, Ar-NH-C=O); MS *m/z* (EI): 523 [M$^+$]. Anal. calcd. for $C_{27}H_{33}N_5O_6$: C, 61.94; H, 6.35; N, 13.38. Found: C, 62.24; H, 6.01; N, 13.76.

*N-(2-Thiazolyl)-2-[4-[3-(7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl]piperazinyl] acetamide **7f***

Yield: 40%; m.p.: 136–138°C; IR (KBr) ν cm^{-1}: 3448, 2927, 2361, 1654, 1636, 1509, 1458, 1430, 1401, 1276, 1251, 1172; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.72–1.76 (m, 2H, CH_2), 2.32–2.37 (m, 2H, CH_2), 2.49 (brs, 4H, 2 CH_2), 2.63 (brs, 4H, 2 CH_2), 3.23 (s, 2H, CH_2), 3.43 (s, 2H, CH_2), 3.61(t, *J* = 7.2 Hz, 2H, CH_2), 3.89 (2s, 6H, 2 OCH_3), 6.21 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.33(d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72(s, 1H, Ar-H), 6.79 (s, 1H, Ar-H), 6.99 (d, *J* = 3.6 Hz,1H, thiazole-H), 7.45 (d, *J* = 3.6 Hz, 1H, thiazole-H), 10.28 (s, 1H, Ar-NH-C=O); MS *m/z* (EI): 485 [M^+]. Anal. calcd. for $C_{24}H_{31}N_5O_4S$: C, 59.36; H, 6.43; N, 14.42. Found: C, 59.73; H, 6.68; N, 14.26.

*General procedure for preparation of compounds **8a–8c***

Compound **6** (5 mmol) and triethylamine (10 mmol) were mixed thoroughly in THF (10 mL). To this solution, acyl chloride (6 mmol) in THF (5 mL) was added dropwise at room temperature. The reaction mixture was stirred for 6 h. Water (15 mL) was added, the mixture was extracted with ethyl acetate (2 × 15 mL) and washed with saturated $NaHCO_3$ solution (2 × 15 mL) and water (2 × 15 mL). The solvent was removed and the compound purified by flash column chromatography (dichloromethane/methanol; 20:1, v/v) to give a white solid. The physical and spectral data of the compounds **8a–8c** are as follows:

*1-[3-(7,8-Dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl]-4-(4-chlorobenzoyl)piperazine **8a***

Yield: 47%; m.p.: 70–72°C; IR (KBr) ν cm^{-1}: 3297, 2945, 1700, 1639, 1533, 1518, 1461, 1405, 1283, 1270, 1238; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.70–1.74 (m, 2H, CH_2), 2.30–2.34 (m, 6H, 3 CH_2), 2.35 (brs, 4H, 2 CH_2), 3.43 (s, 2H, CH_2), 3.61 (t, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.20 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.34 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.71 (s, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 7.33 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.2 Hz, 2H, Ar-H); MS *m/z* (EI): 483 [M^+]. Anal. calcd. for $C_{26}H_{30}ClN_3O_4$: C, 64.52; H, 6.25; N, 8.68. Found: C, 64.81; H, 6.43; N, 8.56.

*1-[3-(7,8-Dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl]-4-(4-methoxybenzoyl)piperazine **8b***

Yield: 45%; m.p.: 76–78°C; IR (KBr) ν cm^{-1}: 3463, 2933, 1655, 1636, 1513, 1460, 1431, 1277, 1238, 1101; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.70–1.74 (m, 2H, CH_2), 2.30 (t, *J* = 6.8 Hz, 2H, CH_2), 2.32 (brs, 4H, 2 CH_2), 2.40 (brs, 4H, 2 CH_2), 3.43 (s, 2H, CH_2), 3.62 (t, *J* = 6.8 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.21 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.34(d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72 (s, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 6.90 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.8 Hz, 2H, Ar-H); MS *m/z* (EI): 479 [M^+]. Anal. calcd. for $C_{27}H_{33}N_3O_5$: C, 67.62; H, 6.94; N, 8.76. Found: C, 67.28; H, 6.71; N, 8.96.

*1-[3-(7,8-Dimethoxy-1,3-dihydro-2H-3-benzazepin-2-on-3-yl)propyl]-4-(4-nitrobenzoyl)piperazine **8c***

Yield: 48%; m.p.: 78–80°C; IR (KBr) ν cm^{-1}: 3448, 2925, 1636, 1601, 1516, 1458, 1438, 1401, 1351,1274; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.68–1.72 (m, 2H, CH_2), 2.31 (brs, 6H, 3 CH_2), 2.47 (brs, 4H, 2 CH_2), 3.42 (s, 2H, CH_2), 3.60 (t, *J* = 6.8 Hz, 2H, CH_2), 3.88 (2s, 6H, 2 OCH_3), 6.20 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.35 (d, *J* = 9.2 Hz, 1H, Ar-CH=CH-), 6.72(s, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 7.54 (d, *J* = 6.8 Hz, 2H, Ar-H), 8.28 (d, *J* = 6.8 Hz, 2H, Ar-H); MS *m/z* (EI): 494 [M^+]. Anal. calcd. for $C_{26}H_{30}N_4O_6$: C, 63.15; H, 6.11; N, 11.33. Found: C, 62.85; H, 5.91; N, 11.66.

Biological evaluation

Effects on isolated aortic strips of the rat

Vascular rings were prepared from the aorta of male Sprague-Dawley rats (four to six months old and weighing on average 250 g; received from the experimental animals center, Sun Yat-Sen University, Guangzhou, experimental animals permission number: 2008A063.) and contraction studies were performed following the general procedure detailed in the literature [16, 29]. After an equilibration period of at least 1 h, isometric contractions induced by KCl (80 mM) and $CaCl_2$ (2 mM) were obtained. When the contraction of the tissue in response to this vasoconstrictor agent had stabilized (after about 20 min), cumulatively increasing concentrations of the test compounds were added to the bath at 15–20 min intervals (the time was needed to obtain a steady-state relaxation). Control tissues were simultaneously subjected to the same procedures, but omitting the compounds and adding the vehicle. The benzazepin-2-ones induced maximal relaxation. E_{max} in aortic rings was calculated as a percentage of the contraction in response to KCl (80 mM) and $CaCl_2$ (2 mM). The half-maximum effective concentration (EC_{50}) was defined as the concentration of the title compound that induced 50% of maximum relaxation from the contraction elicited by KCl (80 mM) and $CaCl_2$ (2 mM) and was calculated from the concentration–response curve by nonlinear regression (curve fit) using GraphPad Prism (Version 4.0).

Experiments with isolated guinea pig atria

Guinea pigs of various breeds, 300–500 g of either sex, (experimental animals center, Sun Yat-Sen University, Guangzhou, experimental animals permission number: 2008A007.) were killed by a blow on the head, the heart was removed and the atria were dissected. The preparation was suspended in 40 mL of modified Tyrode's solution (136.8 mM NaCl, 2.68 mM KCl, 0.26 mM $MgCl_2$, 0.42 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 15 mM glucose), gassed with a mixture of 98% O_2 + 2% CO_2. The resulting tension on the muscle was 1 g. Mechanograms were recorded isometrically via a strain gauge on a multichannel recorder.

Drug effects on atrial rate were tested in spontaneously beating atria, bath temperature at 37°C, after an equilibrium period of at least 30 min, until the rate did not change by more than 5 beats/min [6, 7].

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