

Studies on Cardiotonic Agents. IV.¹⁾ Synthesis of Novel 1-(6,7-Dimethoxy-4-quinazolinyl)piperidine Derivatives Carrying Substituted Hydantoin and 2-Thiohydantoin Rings

Yuji NOMOTO,^{*,a} Haruki TAKAI,^a Tadashi HIRATA,^a Masayuki TERANISHI,^a Tetsuji OHNO^b and Kazuhiro KUBO^b

Tokyo Research Laboratory, Kyowa Hakko Kogyo Co., Ltd.,^a Asahimachi 3-6-6, Machidashi, Tokyo 194, Japan and Pharmaceutical Research Laboratory, Fuji, Kyowa Hakko Kogyo Co., Ltd.,^b Shimotogari 1188, Nagaizumicho, Shizuoka 411, Japan. Received April 11, 1990

A series of novel 1-(6,7-dimethoxy-4-quinazolinyl)piperidines carrying substituted hydantoin and 2-thiohydantoin rings was synthesized and examined for cardiotonic activity in anesthetized dogs. Introduction of isopropyl and *sec*-butyl group at the 5-position of the hydantoin and thiohydantoin rings led to potent inotropic activity. Effects of insertion of an alkyl chain between the piperidine and the hydantoin rings were also examined. The structural requirements necessary for optimal cardiotonic activity within the series were investigated.

Keywords cardiotonic agent; structure-activity relationship; piperidine; quinazoline; hydantoin; thiohydantoin

As a part of an ongoing project to discover novel compounds bearing a potent positive inotropic activity for treatment of congestive heart failure,²⁾ we recently reported the synthesis of a series of 1-(6,7-dimethoxy-4-quinazolinyl)-4-piperidine derivatives.^{1,3)} In the course of our studies, we found some of these compounds showed potent inotropic activity. Encouraged by these results, we carried out further studies to synthesize other analogues of the series. This paper describes the synthesis and pharmacological activities of 1-(6,7-dimethoxy-4-quinazolinyl)piperidine derivatives carrying hydantoin and 2-thiohydantoin rings at the 4-position of the piperidine ring (Chart 1, formula A), as summarized in Table III.

Chemistry

We attempted to synthesize the hydantoin and the 2-thiohydantoin derivatives listed in Table III. The hydantoin derivatives were prepared in 3 steps from the 1-

(6,7-dimethoxy-4-quinazolinyl)-4-piperidinylalkylamines (Ia—Ic)⁴⁾ and *N*-*tert*-butoxycarbonyl (Boc)-L-amino acids (Chart 2, method A). Thus, condensation of I with Boc-L-amino acid afforded II (Table I), followed by deprotection of II with trifluoroacetic acid (TFA) gave the aminoacetamides (III) (Table II). Cyclization of III with *N,N'*-carbonyldiimidazole (CDI) gave IV. In these reactions, complete racemization occurred at the 5-position of the hydantoin, so optically active compounds were not obtained. In the case of the 2-(4-piperidinyl)ethylamine (Ic), addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was essential for completion of cyclization of the corresponding aminoacetamides (III) with CDI. Compounds IVa—IVm were synthesized by method A.

The synthesis of the 2-thiohydantoins (V) is also outlined in Chart 2. The aminoacetamides (III) were cyclized with CS₂ to afford V (method B). By this method, compounds Va—Vb and Ve—Vf were prepared. In the reactions, racemization occurred at the 5-position of the thiohydantoin ring.

An alternative synthetic route of 2-thiohydantoins is outlined in Chart 3 (method C).⁵⁾ Treatment of I with CS₂ and subsequent methylation with MeI gave the dithiocarbamates (VI). Without isolation, VI reacted with L-amino acids to afford the 2-thiohydantoins V. The 1-(4-piperidinyl)methyl derivatives (Vg—Vs) were prepared from the dithiocarbamate VIb (X=CH₂) using this procedure.

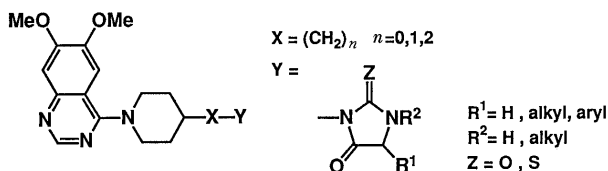


Chart 1

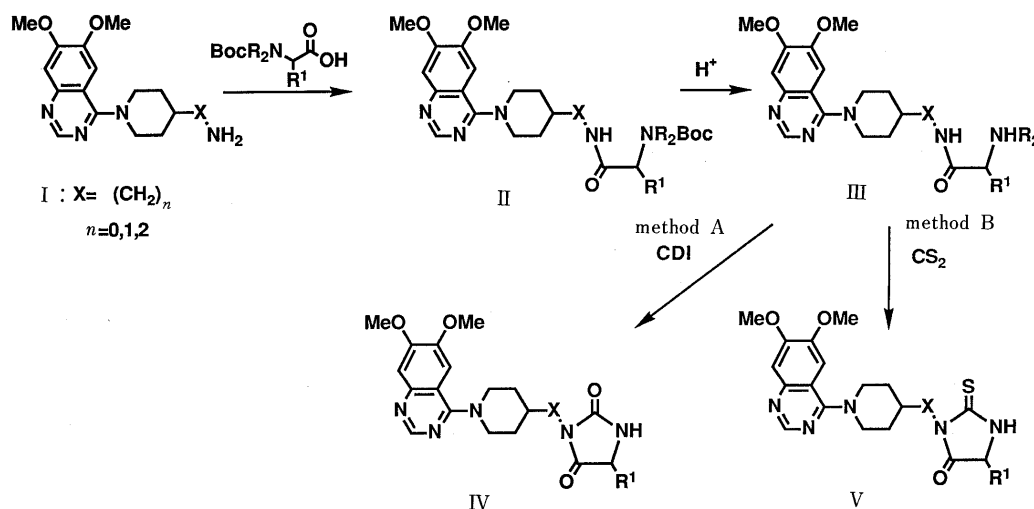


Chart 2

TABLE I

Compd. No.	R ¹	R ²	X	Yield (%)	[α] _D (MeOH)	mp (°C) (Recrystn. solv.)	Formula	Analysis (%)			¹ H-NMR (δ ppm, CDCl ₃)
								Calcd	Found	N	
Ia	Me	H	—	96	−8.9 (c=1.1)	210 (MeOH–Et ₂ O)	C ₂₃ H ₃₃ N ₅ O ₅ ·H ₂ O	57.83 (57.57)	7.40 7.02	14.65 14.45	1.42 (3H, d, <i>J</i> =7 Hz, CHCH ₃)
Iib	iso-Pr	H	—	74	3.0 (c=1.0)	Amorphous	C ₂₅ H ₃₇ N ₅ O ₅	Calcd 487.2796 ^{c)} Found 487.2812			0.97, 0.94 (each 3H, d, <i>J</i> =7 Hz, CH (CH ₃) ₂)
Iic	CH ₂ CH ₂ SMe	H	—	70	−5.2 (c=1.0)	Amorphous	C ₂₅ H ₃₇ N ₅ O ₅ S	Calcd 519.2516 ^{c)} Found 519.2525			2.10 (3H, s, SCH ₃)
Iid	CH ₂ Ph	H	—	95	17.6 (c=1.0)	Amorphous	C ₂₉ H ₃₇ N ₅ O ₅	Calcd 535.2795 ^{c)} Found 535.2779			7.17 (6H, s, Ar-H, C ₆ H ₅)
Iie	H	H	CH ₂	82	—	Amorphous	C ₂₃ H ₃₃ N ₅ O ₅	Calcd 459.2482 ^{c)} Found 459.2475			3.77 (2H, d, <i>J</i> =7 Hz, COCH ₂)
Iif	Me	H	CH ₂	80	−12.2 (c=1.1)	Amorphous	C ₂₄ H ₃₅ N ₅ O ₅	Calcd 473.2648 ^{c)} Found 473.2660			1.37 (3H, d, <i>J</i> =8 Hz, CHCH ₃)
Iig	iso-Pr	H	CH ₂	76	−10.1 (c=1.0)	Amorphous	C ₂₆ H ₃₉ N ₅ O ₅	Calcd 501.2952 ^{c)} Found 501.2939			0.98, 0.95 (each 3H, d, <i>J</i> =7 Hz, CH(CH ₃) ₂)
Iih	iso-Bu	H	CH ₂	92	−13.8 (c=0.98)	Amorphous	C ₂₇ H ₄₁ N ₅ O ₅	Calcd 515.3108 ^{c)} Found 515.3091			0.97, 0.95 (each 3H, d, <i>J</i> =7 Hz, CH(CH ₃) ₂)
Iii	Ph ^{a)}	H	CH ₂	51	−29.6 (c=0.98)	Amorphous	C ₂₉ H ₃₇ N ₅ O ₅	Calcd 535.2795 ^{c)} Found 535.2789			7.27 (5H, s, C ₆ H ₅)
Iij	CH ₂ Ph ^{b)}	H	CH ₂	98	—	134–135.5 (Me ₂ CO)	C ₃₀ H ₃₉ N ₅ O ₅ ·1/2H ₂ O	64.50 (64.21)	7.22 7.45	12.54 12.46	7.25 (6H, s, Ar-H, C ₆ H ₅)
Iik	CH ₂ Ph(4-OBzl)	H	CH ₂	51	2.5 (c=1.1)	151–154.5 (Me ₂ CO)	C ₃₇ H ₄₅ N ₅ O ₆	67.77 (67.81)	6.92 7.10	10.68 10.33	7.35 (5H, s, C ₆ H ₅), 7.10, 6.90 (each 2H, <i>J</i> =8 Hz, Ar-H)
III	iso-Pr	H	CH ₂ CH ₂	75	−9.9 (c=0.96)	Amorphous	C ₂₇ H ₄₁ N ₅ O ₅	Calcd 515.3108 ^{c)} Found 515.3132			0.97, 0.94 (each 3H, d, <i>J</i> =7 Hz, CH(CH ₃) ₂)
IIm	−CH ₂ CH ₂ CH ₂ −		CH ₂ CH ₂	65	−27.2 (c=0.76)	Amorphous	C ₂₇ H ₃₉ N ₅ O ₅	Calcd 513.2951 ^{c)} Found 513.2966			4.30–1.45 (20H, m, piperidine, proline, CH ₂ CH ₂)

a) Boc-D-phenylglycine was used. b) Boc-DL-phenylalanine was used. c) Determined by high-resolution mass spectrometry.

method C

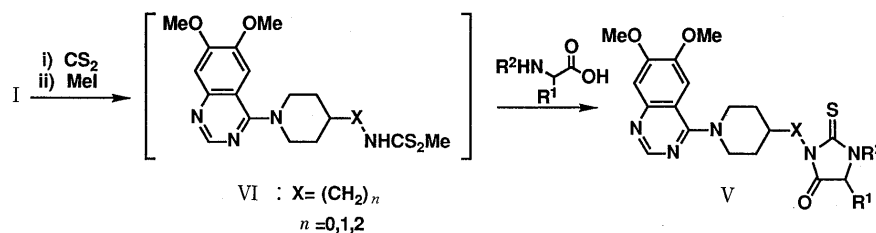


Chart 3

method D

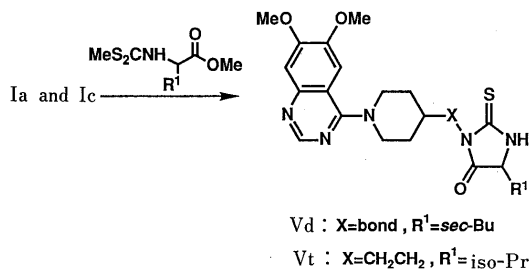


Chart 4

The 1-methyl-2-thiohydantoin (Vc) was also obtained by reaction of the dithiocarbamate VIa (X=bond) with *N*-methyl-L-valine in 43% yield. But reactions of VIa and

VIc (X=CH₂CH₂) with L-valine did not afford the desired thiohydantoins.

Method D involves the use of *N*-(methylthio)thioxomethyl-L-amino acid methyl esters.⁶⁾ Compound Vd was synthesized from the reaction of Ia with *N*-(methylthio)thioxomethyl-L-isoleucine methyl ester in dimethylformamide (DMF) at 120 °C. Similarly, Vt was obtained from the reaction of Ic with *N*-(methylthio)thioxomethyl-L-valine methyl ester (Chart 4).

Reaction of the 4-piperidinylmethylisothiocyanate (VII) with L-valine ethyl ester also gave Vi (method E, Chart 5).⁷⁾ The intermediate VII was prepared from Ib by reaction with CS₂ and subsequent treatment with ethyl chloroformate.

In all of these methods (methods B–E), complete racemi-

method E

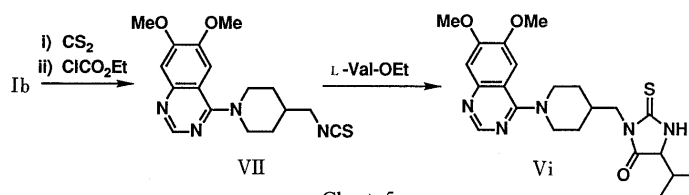


TABLE II

Compd. No.	R ¹	R ²	X	Yield ^{a)} (%)	[α] _D (MeOH)	mp (°C) (Recrystn. solv.)	Formula	Analysis (%)			¹ H-NMR (δ ppm, CDCl ₃)
								Calcd	Found	N	
IIIa	Me	H	—	91	2.9 (c=0.48)	Amorphous	C ₁₈ H ₂₅ N ₅ O ₃	Calcd 359.1958 ^{b)}	Found 359.1984		1.33 (3H, d, J=7 Hz, CHCH ₃)
IIIb	iso-Pr	H	—	80	3.1 (c=0.78)	Amorphous	C ₂₀ H ₂₉ N ₅ O ₃	Calcd 387.2271 ^{b)}	Found 387.2267		0.98, 0.85 (each 3H, d, J=7 Hz, CH(CH ₃) ₂)
IIIc	CH ₂ CH ₂ SMe	H	—	99	0.3 (c=0.60)	160—162 (MeOH-Et ₂ O)	C ₂₀ H ₂₉ N ₅ O ₃ S	57.26 6.97 16.69 (57.32 6.59 16.66)			2.10 (3H, s, SCH ₃)
IIId	CH ₂ Ph	H	—	91	−9.6 (c=2.1)	Amorphous	C ₂₄ H ₂₉ N ₅ O ₃	Calcd 435.2270 ^{b)}	Found 435.2240		7.22 (6H, s, Ar-H, C ₆ H ₅)
IIIe	H	H	CH ₂	72	—	Amorphous	C ₁₈ H ₂₅ N ₅ O ₃	Calcd 359.1958 ^{b)}	Found 359.1924		3.37 (2H, s, COCH ₂)
IIIf	Me	H	CH ₂	79	−3.2 (c=0.66)	143—146 (MeOH-Et ₂ O)	C ₁₉ H ₂₇ N ₅ O ₃	61.11 7.29 18.75 (61.28 7.48 18.97)			1.35 (3H, d, J=7 Hz, CHCH ₃)
IIIg	iso-Pr	H	CH ₂	83	4.4 (c=0.72)	121—124 (MeOH-Et ₂ O)	C ₂₁ H ₃₁ N ₅ O ₃	62.82 7.78 17.44 (63.00 7.98 17.71)			0.98, 0.82 (each 3H, d, J=7 Hz, CH(CH ₃) ₂)
IIIh	iso-Bu	H	CH ₂	98	0.2 (c=1.0)	Amorphous	C ₂₂ H ₃₃ N ₅ O ₃	Calcd 415.2584 ^{b)}	Found 415.2615		0.99, 0.95 (each 3H, d, J=7 Hz, CH(CH ₃) ₂)
IIIi	Ph	H	CH ₂	78	−22.9 (c=1.3)	Amorphous	C ₂₄ H ₂₉ N ₅ O ₃	Calcd 435.2271 ^{b)}	Found 435.2253		7.27 (6H, s, C ₆ H ₅ , NH)
IIIj	CH ₂ Ph	H	CH ₂	82	—	Amorphous	C ₂₅ H ₃₁ N ₅ O ₃	Calcd 449.2427 ^{b)}	Found 449.2433		7.20 (6H, s, Ar-H, C ₆ H ₅)
IIIk	CH ₂ Ph(4-OBzl)	H	CH ₂	71	2.9 (c=0.86)	Amorphous	C ₃₂ H ₃₇ N ₅ O ₄	Calcd 555.2846 ^{b)}	Found 555.2842		7.32 (5H, s, C ₆ H ₅), 7.12, 6.87 (each 2H, J=9 Hz, Ar-H)
IIIl	iso-Pr	H	CH ₂ CH ₂	64	1.8 (c=0.60)	Amorphous	C ₂₂ H ₃₃ N ₅ O ₃	Calcd 415.2584 ^{b)}	Found 415.2588		0.98, 0.83 (each 3H, d, J=7 Hz, CH(CH ₃) ₂)
IIIIm ^{c)}	−CH ₂ CH ₂ CH ₂ −		CH ₂ CH ₂								

a) Yields were calculated as 2HCl salt. Physical and spectral data were measured after freeing from HCl. b) Determined high-resolution mass spectrometry. c) Not isolated.

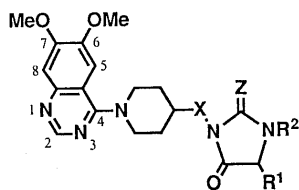
zation occurred at the 5-position of the thiohydantoin ring.

Biological Results

Cardiotonic activities of the compounds listed in Table III were evaluated in anesthetized open chest dogs using procedures previously described.³⁾ The results of the test are shown in Table IV. The positive cardiotonic activity of the test compounds was determined by measuring percent increase in maximum dP/dt left ventricular pressure (LVdP/dt max, Δ%) after i.v. administration (0.30 mg/kg) in anesthetized mongrel dogs of either sex (8—15 kg). The potency of cardiotonic activity of the test compounds was compared with that of milrinone⁸⁾ (0.10 mg/kg i.v.). Relative potency was calculated as the ratio of LVdP/dt max of each compound to that of milrinone (milrinone = 1) in the same dog.

Effects of the substituents at the 5-position of the thiohydantoin and the thiohydantoin rings were examined first. In a series of the thiohydantoin (Va—Vt), introduction of an isopropyl group at the 5-position of the thiohydantoin ring generally conferred the most potent and prolonged activity (Vb, Vi, Vt). The *sec*-butyl derivative (VI) retained the activity. In contrast, the isobutyl (Vk) and the methyl (Va, Vg) derivatives were considerably less potent than Vi. These findings may indicate that an α-branched alkyl group at the 5-position of the thiohydantoin ring is required for significant positive inotropic activity. Introduction of methyl group at the 1-position of the thiohydantoin ring retained activity (Vj). Marked loss in activity was observed in the hydroxyalkyl derivatives (Vp, Vq). The 2-methylthioethyl derivatives (Ve, Vn) showed moderate to potent cardiotonic activity.

TABLE III



Compd. No.	R ¹	R ²	X	Z	Method Yield (%)	mp (°C) (Recrystn. solv.)	Formula	Analysis (%)		
								Calcd	(Found)	
								C	H	N
IVa	Me	H	—	O	A ^{a)} 27	236—239 (MeOH-Et ₂ O)	C ₁₉ H ₂₃ N ₅ O ₄ ·HCl·1/2H ₂ O	52.96 (52.90)	5.85 (5.98)	16.25 (15.95)
IVb	iso-Pr	H	—	O	A 15	135—137 (MeOH-Et ₂ O)	C ₂₁ H ₂₇ N ₅ O ₄ ·H ₂ O	58.46 (58.83)	6.77 (6.51)	16.23 (16.10)
IVc	CH ₂ CH ₂ SMe	H	—	O	A 58	105—108 (MeOH-Et ₂ O)	C ₂₁ H ₂₇ N ₅ O ₄ S	56.61 (56.57)	6.11 (6.18)	15.72 (15.63)
IVd	CH ₂ Ph	H	—	O	A 89	147—148 (MeOH-Et ₂ O)	C ₂₅ H ₂₇ N ₅ O ₄ ·H ₂ O	62.62 (62.72)	6.10 (6.00)	14.60 (14.90)
IVe	H	H	CH ₂	O	A 39	236—237 (MeOH-CHCl ₃)	C ₁₉ H ₂₃ N ₅ O ₄	59.21 (59.32)	6.01 (5.96)	18.17 (17.89)
IVf	Me	H	CH ₂	O	A 32	166—169 (Me ₂ CO)	C ₂₀ H ₂₅ N ₅ O ₄	60.14 (59.85)	6.31 (6.51)	17.53 (17.50)
IVg	iso-Pr	H	CH ₂	O	A 38	220—221 (MeOH)	C ₂₂ H ₂₉ N ₅ O ₄	61.81 (61.72)	6.84 (6.87)	16.38 (16.29)
IVh	iso-Bu	H	CH ₂	O	A 35	214—216 (MeOH)	C ₂₃ H ₃₁ N ₅ O ₄ ·3/2H ₂ O	58.96 (58.79)	7.31 (7.29)	14.95 (14.85)
IVi	Ph	H	CH ₂	O	A 53	300 (dec.) (MeOH)	C ₂₅ H ₂₇ N ₅ O ₄	65.06 (64.91)	5.90 (5.88)	15.17 (15.16)
IVj	CH ₂ Ph	H	CH ₂	O	A 34	199—200 (MeOH)	C ₂₆ H ₂₉ N ₅ O ₄	65.67 (65.50)	6.15 (6.19)	14.73 (14.58)
IVk	CH ₂ Ph(4-OBzl)	H	CH ₂	O	A 36	159—161 (MeOH-CHCl ₃)	C ₃₃ H ₃₅ N ₅ O ₅ ·H ₂ O	66.10 (66.16)	6.22 (6.01)	11.68 (11.55)
IVl	iso-Pr	H	CH ₂ CH ₂	O	A 40	276—279 (MeOH-Et ₂ O)	C ₂₃ H ₃₁ N ₅ O ₄	62.57 (62.78)	7.08 (7.12)	15.86 (15.73)
IVm	—CH ₂ CH ₂ CH ₂ —		CH ₂ CH ₂	O	A 15 ^{b)}	168—169 (MeOH-Et ₂ O)	C ₂₃ H ₂₉ N ₅ O ₄	62.85 (62.91)	6.65 (6.60)	15.93 (16.06)
Va	Me	H	—	S	B 45	230 (MeOH-CHCl ₃)	C ₁₉ H ₂₃ N ₅ O ₃ S·H ₂ O	54.40 (54.64)	6.01 (5.64)	16.69 (16.69)
Vb	iso-Pr	H	—	S	B 10	263—267 (MeOH-Et ₂ O)	C ₂₁ H ₂₇ N ₅ O ₃ S·H ₂ O	56.36 (56.42)	6.53 (6.49)	15.65 (15.46)
Vc	iso-Pr	Me	—	S	C 43	208—209 (DMF-H ₂ O)	C ₂₂ H ₂₉ N ₅ O ₃ S	59.57 (59.28)	6.59 (6.73)	15.79 (15.40)
Vd	sec-Bu	H	—	S	D ^{a)} 84	235—238 (MeOH)	C ₂₂ H ₂₉ N ₅ O ₃ S·HCl·H ₂ O	53.06 (53.22)	6.48 (6.29)	14.06 (13.89)
Ve	CH ₂ CH ₂ SMe	H	—	S	B 24	175 (MeOH)	C ₂₁ H ₂₇ N ₅ O ₃ S ₂	54.64 (54.66)	5.90 (5.83)	15.17 (15.22)
Vf	CH ₂ Ph	H	—	S	B 66	160—168 (EtOH-CHCl ₃)	C ₂₅ H ₂₇ N ₅ O ₃ S·3/2H ₂ O	59.51 (59.73)	5.99 (5.85)	13.88 (13.79)
Vg	Me	H	CH ₂	S	C 17	177—179 (MeOH)	C ₂₀ H ₂₅ N ₅ O ₃ S·H ₂ O	55.41 (55.33)	6.28 (6.24)	16.15 (16.03)
Vh	n-Pr	H	CH ₂	S	C ^{a)} 43	216 (MeOH)	C ₂₂ H ₂₉ N ₅ O ₃ S·HCl	55.05 (54.85)	6.30 (6.36)	14.59 (14.37)
Vi	iso-Pr	H	CH ₂	S	C 41	219—220 (CHCl ₃ -EtOH)	C ₂₂ H ₂₉ N ₅ O ₃ S	59.57 (59.52)	6.59 (6.72)	15.79 (15.51)
Vj	iso-Pr	Me	CH ₂	S	E 33	159—161 (MeOH)	C ₂₃ H ₃₁ N ₅ O ₃ S·HCl·5/2H ₂ O	51.23 (50.98)	6.93 (6.56)	12.98 (13.48)
Vk	iso-Bu	H	CH ₂	S	C 23	200—204 (CHCl ₃ -EtOH)	C ₂₃ H ₃₁ N ₅ O ₃ S	60.37 (60.22)	6.83 (6.79)	15.30 (15.04)
VI	sec-Bu	H	CH ₂	S	C ^{a)} 31	201—204 (MeOH)	C ₂₃ H ₃₃ N ₅ O ₃ S·HCl	55.92 (55.80)	6.53 (6.65)	14.18 (13.88)
Vm	sec-Bu	Me	CH ₂	S	C ^{a)} 48	188—191 (MeOH)	C ₂₄ H ₃₃ N ₅ O ₃ S·HCl·H ₂ O	54.79 (54.92)	6.90 (7.17)	13.31 (13.19)
Vn	CH ₂ CH ₂ SMe	H	CH ₂	S	C 10	200 (dec.) (CHCl ₃ -EtOH)	C ₂₂ H ₂₉ N ₅ O ₃ S ₂	55.56 (55.79)	6.15 (6.30)	14.72 (14.50)
Vo	CH ₂ Ph	H	CH ₂	S	C 46	126—128 (MeOH)	C ₂₆ H ₂₉ N ₅ O ₃ S·H ₂ O	61.28 (61.52)	6.13 (6.11)	13.74 (13.82)
Vp	CH ₂ CH ₂ OH	H	CH ₂	S	C 52	136—140 (MeOH-H ₂ O)	C ₂₁ H ₂₇ N ₅ O ₄ S·H ₂ O	54.41 (54.34)	6.31 (6.29)	15.11 (14.98)
Vq	CH(Me)OH	H	CH ₂	S	C ^{a)} 29	247 (dec.) (MeOH)	C ₂₁ H ₂₇ N ₅ O ₄ S·HCl	52.33 (52.32)	5.86 (5.85)	14.53 (14.29)
Vr	CH ₂ (4-imidazolyl)	H	CH ₂	S	C 27	205—207 (MeOH)	C ₂₃ H ₂₇ N ₇ O ₃ S	57.36 (57.27)	5.65 (5.71)	20.36 (20.11)

TABLE III. (continued)

Compd. No.	R ¹	R ²	X	Z	Method Yield (%)	mp (°C) (Recrystn. solv.)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
Vs	-CH ₂ CH ₂ CH ₂ -		CH ₂	S	C ^{a)} 67	241—245 (MeOH)	C ₂₂ H ₂₇ N ₅ O ₃ S· HCl	55.28 (55.14)	5.90 (6.01)	14.65 (14.56)
Vt	iso-Pr	H	CH ₂ CH ₂	S	D 35	208—209 (MeOH)	C ₂₃ H ₃₁ N ₅ O ₃ S	60.37 (60.42)	6.83 (6.92)	15.30 (15.31)

a) As HCl salt. b) Yield from IIIm.

TABLE IV. Cardiotonic Activity of Some Quinazoline Derivatives in Anesthetized Dogs

Compd. No.	Cardiotonic activity		
	LVdP/dt max ^{a)} (4%)	Relative ^{b)} potency	Duration (min)
IVa	40.7 ± 5.8	0.89	60
IVb	39.3	(2) 0.89	30
IVc	66.8 ± 16.9	1.02	30
IVd	57.3 ± 7.3	0.79	30
IVg	57.1 ± 13.9	0.87	>60
IVh	22.8 ± 4.0	0.37	30
IVi	34.6 ± 11.2	0.46	15
IVj	47.9 ± 4.0	0.68	30
IVk	2.0	(2) —	—
IVl	87.1 ± 6.9	1.27	45
Va	32.7 ± 0.7	0.57	15
Vb	36.3 ± 8.5	0.90	60
Ve	41.0 ± 2.8	0.63	30
Vg	37.3 ± 6.0	0.69	15
Vi	65.6 ± 3.4	1.12	>60
Vj	67.8 ± 1.2	0.98	>60
Vk	33.8 ± 3.4	0.50	30
VI	65.6 ± 17.0	1.07	>60
Vn	46.9 ± 10.6	0.83	30
Vo	52.9 ± 4.6	0.75	30—45
Vp	32.9 ± 6.2	0.50	30
Vq	17.1 ± 3.6	0.29	15
Vr	8.3 ± 3.4	—	—
Vt	68.7 ± 12.4	0.95	>60

a) Each value represents the mean ± standard error of triplicate experiments except where otherwise noted in parentheses. b) Compared to the percent increase in LVdP/dt max observed with milrinone (0.1 mg/kg) in the same dog.

Similar results were obtained in the hydantoin derivatives. Thus, the isopropyl derivatives (IVb, IVg, IVl) exhibited potent activity, but these compounds generally showed shorter activity than the corresponding thiohydantoin derivatives.

Next, effects of insertion of an alkyl chain between the piperidine ring and the hydantoin or the thiohydantoin ring were also examined. In a series of 5-isopropylhydantoins (IVb, IVg, IVl), IVl (X=CH₂CH₂) showed the most potent activity, and IVg (X=CH₂) exhibited the most prolonged, while in a series of 5-isopropyl-2-thiohydantoins (Vb, Vi, Vt), Vi (X=CH₂) showed the most potent and prolonged activity.

In summary, we examined the positive inotropic activity of a series of 1-(6,7-dimethoxy-4-quinazolinyl)piperidine derivatives carrying substituted hydantoin and 2-thiohydantoin rings and clarified the structure-activity relationships.

Experimental

All melting points were determined on a micro melting point apparatus

(Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a Shimadzu IR-27G spectrophotometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were measured on a Varian EM-390 and a JNM-PS-100 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were run on a JEOL-JMS-O1SG-2 and a JMS-SX102 spectrometer. Specific rotations were measured on a JASCO DIP-370 digital polarimeter.

Method A. 3-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-5-isopropyl-2,4-dioximidazolidine (IVb) Compound I (*n*=0) (0.9 g, 3.1 mmol) was added to a mixture of Boc-L-valine (1.3 g, 6.0 mmol) and dicyclohexylcarbodiimide (DCC, 0.70 g, 3.4 mmol) in CH₃CN (30 ml) while cooling with ice. The mixture was stirred at room temperature for 30 min. Insoluble substances were removed from the reaction mixture by filtration. The filtrate was concentrated and partitioned between ethyl acetate and saturated NaHCO₃ solution. The organic layer was dried over anhydrous MgSO₄ and concentrated. By purification using a 40 g silica gel column (2% MeOH-CHCl₃), IIb (1.0 g, 74%) was obtained as oil. IR (KBr): 1700, 1650, 1505 cm⁻¹. NMR (CDCl₃) δ: 8.64 (1H, s, Ar-H), 7.22 (1H, s, Ar-H), 7.05 (1H, s, Ar-H), 6.20 (1H, m, NH), 5.08 (1H, m, NH), 4.18 (2H, m, piperidine), 4.01, 3.99 (each 3H, s, OCH₃), 3.85—1.58 (9H, m, piperidine, -CHCH-), 1.44 (9H, s, Boc), 0.96, 0.93 (each 3H, d, *J*=7 Hz, CH(CH₃)₂). An ethyl acetate solution (1 ml) saturated with hydrogen chloride was added to a solution of IIb (0.8 g, 1.6 mmol) in MeOH (5 ml). The reaction mixture was stirred for 12 h, and the precipitated crystals were collected by filtration. The crystals were washed with ethyl acetate and dried to give IIb·2HCl (0.90 g, 80%), which was used in the next reaction without further purification. Data were measured after it had been divested of HCl. IR (KBr): 1665, 1620, 1505 cm⁻¹. NMR (CDCl₃) δ: 7.72 (1H, s, Ar-H), 7.50 (1H, br, NH), 7.38 (1H, s, Ar-H), 7.08 (1H, s, Ar-H), 4.18 (2H, m, piperidine), 4.03, 4.00 (each 3H, s, OCH₃), 3.92—1.50 (11H, m, piperidine, -CHCH-, NH₂), 1.03, 0.87 (each 3H, d, *J*=7 Hz, CH(CH₃)₂). Et₃N (0.40 ml, 2.9 mmol) and CDI (0.30 g, 1.9 mmol) were added to a suspension of the resulting material in acetonitrile (90 ml). The whole was stirred at 50°C for 2 h and concentrated. The residue was partitioned between CHCl₃ and water. The separated organic layer was dried over MgSO₄ and evaporated. The residue was purified using a 40 g silica gel column (8% MeOH-CHCl₃) to yield IVb (0.10 g, 15%). The product was recrystallized from MeOH-Et₂O. NMR (CDCl₃) δ: 8.75 (1H, s, Ar-H), 7.30 (1H, s, Ar-H), 7.18 (1H, s, Ar-H), 5.49 (1H, s, NH), 4.32 (2H, m, piperidine), 4.05, 4.02 (each 3H, s, OCH₃), 3.60—1.40 (9H, m, piperidine, -CHCH-), 1.06, 0.98 (each 3H, d, *J*=7 Hz, -CH(CH₃)₂).

3-[2-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]ethyl]-5-isopropyl-2,4-dioximidazolidine (IVl) A mixture of compound IIII (0.30 g, 0.72 mmol), DBU (0.21 ml, 1.40 mmol) and CDI (0.5 g, 3.1 mmol) in CH₃CN (20 ml) was stirred at room temperature for 30 min. The reaction mixture was concentrated and DMF (10 ml) was added thereto. The mixture was stirred at 120°C for 1 h and concentrated. The residue was purified using a 20 g silica gel column (2% MeOH-CHCl₃) to yield IVl (0.14 g, 45%) which was recrystallized from MeOH-Et₂O. IR (KBr): 1765, 1705, 1500 cm⁻¹. NMR (CDCl₃) δ: 8.60 (1H, s, Ar-H), 7.27 (1H, s, Ar-H), 7.22 (1H, s, Ar-H), 7.05 (1H, s, NH), 4.20 (2H, m, piperidine), 3.99, 3.93 (each 3H, s, OCH₃), 3.55—1.30 (13H, m, piperidine, -CHCH-, -CH₂CH₂-), 0.93 (6H, d, *J*=7 Hz, -CH(CH₃)₂).

Method B. 3-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-5-isopropyl-4-oxo-2-thioximidazolidine (Vb) A mixture of IIb·2HCl (0.40 g, 0.95 mmol), CS₂ (0.90 ml, 15.0 mmol) and Et₃N (0.4 ml, 2.9 mmol) in EtOH (20 ml) was heated at reflux for 6 h. The reaction mixture was cooled and concentrated. Water was added and the precipitate crystals were collected by filtration. The crystals were purified using a 40 g silica gel column (2% MeOH-CHCl₃) to yield Vb (0.10 g, 16%). The product was recrystallized from MeOH-Et₂O. IR (KBr): 1740, 1500, 1435 cm⁻¹. NMR (CDCl₃) δ:

8.71 (1H, s, Ar-H), 7.49 (1H, br, NH), 7.28 (1H, s, Ar-H), 7.13 (1H, s, Ar-H), 4.32 (2H, m, piperidine), 4.04, 4.00 (each 3H, s, OCH₃), 3.57–1.68 (9H, m, piperidine, –CHCH–), 1.08, 0.96 (each 3H, d, $J=7$ Hz, –CH(CH₃)₂).

3-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]methyl-5-isopropyl-4-oxo-2-thioxoimidazolidine (Vi). **a) Method C** A mixture of **1** ($n=1$) (0.30 g, 1.0 mmol), CS₂ (0.066 ml, 1.0 mmol) and Et₃N (0.14 ml, 1.0 mmol) in EtOH (3 ml) was stirred at room temperature for 2 h. Methyl iodide (0.062 ml, 1.0 mmol) was added to the mixture, and the reaction mixture was stirred for 1 h to give **VI** ($n=1$). L-Valine (0.35 g, 3.0 mmol) and Et₃N (0.42 ml, 3.0 mmol) were added to the mixture, and the whole was refluxed for 10 h. The mixture was kept at room temperature for 12 h, and the precipitated crystals were collected by filtration. The crystals were successively washed with 10% NaHCO₃ solution, water and EtOH and dried. The material was recrystallized from CHCl₃–EtOH to yield **Vi** (0.19 g, 41%). IR (KBr): 1742, 1619, 1579, 1508 cm⁻¹. NMR (CDCl₃) δ : 8.65 (1H, s, Ar-H), 8.00 (1H, br, NH), 7.26 (1H, s, Ar-H), 7.08 (1H, s, Ar-H), 4.20 (2H, m, piperidine), 4.04, 4.00 (each 3H, s, OCH₃), 3.82 (2H, d, $J=9$ Hz, –CH₂–), 3.25–1.68 (9H, m, piperidine, –CHCH–), 1.07, 0.96 (each 3H, d, $J=9$ Hz, –CH(CH₃)₂).

b) Method E A mixture of **Ib** (0.91 g, 3.0 mmol), Et₃N (0.42 ml, 3.0 mmol) and CS₂ (0.20 ml, 3.3 mmol) in EtOH (10 ml) was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between CHCl₃ and water. The organic layer was dried over MgSO₄, and evaporated. The residue was dissolved in CHCl₃. Et₃N (0.42 ml, 3.0 mmol) and ethyl chloroformate (0.29 ml, 3.0 mmol) were added to the solution. The mixture was stirred for 1 h and partitioned between CHCl₃ and water. The organic layer was dried over MgSO₄ and concentrated. The crystalline residue was recrystallized from Et₂O to give the isothiocyanate **VII** (0.68 g, 66%), mp 118°C. Anal. Calcd for C₁₇H₂₀N₄O₂S; C, 59.28; H, 5.85; N, 16.27. Found: C, 59.32; H, 5.89; N, 16.04. IR (KBr): 2175, 2100, 1615, 1570 cm⁻¹. NMR (CDCl₃) δ : 8.63 (1H, s, Ar-H), 7.23 (1H, s, Ar-H), 7.06 (1H, s, Ar-H), 4.22 (2H, m, piperidine), 4.02, 4.00 (3H, each, s, OCH₃), 3.52–1.20 (9H, m, piperidine, –CH₂–). A mixture of **VII** (0.17 g, 0.50 mmol), L-valine

methyl ester-HCl (0.084 g, 0.50 mmol) and Et₃N (0.070 ml, 0.50 mmol) in CHCl₃ (3 ml) was stirred for 15 h. Water was added to the mixture for partition. The organic layer was dried over MgSO₄ and concentrated. The oily residue was crystallized from MeOH to give **Vi** (0.11 g, 50%).

Method D. 3-[2-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]ethyl]-5-isopropyl-4-oxo-2-thioxoimidazolidine (**Vt**) Compound **Ic** (0.10 g, 0.32 mmol) and *N*-(methylthio)thioxomethyl-L-valine methyl ester (0.80 g, 2.9 mmol) were dissolved in DMF (10 ml), and the mixture was stirred at 120 °C for 6 h. The reaction solution was concentrated to give a residue, which was partitioned with CHCl₃ and water. The organic layer was dried over MgSO₄ and concentrated. The residue was purified using a 10 g silica gel column (2% MeOH–CHCl₃) to yield **Vt** (0.10 g, 41%). The product was recrystallized from MeOH. IR (KBr): 1740, 1580, 1505 cm⁻¹. NMR (CDCl₃) δ : 8.71 (1H, s, Ar-H), 7.79 (1H, br, NH), 7.31 (1H, s, Ar-H), 7.15 (1H, s, Ar-H), 4.20 (2H, m, piperidine), 4.02, 3.99 (each 3H, s, OCH₃), 3.90–1.20 (13H, m, piperidine, –CHCH–, –CH₂CH₂–), 1.06, 0.97 (each 3H, d, $J=7$ Hz, –CH(CH₃)₂).

References and Notes

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