Guaiacoxypropanolamine Derivatives of Capsaicin: A New Family of β-Adrenoceptor Blockers with Intrinsic Cardiotonic Properties

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A series of guaiacoxypropanolamine derivatives of capsaicin was synthesized by replacing the phenolic OH of *N*-nonanoylvanillamide with epichlorohydrin, followed by cleavaging the obtained epoxide compound with alkylamines. Intravenous injection of these propanolamine derivatives (1 mg/kg) in normotensive Wistar rats induced a transient fall in blood pressure but significantly reduced the heart rate for more than 30 min. These derivatives (10^{-8}–10^{-6} M) inhibited isoproterenol (10^{-10}–10^{-5} M)-induced positive chronotropic and inotropic effects in isolated guinea pig atrium. On the other hand, these derivatives (10^{-5}–10^{-4} M) exhibited a positive cardiotonic effect that is independent of intrinsic sympathomimetic effects. Investigation of the structure–activity relationship of these derivatives revealed that the position of the oxypropanolamine side chain and substituents of the 4-OH position play significant roles in imparting their pharmacological effects. Of the derivatives tested, the most effective one was compound **9**. In conclusion, the results obtained from in vitro and in vivo studies suggested that these derivatives and compound **9** may be expected to be β-adreneoceptor blocking agents with nonadrenergic positive chronotropic and inotropic properties.

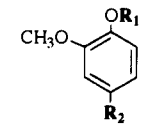
Introduction

Capsaicin, *trans*-8-methyl-*N*-vanillyl-6-nonenamide (**1**, Scheme 1) is a pungent compound produced by chili peppers and related plants of the Capsicum family. Early investigations of its pharmacological effects showed a wide spectrum of activities,[1-3] including the decrease of heart rate that was caused by sensory C-fiber evoked parasympathetic efferent effect[4] and the increase of cardiac contractility force that was caused by the release of CGRP (calcitonin gene-related peptide) from the sensory nerve.[5]

A series of pharmacologic studies and results of **1** and its derivatives in the cardiovascular system[6] encouraged us to synthesize and search for newer derivatives of **1** in the pharmacological treatment of cardiovascular diseases. The propanolamine side chain has been proven to be a key group of β-adrenoceptor blockers in their chemical structure for having β-adrenoceptor blocking activities.[7] The phenolic hydroxyl group of **1** also provided the possibility to introduce 4-ether-linked propanolamine side chains. Taking into consideration the parasympathetic efferent and cardiotonic effects of **1** and its possible propanolamine-introducing β-adrenoceptor blocking activity, we synthesized a number of β-adrenoceptor blockers derived from **1** and evaluated their pharmacologic activities. Alkylamine derivatives of **1** were also synthesized and used as reference compounds in the pharmacologic evaluation test.

Most of the derivatives of **1** have been derived from modifications of either the acylamide linkage or the alkyl chain, and a few have been derived from alterations of the aromatic ring.[8] Recently, by replacing the phenolic hydroxyl group with different hydrophillic substituents we synthesized a series of 4-ether-linked and relatively nonpungent derivatives of **1**.[9]

Scheme 1



Guaiacol: R_1=H; R_2=H

Capsaicin (1): R_1=H; R_2=$CH_2NHCO(CH_2)CH{:}CHCH(CH_3)_2$

Nonivamide (2): R_1=H; R_2=$CH_2NHCO(CH_2)_7CH_3$

Guaiacoxypropanolamines: R_1=$CH_2CH(OH)CH_2NHR$; R=Alkyl
R_2=$CH_2NHCO(CH_2)_7CH_3$

In view of the pharmacological profile similar to that of **1**,[6] *N*-nonanoylvanillamide (**2**; nonivamide; Scheme 1) was used in substitution of **1** to link with various propanolamines and evaluated for the possibility of having β-adrenoceptor blocking activities and for their cardiotonic effects. All clinically used β-blockers share the common feature of being competitive antagonists at β-adrenoceptors. They differ, however, in additional pharmacological properties, such as β-1 or β-2 selectivity, presence or absence of intrinsic sympathomimetic activity (ISA), local anesthetic activity, and pharmacokinetic properties.[10] The intrinsic cardiostimulatory effect of **1** or **2**, but not the ISA, was suggested to be retained in these newly synthesized guaiacoxypropanolamines (Scheme 1). It is well-known that untoward depression of myocardial function or heart failure may limit the clinical benefit of conventional β-blockers. The aim in developing guaiacoxypropanolamine derivatives of **1** or **2** was to further combine the advantages of a β-adrenoceptor blockade and intrinsic positive cardiotonic effects without ISA in one molecule and thus to compensate for the untoward circulatory effect of β-adrenoceptor blockades. To this end a series of ether-linked derivatives were prepared by introducing alkylamine side chains to the guaiacolic phenolic hydroxyl group in position 4 on the aromatic ring. Each guaiacoxypropanolamine was tested for its cardiovascular effects and β-adrenoceptor blocking activities on isoproterenol-induced cardiovascular stimulation.

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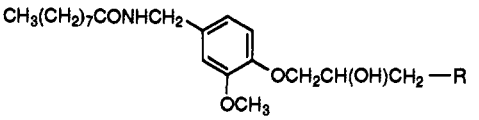
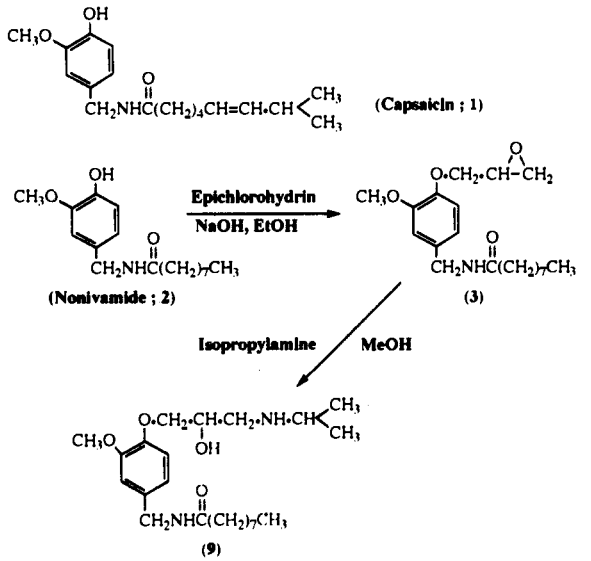
Table 1. Heart Rate and Blood Pressure Changes of Rats Induced by Guaiacoxypropanolamines



compd	R		change in BP (mmHg) or HR (beats/min) at the following times after dosing[a]				
			5 min	10 min	15 min	30 min	60 min
4	$NHCH_3$	BP	−1.11 ± 2.31	−0.22 ± 2.10	−0.56 ± 1.65	1.89 ± 2.14	0.78 ± 1.37
		HR	−34.56 ± 6.79[c]	−17.33 ± 5.31[b]	−12.22 ± 4.33	14.56 ± 7.73	4.78 ± 4.37
5	NHC_2H_5	BP	7.44 ± 3.16	2.56 ± 2.56	1.11 ± 1.78	−2.44 ± 3.05	1.88 ± 1.62
		HR	−38.33 ± 5.94[c]	−32.22 ± 5.36[c]	−28.00 ± 7.02[b]	−21.11 ± 8.75	2.56 ± 11.66
6	NHC_3H_5	BP	−1.56 ± 2.03	−2.67 ± 1.96	−1.89 ± 2.04	−1.11 ± 2.62	4.78 ± 4.96
		HR	−36.78 ± 11.25[b]	−28.22 ± 9.00[b]	−19.89 ± 9.26	−5.00 ± 8.72	−7.56 ± 4.14
7	NH-c-C_3H_5	BP	−0.11 ± 1.09	3.11 ± 2.78	3.89 ± 2.92	3.67 ± 4.10	2.22 ± 2.32
		HR	−47.67 ± 8.88[c]	−38.89 ± 9.47[b]	−23.67 ± 10.01	−11.89 ± 8.73	−2.67 ± 4.14
8	NH-*n*-C_3H_7	BP	−1.78 ± 1.71	−2.56 ± 1.47	−3.11 ± 1.81	−2.44 ± 1.66	−0.56 ± 0.50
		HR	−42.56 ± 7.65[c]	−35.33 ± 6.05[c]	−32.00 ± 5.25[c]	−14.11 ± 5.16	−6.89 ± 4.32
9	NH-*i*-C_3H_7	BP	−0.44 ± 2.05	−1.22 ± 2.29	−2.89 ± 2.03	−6.67 ± 2.51	−1.33 ± 0.98
		HR	−50.22 ± 7.29[c]	−40.78 ± 7.64[c]	−35.44 ± 7.32[c]	−32.67 ± 9.24[b]	−20.00 ± 6.15[b]
10	NH-*n*-C_4H_9	BP	−0.22 ± 1.74	−1.22 ± 1.59	−1.22 ± 1.77	0.11 ± 1.54	3.33 ± 2.82
		HR	−40.00 ± 3.74[c]	−33.78 ± 5.08[c]	−26.22 ± 6.56[b]	−15.33 ± 5.24	−3.67 ± 2.55
11	NH-*i*-C_4H_9	BP	−2.75 ± 2.29	1.63 ± 2.07	1.63 ± 1.71	2.00 ± 1.86	0.25 ± 1.91
		HR	−39.88 ± 8.60[c]	−35.25 ± 7.98[b]	−27.13 ± 7.76	4.13 ± 8.20	3.13 ± 7.90
12	NH-*s*-C_4H_9	BP	4.11 ± 2.76	4.89 ± 3.37	3.33 ± 3.74	−0.88 ± 3.11	1.22 ± 1.47
		HR	−38.56 ± 11.30[b]	−35.44 ± 12.46	−32.33 ± 11.96	−25.11 ± 9.49	−9.56 ± 7.03
13	NH-*t*-C_4H_9	BP	3.13 ± 5.66	3.38 ± 5.08	2.38 ± 5.41	1.25 ± 5.45	4.63 ± 3.51
		HR	−45.00 ± 4.20[c]	−37.75 ± 4.44[c]	−29.50 ± 5.31[c]	−24.88 ± 8.47[b]	−18.50 ± 5.13[b]
14	NH-*n*-C_5H_{11}	BP	−4.67 ± 1.71	−1.67 ± 1.87	−0.88 ± 3.00	3.67 ± 2.66	2.44 ± 1.96
		HR	−25.11 ± 5.81[c]	−23.33 ± 2.41[c]	−10.22 ± 2.38[c]	−5.78 ± 7.89	−6.56 ± 4.38
15	NHC_5H_{11}	BP	−2.78 ± 2.33	−2.56 ± 1.42	−3.22 ± 1.78	−1.33 ± 1.38	0.67 ± 0.47
		HR	−28.11 ± 9.34[b]	−28.89 ± 6.30[c]	−22.78 ± 5.04[c]	−2.22 ± 7.28	−3.33 ± 5.69
16	NH-*n*-C_6H_{13}	BP	−2.22 ± 1.42	−2.89 ± 1.61	−4.44 ± 2.93	−2.11 ± 2.77	1.89 ± 1.13
		HR	−35.56 ± 8.71[b]	−24.11 ± 3.31[c]	−14.89 ± 7.10	−12.67 ± 6.59	−8.00 ± 5.64
17	NH-c-C_6H_{11}	BP	−4.11 ± 2.89	−4.22 ± 2.29	−3.67 ± 2.39	1.33 ± 2.69	0.67 ± 2.45
		HR	−32.33 ± 15.44	−28.44 ± 16.54	−11.67 ± 9.26	−1.78 ± 8.96	2.78 ± 9.64
	propranolol	BP	−2.83 ± 1.81	−6.33 ± 2.16	−6.50 ± 3.26	−4.67 ± 2.66	2.17 ± 3.29
		HR	−57.28 ± 5.94[c]	−63.85 ± 7.18[c]	−65.28 ± 8.43[c]	−62.57 ± 9.06[c]	−52.14 ± 10.93[c]
	saline	BP	2.52 ± 1.51	1.42 ± 1.00	0.72 ± 0.54	0.52 ± 0.43	0.41 ± 0.41
		HR	1.72 ± 1.01	1.01 ± 0.82	1.01 ± 0.71	0.53 ± 0.32	0.32 ± 0.33

[a] Data were expressed as means ± SE ($n = 8$). Administered iv at a dose of 1.0 mg/kg. [b] $p < 0.05$ as compared to saline. [c] $p < 0.001$ as compared to saline.

Scheme 2



Chemistry

The synthesis of compound **9**, as shown in Scheme 2, represents a typical example of the general synthesis of guaiacoxypropanolamine derivatives of **2**. Guaiacoxypropanolamine derivatives (Scheme 1) were obtained by reacting **2** with epichlorhydrin, and the obtained epoxide compound was then reacted with methylamine, ethylamine, allylamine, cyclopropylamine, *n*-propylamine, isopropylamine, *n*-butylamine, isobutylamine, *sec*-butylamine, *tert*-butylamine, *n*-pentylamine, 3-aminopentane, hexylamine, cyclohexylamine, heptylamine, and benzylamine, respectively, to yield **4–19**. Ethylamine derivatives were obtained of reaction **2** with (dimethylamino)ethyl chloride, (diethylamino)ethyl chloride, 2-(chloromethyl)-pyridine hydrochloride, and 2-(chloroethyl)piperidine hydrochloride, respectively, to yield **20–23**.

Pharmacological Results

The cardiovascular activity of these compounds was evaluated in urethane-anesthetized normotensive Wistar rats. As shown in Table 1, intravenous injections of compounds **4–17** (1 mg/kg) all reduced the heart rate and could persist for about 1 h, and compounds **9** and **13** were more effective in reducing the heart rate than other compounds. Blood pressure was mildly decreased within 5 min but changed insignificantly 1 h after iv administration (Figure 1B). Administration of propranolol also showed the sustained bradycardia effects. The whole series was less potent than that of propranolol in bradycardiac effects.

In the isolated right atrium, **9**, as the representative of **4–17**, concentration-dependently inhibited isoproterenol-induced positive chronotropic effects. The pA_2 values of **9** and propranolol are 7.77 and 8.12, respectively. For comparison, the pA_2 values of several other compounds are shown in Table 2. Compound **9** was more active than other compounds.

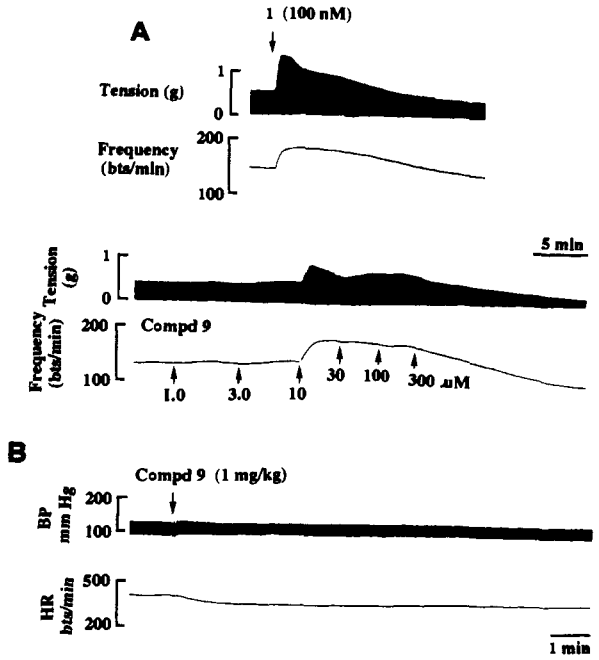


Figure 1. (A) Effects of 1 (capsaicin, 10^{-7} M) and compound **9** (10^{-5}–10^{-4} M) on tension and contractile rate of spontaneously beating guinea pig right atrium. (B) Typical records of systemic blood pressure (BP) and heart rate (HR) following iv injection of compound **9** (1 mg/kg) in anesthetized rats.

Table 2. pA_2 Values of Guaiacoxypropanolamines on Isolated Guinea Pig Atria

	atria (PR[a])	
compd	positive chronotropic	positive inotropic
propranolol	8.12 ± 0.06 (1.00)	8.42 ± 0.09 (1.00)
4	6.53 ± 0.12 (0.03)	7.13 ± 0.02 (0.05)
5	6.93 ± 0.09 (0.07)	7.27 ± 0.09 (0.07)
6	7.03 ± 0.05 (0.08)	7.60 ± 0.08 (0.15)
8	6.79 ± 0.01 (0.05)	7.75 ± 0.07 (0.21)
9	7.77 ± 0.08 (0.45)	8.07 ± 0.06 (0.45)
10	7.23 ± 0.07 (0.13)	7.27 ± 0.07 (0.07)
11	6.93 ± 0.06 (0.06)	7.57 ± 0.11 (0.14)
12	6.92 ± 0.10 (0.07)	7.65 ± 0.09 (0.17)
13	7.40 ± 0.09 (0.19)	7.80 ± 0.07 (0.24)
14	7.19 ± 0.02 (0.12)	7.55 ± 0.04 (0.14)
15	7.25 ± 0.10 (0.14)	7.26 ± 0.08 (0.07)
16	6.03 ± 0.02 (0.01)	7.18 ± 0.06 (0.06)

[a] Potency ratio (PR) = Antilog (pA_2 antagonist − pA_2 propranolol) with respect to propranolol.

Figure 1A shows that compound **2** produced positive inotropic and chronotropic effects in spontaneously beating right atria. Compound **9** and other guaiacoxypropanolamine derivatives (10^{-6} to 3×10^{-5} M) in vitro all directly caused an increase in beating rate and contractile force, but larger concentrations of it can not exhibit more responses. The chronotropic response was a concentration-dependent increase, starting at 10^{-6} M. The effects of compound **9** were not affected by propranolol (10^{-6} M) and reserpine (10 mg/kg, ip) pretreatment (data not shown).

The data in Figure 2 indicates that compounds **1**–**3** significantly decreased blood pressure in rats. Compounds **1** and **2** were previously found to produce a triphasic blood pressure change: a initial sharp reduction (effect A), transiently higher pressure (effect B), and delayed fall (effect C) in blood pressure.[9,11] However, in the present study, vagus reflex was not observed in compound **3** (0.1 mg/kg). Thus, while compound **3** was administered at a dosage of more than 1.0 mg/kg, it still exhibited a triphasic

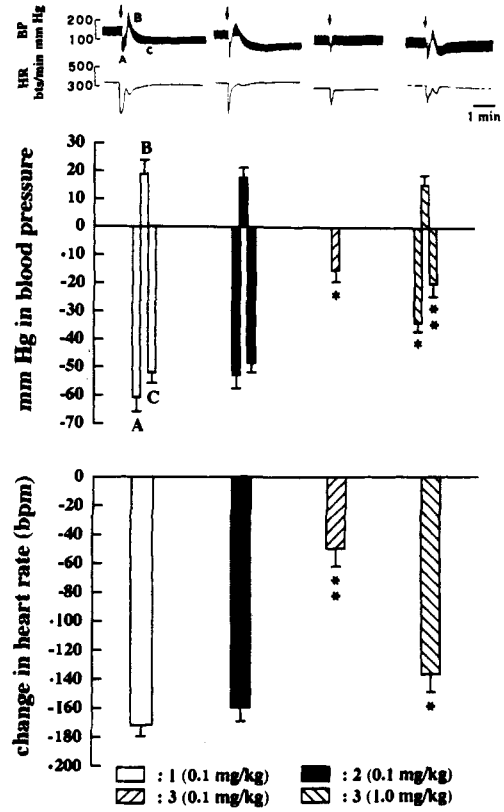


Figure 2. Effects of iv injection of 1 (capsaicin), **2** (nonivamide), and compound **3** on blood pressure and heart rate in normal rats. Vertical lines represent SE (n = 8). Statistically significant differences compared with capsaicin using Student's t test is shown as $^*p < 0.05$ and $^{**}P < 0.001$.

hypotensive response (Figure 2). After retrograde epigastric injection of 1 (10 μg/kg) into the femoral artery of Wistar rats, it was found to induce only a single-phase hypotensive effect. In contrast, it was found that compounds **20**–**26** at a dosage 0.1 mg/kg revealed a similar monophase hypotenson. Intravenous injection of compounds **20**–**26** exhibited a mild transiently hypotensive effect, without significant bradycardia, but showed the vagus reflex and triphasic blood pressure changes at a higher dose (100-fold of capsaicin) (Table 3). Results showed that changing the substituent in position 4 on the aromatic ring leads to far less potency than in compound **1**.

Discussion

Significant differences in the structure–activity relationships also exit between these compounds and other series of β-blockers. Usually the most effective β-blockers contain the branched alkyl N-substituents, such as isopropyl and *tert*-butyl, and a marked reduction in effect is seen with straight-chain substituents. In our series, the isopropyl compound **9** and *tert*-butyl compound **13** were much more effective on in vivo and in vitro pharmacological examines. Intravenous administration of isopropyl compound **9** or propranolol produced a sustained bradycardia effect with urethane-anesthetized rats. On guinea pig isolated atria, isopropyl compound **9** exerted a blocking effect in (−)-isoproterenol-induced positive inotropic and chronotropic effects. β-Blocking activity of compound **9** was around 0.5 of that of propranolol in the guinea pig's atria, and compound **13** was around 0.2.

Table 3. Depressor Effects of Capsaicin and Its 4-Ether-Linked Derivatives

compd	R	dose (mg/kg)	BP change[a]	dose of vagus[b] reflex (mg/kg)
1	H	0.01	−49.5 ± 9.9	0.001
2	H	0.01	−28.3 ± 3.6	0.005
20	$CH_2CH_2N(CH_3)_2$	0.1	−21.6 ± 1.8	0.5
21	$CH_2CH_2N(C_2H_5)_2$	0.1	−15.0 ± 2.1	0.5
22	$CH_2C_5H_4N$	0.1	−24.2 ± 0.9	0.5
23	$CH_2CH_2C_5H_{10}N$	0.1	−20.8 ± 2.2	0.5
24[d]	CH_2CH_2OH	0.1	−44.2 ± 3.9	0.3
25[d]	CH_2OHCH_2OH	0.1	−40.1 ± 4.8	0.5
26[d]	CH_2COONa	0.1	−20.2 ± 3.4	–[c]

[a] Changes in mmHg induced by ia injection through superficial epigastric artery. [b] Minimum dose of iv injection of each compound that shows vagus reflex and a heart rate decrease of 50 beats/min in nonvagotomized rats (see text). [c] Ineffective (less than 3 mg/kg). [d] See ref 9. Data were expressed as means ± SE (n = 8).

Capsaicin shows potent positive chronotropic and inotropic effects on the atrial muscles of rats and guinea pigs, in a mechanism independent of β-adrenoceptor activation. The responses of capsaicin are firstly due to the release of CGRP from the sensory nerves and then to production of positive cardiotonic effects.[5] The present data showed that compound **9** caused an increase in heart rate and contractile force. It is interesting that isopropyl compound **9** has both β-blocking-like activity, and the intrinsic cardiotonic effect is increased. Since the responses of compound **9** are not inhibited by propranolol and reserpine, it is likely that this mechanism may be dependent on a capsaicin-like effect.

It has been shown that even a minor chemical modification of the substituents on the aromatic ring of capsaicin can result in a marked reduction of pain-producing potency and may also lead to a complete loss of antinociceptive activities.[6,9,12] Walpole et al. reported that complete removal of the 4-OH substituent leads to loss of agonist activity.[13] In a preliminary experiment, iv injection of capsaicin elicited triphasic blood pressure responses. Effects A and C were proposed to be attributable to stimulation of capsaicin-sensitive small-diameter afferent fibers.[11] Intravenous administration of compounds **3** and **20–26** in an equal dose showed only monophasic hypotension, but at a high dose could elicit triphasic responses (Table 3). The depressor reflex following ia injection of capsaicin was suggested to be induced by stimulating the perivascular pain receptor[14] and was converted to a pressor reflex after degeneration of small diameter afferents in capsaicin-pretreated rats. Sensory C-fibers are reported to be selectively stimulated by capsaicin from the afferent neuron of the depressor reflexes.[15] However, ia injection of compounds **20–26** in rats evoked a depressor response similar to that observed in the control, but the substituents were less potent than compound **1**. The results of the present study further confirms and extends previous finding that 4-ether-linked alkylhydroxyl derivatives of **1** retain the antinociceptive and hypotensive effects but with less pungency and vagus reflex than **1** or **2**.[6,9,12,13]

It is well-known that both sympatholytic β-1 and parasympathomimetic activation of drugs often result in the decrease of heart rate, cardia output and other cardia functions. To this date, no other researchers have used the idea of combining sympatholytic β-1 and parasympathomimetic activation to develop new drugs. Capsaicin-related parasympathetic efferent activation associated with propanolamine-introduced β-1 blocking activities were taken into consideration in the present study. It is established that 4-ether-linked propanolamine derivatives (**4–19**) show chronotropic effects and antagonism on isoproterenol-induced blood pressure and heart rate changes as found in propranolol in in vivo tests (data not shown). On the other hand, this phenolic hydroxyl alkylation of **2** with propranolamine is also without sensory-C-fiber evoked parasympathetic efferent effects, i.e. vagus reflex, as compared with **1**, **2**, and their 4-(ethylamino) derivatives (**20–23**). A nonspecific capsaicin-dependent cation influx mechanism was suggested to be involved in this cardiotonic effect.[16] Fine investigation on the action mechanism of cardiotonic effects of capsaicin derivatives will be described in our further report.

The present 4-ether-linked phenoxypropanolamines of guacol based *N*-nonanoylvanillamide (synthetic capsaicin), chemically different from other para-substituted phenoxypropanolamines and a number of cardioselective agents of this type, e.g. atenolol, practolol, betaxolol, metoprolol, and pamatolol, reveals β-adrenergic blocking activities and novel intrinsic cardiotonic activity.

Experimental Section

General Information. All melting points were measured with a Yanaco MP-J3 micromelting point apparatus and are uncorrected. Infrared spectra were recorded through a KBr disk (ν in cm^{-1}) on a Hitachi 270-30 IR spectrophotometer. ^1H nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 FT-NMR spectrometer, using DMSO-d_6 as solvent and TMS as internal standard (chemical shift in δ, ppm). Mass spectra were recorded with a JEOR-D100 GC–mass spectrometer. Elemental analyses were performed on a Heracous CHN-O-Rapid analyzer and were within 0.4% of the theoretical values unless otherwise indicated.

Capsaicin was purchased from Sigma Co. Nonivamide, (dimethylamino)ethyl chloride, (diethylamino)ethyl chloride, 2-(chloromethyl)pyridine hydrochloride, and 2-(chloroethyl)-piperidine hydrochloride were obtained from Tokto Chemical Industry Co. (TCI). All other reagents used in this study were EP-grade products of E. Merck. Animals were obtained from the Experimental Animal Center, Cheng-Kung National University Medical College, Tainan, Taiwan.

Synthesis. *N*-[4-(2,3-Epoxypropoxy)-3-methoxybenzyl]-nonanamide (3). Epichlorohydrine (30 mL) was added to a solution of **2** (nonivamide) (10 g, 34 mmol) in an aqueous ethanol solution (60 mL) containing 3 g of sodium hydroxide. The resulting solution was heated at 80 °C for 3 h. The white precipitate in the cooled reaction mixture was filtered off, and the filtrate was then concentrated under reduced pressure. The residual product was crystallized from absolute ethanol to afford **3** (10.1 g, 85%) as white crystals: mp 124–125 °C; UV (MeOH) λ_{max} nm (log ϵ) 228.5 (3.98), 278 (3.48); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3), 1.26 (m, 10H, $CH_2 \times 5$), 1.65 (s, 2H, $CH_2 \times 1$), 2.20 (t, 2H, $CH_2 \times 1$), 2.74–2.90 (m, 2H, CH_2 of the epoxide), 3.36 (br s, 1H, CH of epoxide), 3.86 (s, 3H, OCH_3), 4.03–4.12 (dd, 2H, Ar-OCH_2), 4.36 (d, 2H, Ar-CH_2), 5.71 (s, 1H, NH), 6.81–6.91 (m, 3H, Ar); IR (KBr) 1640, 1600, 1220 cm^{-1}; MS m/z 349 $(M + H)^+$. Anal. ($C_{20}H_{31}NO_4$) C, H, N.

The general method for the amination of 3–10 mL of each amine such as methylamine, ethylamine, allylamine, cyclopropylamine, *n*-butylamine, isobutylamine, *sec*-butylamine, *tert*-butylamine, *n*-pentylamine, 3-aminopentane, *n*-hexylamine, cyclohexylamine, heptylamine, and benzylamine was to add 5 g (14.3 mol) of 3 and 50 mL of methanol, respectively. Each mixture was heated under nitrogen at 50–55 °C for 4 h, with stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residual product was extracted with 40 mL of *n*-hexane, and the *n*-hexane layer was concentrated and crystallized from *n*-hexane to produce **4–19**.

N-[4-(2-Hydroxy-3-(methylamino)propoxy)-3-methoxybenzyl]nonanamide (4). An 84% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 98–101 °C; UV (MeOH) λ_{max} nm (log ϵ) 229 (3.70), 278 (3.38); ^{1}H NMR ($CDCl_3$) δ 1.96 (br s, 1H, exchangeable, O*H*), 2.47 (s, 3H, NHCH_3), 2.79 (dd, 2H, CH_2NH), 4.01 (d, 2H, ArOCH_2), 4.08 (m, 1H, C*H*(OH)), 5.69 (s, 1H, N*H*); MS *m/z* 380 (M + H)$^+$. Anal. ($C_{21}H_{36}N_2O_4$) C, H, N.

N-[[4-(2-Hydroxy-3-(ethylamino)propoxy)-3-methoxybenzyl]nonanamide (5). An 85% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 102–103 °C; UV (MeOH) λ_{max} nm (log ϵ) 229 (3.72), 278.5 (3.27); ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3H, CH_3), 2.62 (br s, 1H, exchangeable, O*H*), 2.63–2.83 (m, 4H, CH_2NHCH_2), 3.98 (d, 2H, ArOCH_2), 4.05 (m, 1H, C*H*(OH)), 5.88 (s, 1H, N*H*); MS *m/z* 393 (M + H)$^+$. Anal. ($C_{22}H_{38}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(allylamino)propoxy)-3-methoxybenzyl]nonanamide (6). An 83% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 98–99 °C; UV (MeOH) λ_{max} nm (log ϵ) 228.5 (4.19), 278 (3.69); ^{1}H NMR ($CDCl_3$) δ 2.40 (br s, 1H, exchangeable, O*H*), 2.82 (m, 2H, (OH)CHCH_2NH), 3.28 (dt, 2H, NHCH_2CH=), 4.02 (m, 3H, ArOCH_2C*H*(OH)), 5.15 (m, 2H, CH=CH_2), 5.77 (s, 1H, N*H*), 5.89 (m, 1H, C*H*=CH$_2$); MS *m/z* 406 (M + H)$^+$. Anal. ($C_{23}H_{38}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(cyclopropylamino)propoxy)-3-methoxybenzyl]nonanamide (7). An 87% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 120–122 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (3.71), 278 (3.30); ^{1}H NMR ($CDCl_3$) δ 0.40 (m, 4H, CH_2CH_2), 2.19 (m, 1H, NHC*H*), 2.33 (br s, 1H, exchangeable, O*H*), 2.90 (m, 2H, CHCH_2NH), 4.12 (m, 3H, ArOCH_2C*H*(OH)), 5.77 (s, 1H, N*H*); MS *m/z* 406 (M + H)$^+$. Anal. ($C_{23}H_{38}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*n*-propylamino)propoxy)-3-methoxybenzyl]nonanamide (8). A 91% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 132–133 °C; UV (MeOH) λ_{max} nm (log ϵ) 228 (4.23), 277.5 (3.73); ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3H, CH_3), 1.85–1.95 (qt, 2H, CH_2CH$_3$), 3.05 (br s, 1H, exchangeable, O*H*), 3.03–3.38 (m, 4H, CH_2NHCH_2), 4.02 (m, 3H, ArOCH_2C*H*(OH)); MS *m/z* 407 (M)$^-$. Anal. ($C_{23}H_{40}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(isopropylamino)propoxy)-3-methoxybenzyl]nonanamide (9). A 90% yield as a white solid: mp 120–121 °C; UV (MeOH) λ_{max} nm (log ϵ) 228.5 (3.95), 278 (3.47); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3), 1.11 (d, 6H, CH_3 × 2), 1.26–2.24 (m, 14H, CH_2 × 7), 2.54 (br s, 1H, exchangeable, O*H*), 2.70–2.90 (m, 3H, CH_2NHC*H*), 3.83 (s, 3H, OCH_3), 3.95–4.06 (m, 3H, ArOCH_2C*H*(OH)), 4.35 (d, 2H, ArCH_2), 5.71 (s, 1H, N*H*), 6.81–6.91 (m, 3H, Ar); IR (KBr) 3400, 1640 cm^{-1}; MS *m/z* 408 (M + H)$^+$. Anal. ($C_{23}H_{40}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*n*-butylamino)propoxy)-3-methoxybenzyl]nonanamide (10). An 84% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 125–127 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.21), 278 (3.74); ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H, CH_3), 1.45 (m, 4H, CH_2 × 2), 2.42 (br s, 1H, exchangeable, O*H*), 2.63 (t, 2H, NHCH_2), 2.80 (m, 2H, CH_2NH), 4.02 (m, 3H, AroCH_2C*H*(OH)), 5.78 (s, 1H, N*H*); MS *m/z* 422 (M + H)$^+$. Anal. ($C_{24}H_{42}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(isobutylamino)propoxy)-3-methoxybenzyl]nonanamide (11). An 89% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 130–132 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.20), 278 (3.72); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 6H, CH_3 × 2), 1.75 (m, 1H, NHCH$_2$C*H*), 2.12 (br s, 1H, exchangeable, O*H*), 2.46 (d, 2H, NHCH_2CH), 2.80 (m, 2H, CH_2-NH), 4.04 (m, 3H, ArOCH_2C*H*(OH)), 5.78 (s, 1H, N*H*); MS *m/z* 422 (M + H)$^+$. Anal. ($C_{24}H_{42}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*sec*-butylamino)propoxy)-3-methoxybenzyl]nonanamide (12). An 85% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 120–122 °C; UV (MeOH) λ_{max} nm (log ϵ) 228 (4.28), 278 (3.82); ^{1}H NMR ($CDCl_3$) δ 0.94 (m, 3H, CH_3), 1.05 (d, 3H, CH(CH_2)), 2.16 (br s, 1H, exchangeable, O*H*), 2.65 (m, 1H, NHC*H*), 2.80 (m, 2H, (OH)-CHCH_2NH), 4.02 (m, 3H, ArOCH_2C*H*(OH)), 5.78 (s, 1H, N*H*); MS *m/z* 422 (M + H)$^+$. Anal. ($C_{24}H_{42}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*tert*-butylamino)propoxy)-3-methoxybenzyl]nonanamide (13). An 88% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 95–96 °C; UV (MeOH) λ_{max} nm (log ϵ) 228 (3.51), 277.5 (3.01); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H, CH_3 × 3), 2.47 (br s, 1H, exchangeable, O*H*), 2.75 (m, 2H, CH_2NHC), 3.99 (m, 3H, ArOCH_2C*H*(OH)), 5.77 (s, 1H, N*H*); MS *m/z* 422 (M + H)$^+$. Anal. ($C_{24}H_{42}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*n*-pentylamino)propoxy)-3-methoxybenzyl]nonanamide (14). An 85% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 105–106 °C; UV (MeOH) λ_{max} nm (log ϵ) 228 (3.56), 278 (3.10); ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 3H, CH_3), 1.26 (m, 4H, CH_2 × 2), 1.49 (t, 2H, CH_2 × 1), 2.75 (br s, 1H, exchangeable, O*H*), 2.60–2.82 (m, 4H, CH_2-NHCH_2), 3.99 (m, 3H, ArOCH_2C*H*(OH)), 5.91 (s, 1H, N*H*); MS *m/z* 436 (M + H)$^+$. Anal. ($C_{25}H_{44}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-((3-aminopentyl)amino)propoxy)-3-methoxybenzyl]nonanamide (15). An 81% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 122–123 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.16), 278 (3.72); ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6H, CH_3 × 2), 1.42 (m, 4H, CH_2 × 2), 2.42 (br s, 1H, exchangeable, O*H*), 2.37 (m, 1H, NHC*H*), 2.82 (m, 2H, CH_2NH), 4.00 (m, 3H, ArOCH_2C*H*(OH)), 5.81 (s, 1H, N*H*); MS *m/z* 436 (M + H)$^+$. Anal. ($C_{25}H_{44}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*n*-hexylamino)propoxy)-3-methoxybenzyl]nonanamide (16). An 85% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 130–132 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.17), 278 (3.74); ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 3H, CH_3), 1.26 (m, 4H, CH_2 × 2), 1.49 (t, 2H, CH_2 × 1), 2.75 (br s, 1H, exchangeable, O*H*), 2.60–2.82 (m, 4H, CH_2-NHCH_2), 3.99 (m, 3H, ArOCH_2C*H*(OH)), 5.91 (s, 1H, N*H*); MS *m/z* 450 (M + H)$^+$. Anal. ($C_{26}H_{46}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(cyclohexylamino)propoxy)-3-methoxybenzyl]nonanamide (17). An 86% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 95–98 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.15), 278 (3.74); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 4H, CH_2 × 2), 1.67 (m, 4H, CH_2 × 2), 1.90 (d, 2H, CH_2 × 1), 2.21 (br s, 1H, exchangeable, O*H*), 2.43 (m, 1H, NHC*H*), 2.87 (m, 4H, CH_2NH), 3.99 (m, 3H, ArOCH_2C*H*(OH)), 5.76 (s, 1H, N*H*); MS *m/z* 448 (M + H)$^+$. Anal. ($C_{28}H_{44}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(*n*-heptylamino)propoxy)-3-methoxybenzyl]nonanamide (18). An 84% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 93–97 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (3.86), 278 (3.42); ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 3H, CH_3), 1.26 (s, 8H, CH_2 × 4), 1.48 (t, 2H, CH_2 × 1), 2.05 (br s, 1H, exchangeable, O*H*), 2.68 (dd, 2H, NHCH_2), 2.81 (m, 2H, CH_2NH), 4.08 (m, 3H, ArOCH_2C*H*(OH)), 5.78 (s, 1H, N*H*); MS *m/z* 464 (M + H)$^+$. Anal. ($C_{27}H_{48}N_2O_4$) C, H, N.

N-[4-(2-Hydroxy-3-(benzylamino)propoxy)-3-methoxybenzyl]nonanamide (19). A 91% yield as a white solid was extracted and recrystallized from *n*-hexane: mp 96–102 °C; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.17), 278 (3.72); ^{1}H NMR ($CDCl_3$) δ 2.58 (br s, 1H, exchangeable, O*H*), 2.85 (m, 2H, CH_2NH), 3.81 (d, 2H, NHCH_2Ar), 4.01 (m, 3H, ArOCH_2C*H*(OH)), 5.82 (s, 1H, N*H*), 7.33 (m, 3H, Ar); MS *m/z* 456 (M + H)$^+$. Anal. ($C_{27}H_{40}N_2O_4$) C, H, N.

General Method for the O-Alkylation of Nonivamide. To the mixture of alkylamine (1.3 g) and **2** (2.0 g) in a three-neck flask equipped with mechanical stirrer was added dropwise 4 mL of 30% NaOH over 30 min at room temperature with vigorous stirring. The reaction mixture was then boiled on a mantle heater for 7 h. After cooling, benzene was added to precipitate the insolvated salt. The benzene layer was then removed under reduced pressure. *n*-Hexane or benzene was used to extract the residue several times. After evaporation of the solvent, the product that formed was filtered and recrystallized from *n*-hexane or benzene.

N-[4-((Dimethylamino)ethoxy)-3-methoxybenzyl]nonanamide (20). A 73% yield as colorless white-brown needles that recrystallized from *n*-hexane: mp 78–80 °C; UV (MeOH) λ_{max} nm (log ϵ) 201 (5.47); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3), 1.20–2.25 (m, 14 H, CH_2 × 7), 2.39–2.43 (s, 6H, (CH_3)$_2$N), 2.8–2.9 (t, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 4.13 (t, 2H, OCH_2), 4.36–4.40 (d, 2H, ArCH_2), 5.70 (br, 1H, N*H*), 6.81–6.83 (m, 3H, Ar); IR (KBr) 3300, 3100, 2800–3000, 1600, 1500, 1200, 650 cm^{-1}; MS (FAB) *m/z* 365 (M$^+$). Anal. ($C_{21}H_{36}N_2O_3$) C, H, N.

N-[4-((Diethylamino)ethoxy)-3-methoxybenzyl]nonanamide (21). A 68% yield as colorless white-brown needles that recrystallized from *n*-hexane: mp 51–53 °C; UV (MeOH) λ_{max}

nm (log ε) 201 (5.14); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3), 1.05–1.13 (t, 6H, $CH_3 \times 2$), 1.20–2.25 (m, 14H, $CH_2 \times 7$), 2.60–2.75 (q, 4H, $(CH_2)_2N$), 2.95–3.0 (t, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 4.11 (t, 2H, OCH_2), 4.32–4.40 (d, 2H, $ArCH_2$), 5.70 (br, 1H, NH), 6.78–6.90 (m, 3H, Ar); IR (KBr) 3300, 2800–3000, 1620, 1520, 1250, 800, 650 cm^{-1}; MS (FAB) *m/z* 393 (M^+). Anal. ($C_{23}H_{40}N_2O_3$) C, H, N.

***N*-[4-(Pyridylmethoxy)-3-methoxybenzyl]nonanamide (22).** An 82% yield as colorless white-brown needles that was extracted and recrystallized from benzene: mp 99–101 °C; UV (MeOH) λ_{max} nm (log ε) 280 (4.15), 314 (3.18), 327 (3.20); ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 3H, CH_3), 1.25–2.22 (m, 14H, $CH_2 \times 7$), 3.5 (s, 3H, OCH_3), 3.9 (s, 2H, NCH_2Ar), 4.5 (d, 2H, OCH_2Ar), 5.3 (s, 1H, CONH), 6.8 (m, 3H, Ar), 7.2–7.8 (m, 4H, Ar); IR (KBr) 3300, 2850–3000, 1620, 1525, 1280, 800, 750 cm^{-1}; MS (FAB) *m/z* 386 (M^+). Anal. ($C_{23}H_{32}N_2O_3$) C, H, N.

***N*-[4-(Piperidylethoxy)-3-methoxybenzyl]nonanamide (23).** A 78% yield as colorless white-brown needles that was extracted and recrystallized from benzene: mp 77–78 °C; UV (MeOH) λ_{max} nm (log ε) 280 (3.50); ^{1}H NMR ($CDCl_3$) δ 0.8–0.9 (t, 3H, CH_3), 1.2–1.6 (m, 6H, $CH_2 \times 3$), 1.2–2.8 (m, 14 H, $CH_2 \times 7$), 2.62–2.75 (m, 6H, $(CH_2)_3N$), 3.4 (m, 2H, CH_2NCO), 3.7 (s, 3H, OCH_3), 4.0–4.2 (m, 2H, OCH_2), 6.7–6.8 (m, 3H, Ar), 8.2 (s, 1H, CONH); IR (KBr) 3300, 2850–3000, 1620, 1510, 1220, 800, 750 cm^{-1}; MS (FAB) *m/z* 404 (M^+). Anal. ($C_{24}H_{40}N_2O_3$) C, H, N.

Pharmacology. Measurement of Blood Pressure and Heart Rate. The in vivo experiments have been described previously.[11,17] In brief, male Wistar rats, weighing 250–350 g, were anesthetized with urethane (1.5 g/kg, ip). Following tracheal cannulation, systemic arterial blood pressure and heart rate were recorded from the femoral artery with a pressure transducer (Gould Inc., Model P50) connected to a pressure processor amplifier (13-4615-52, Gould) and displayed on a recorder (8188-4402, Gould). Body temperature was maintained at 37 °C. The femoral vein was cannulated for iv injections and a retrograde cannulation was performed on a superficial epigastric artery for ia injections into the hind leg via the femoral artery. The magnitudes of the changes in arterial blood pressure and heart rate between the responses and basal blood pressure or heart rate. Statistical analysis of the results was performed by using analysis of variance.

Measurement of Isolated Atria of the Guinea Pig. Experiments were performed following the method described in a previous publication from this laboratory.[18] Right atrial preparation which retained a spontaneous rhythm was used for assessment of chronotropic effects, while inotropic effects were examined with left atrial preparations. The experiments were carried out at 32.5 °C containing Kreb's solution of the following composition (mM): NaCl 113, KCl 4.8, $CaCl_2$ 2.2, KH_2PO_4 1.2, $MgCl_2$ 1.2, $NaHCO_3$ 25, dextrose 11.0, bubbled with 95% O_2 and 5% CO_2. As β-agonist, 1-isoproterenol was administered to the preparation in a cumulative fashion after an equilibration period of 90 min in Kreb's solution and a concentration–response curve was established. The atria were then allowed a 30–60 min washout period to restabilize, after which time various concentrations of the test compound were incubated with the atrium 15 min before isoproterenol. The activity of the test compound was expressed as pA_2 value, which was calculated from the parallel shifts of the cumulative concentration–response curve of isoproterenol.[19]

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References

(1) Monsereenusorn, Y.; Kongsamut, S.; Pezalla, P. D. Capsaicin—a Literature Survey. *CRC Crit. Rev. Toxicol.* **1982**, *10*, 321–339.

(2) Buck, S. H.; Burks, T. F. The Neuropharmacology of Capsaicin: Review of Some Recent Observations. *Pharmacol Rev.* **1986**, *38*, 179–226.

(3) Holzer, P. Capsaicin: Cellular Targets, Mechanisms of Action, and Selectivity for the Sensory Neurons. *Pharmacol. Rev.* **1991**, *43*, 143–201.

(4) Chahl, L. A.; Lynch, A. M. The Acute Effects of Capsaicin on the Cardiovascular System. *Acta Physiol. Hung.* **1987**, *69*, 413–419.

(5) Franco-Cereceda, A.; Lundberg, J. M.; Saria, A.; Schreibmayer, W.; Tritthart, H. A. Calcitonin Gene-Related Peptide: Release by Capsaicin and Prolongation of the Action Potential in the Guinea-Pig Heart. *Acta Physiol. Scand.* **1988**, *132*, 181–190.

(6) Szolcsányi, J.; Jancsó-Gábor, A. Sensory Effects of Capsaicin Congeners. I. Relationship Between Chemical Structure and Pain-Producing Potency of Pungent Agents. *Arzneim.-Forsch. Drug Res.* **1975**, *25*, 1877–1881.

(7) Wu, E. S. C.; Cole, T. E.; Davidson, T. A.; Blosser, J. C.; Borrelli, A. R.; Kinsolving, C. R.; Milgate, T. E.; Parker, R. B. Flavones. 1. Synthesis and Antihypertensive Activity of (3-Phenylflavonoxy)-propanolamines without β-Adrenoceptor Antagonism. *J. Med. Chem.* **1987**, *30*, 788–792.

(8) Fujii, T.; Ohbuchi, Y.; Takahashi, S.; Sakurada, T.; Sakurada, S.; Ando, R.; Kisara, K. Studies on the Hypothermic Response of Capsaicin and its Analogue in Mice. *Arch. Int. Pharmacodyn.* **1986**, *280*, 165–176.

(9) Chen, I. J.; Yang, J. M.; Yeh, J. L.; Wu, B. N.; Lo, Y. C.; Chen, S. J. Hypotensive and Antinociceptive Effects of Ether-Linked and Relatively Nonpungent Analogues of N-Nonanoyl Vanillylamide. *Eur. J. Med. Chem.* **1992**, *27*, 187–192.

(10) Harada, S.; Ban, T.; Fujita, T.; Koshiro, A. Negative Inotropic effects and the Hydrophobicity of Beta-Adrenergic Blocking Agents. *Arch. Int. Pharmacodyn.* **1981**, *252*, 262–271.

(11) Yeh, J. L.; Lo, Y. C.; Wang, Y.; Chen, I. J. Cardiovascular Interactions of Nonivamide, Glyceryl Nonivamide, Capsaicin Analogues, and Substance P Antagonist in Rats. *Brain Res. Bull.* **1993**, *30*, 641–648.

(12) Szolcsányi, J.; Jancsó-Gábor, A. Sensory Effects of Capsaicin Congeners. II. Importance of Chemical Structure and Pungency in Desensitizing Activity of Capsaicin-Type Compounds. *Arzneim.-Forsch. Drug Res.* **1976**, *26*, 33–37.

(13) Walpole, C. S. J.; Wrigglesworth, R.; Bevan, S.; Campbell, E. A.; Dray, A.; James, D. F.; Perkins, M. N.; Reid, D. J.; Winter, J. Analogues of Capsaicin with Agonist Activity as Novel Analgesic Agents; Structure-Activity Studies. 1. The Aromatic "A-Region". *J. Med. Chem.* **1993**, *36*, 2362–2372.

(14) Szolcsányi, J. A. Pharmacological Approach to Elucidation of the Role of Different Nerve Fibres and Receptor Endings in Mediation of Pain. *J. Physiol.* Paris **1977**, *73*, 251–259.

(15) Donnerer, J.; Lembeck, F. Capsaicin-Induced Reflex Fall in Rat Blood Pressure is Mediated by Afferent Substance P-Containing Neurones via a Reflex Center in the Brain Stem. *Naunyn-Schmiedeberg's Arch Pharmacol.* **1983**, *324*, 293–295.

(16) O'Neill, T. P. Mechanism of Capsaicin Action: Recent Learnings. *Repair Med.* **1991**, *85* (Suppl. A), 35–41.

(17) Yang, J. M.; Wu, S. N.; Chen, I. J. Spinal Adenosine Modulates Capsaicin-Induced Depressor Reflex: Involvement of Adenosine A_2 Receptor. *Gen. Pharm.* **1993**, *24*, 961–970.

(18) Chen, I. J.; Liou, S. J.; Liou, S. S.; Lin, C. N. Xanthonolol: a Calcium Channel and Beta-Adrenoceptor Blocker with Vasodilating Properties. *Gen. Pharm.* **1993**, *24*, 1425–1433.

(19) Arunlakshana, O.; Schild, H. O. Some Quantitative Uses of Drug Antagonists. *Br. J. Pharmacol.* **1959**, *14*, 48–57.