Studies on Cardiotonic Agents. I. Synthesis of Some Quinazoline Derivatives

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A series of quinazoline derivatives with various 4-heterocyclylpiperidino groups at the 4-position was synthesized and tested for cardiotonic activity in anesthetized dogs. Among them, several 6,7-dimethoxyquinazoline derivatives showed potent cardiotonic activity.

Keywords positive inotropic activity; cardiotonic agent; structure–activity relationship; quinazoline; piperidine

In recent years, a variety of noncatecholamine, nonglycoside cardiotonic agents have been described.[1] Some of these new drugs have both inotropic and vasodilatory properties at the same time. Two of these agents (buquineran (**1**) and **2**, Chart 1) demonstrate a cardiac phosphodiesterase (PDE) inhibitory activity[2] which is believed to be the principal mechanistic component of positive inotropic action.[3] The interesting pharmacological properties of these compounds prompted us to synthesize related compounds which might possess inotropic activity.

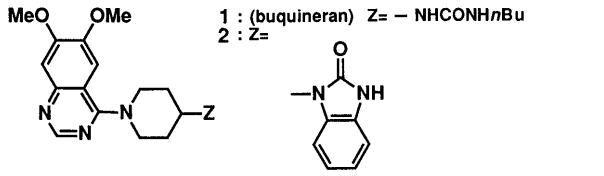
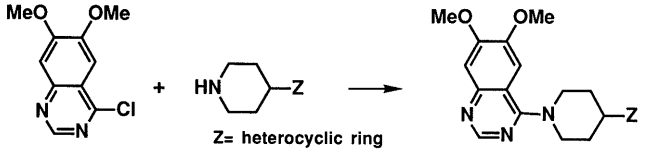


Chart 1



II I

Chart 2

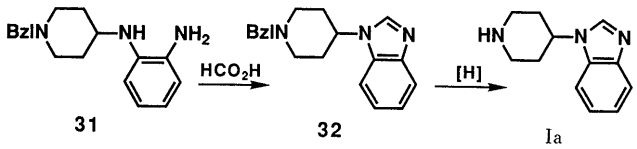


Chart 3

Previous reports[4] from our laboratory described the synthesis of various piperidines with a heterocyclic ring at the 4-position as intermediates of antihypertensive agent. It seemed attractive to replace the butylureido and 1,3-dihydro-2-oxo-2*H*-benzimidazolylpiperidino groups of **1** and **2** respectively by these heterocyclylpiperidino group, and to replace the methoxy group of quinazoline moiety by other substituents for pharmacological evaluation. In this report, we describe the synthesis and cardiotonic activity of some 6,7,8-substituted quinazoline derivatives bearing various piperidines as shown in Table I.

Chemistry The Pfizer group reported[2] that **1** and **2** were synthesized from the chloroquinazoline derivative (II) by treatment with appropriate piperidines. In a similar way, we synthesized the 6,7-dimethoxyquinazoline derivatives by reaction of II with the piperidines (I) (Chart 2).

Most of the starting piperidines are known,[4,5] and the new one (Ia, Z: 1*H*-benzimidazol-1-yl) was synthesized by cyclization of **31** with formic acid and subsequent debenzylation by catalytic hydrogenation (Chart 3).

On the other hand, 6,7,8-trimethoxyquinazoline derivatives (**29**, **30**) were synthesized by condensation of the arylthio derivatives (IIIa) with Ib (Z: 1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl) and Ic (Z: 2-oxo-1-imidazolidinyl) with good yield. Compound III was synthesized from the reaction of the thione (**34**) which was prepared by thiation of the 4(3*H*)-quinazolinone (**33**),[6] with 2,4-dichloronitrobenzene (**35**) in dimethylformamide (DMF) (Chart 4). Reaction of the methylthio derivative (IIIb) with Ib afforded **29** a poor yield.

The 6-acetamido-7-methoxyquinazoline derivative (**24**) was prepared from the chloride IV. Compound IV was obtained by a method analogous to that described for II. Thus, nitration of **36** by treatment of NO_2BF_4 in CH_3CN

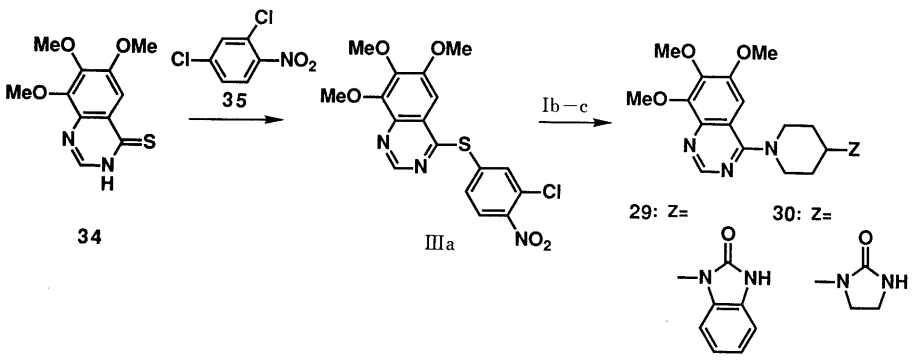


Chart 4

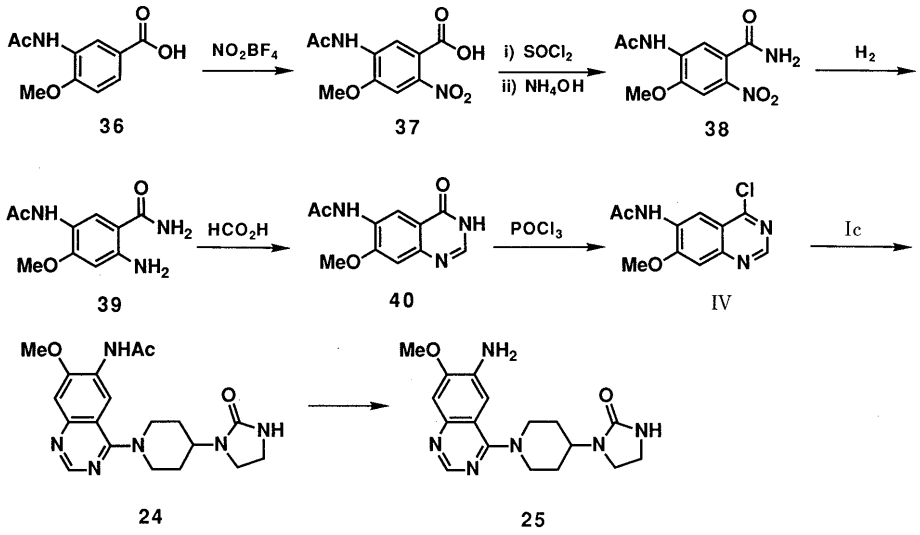


Chart 5

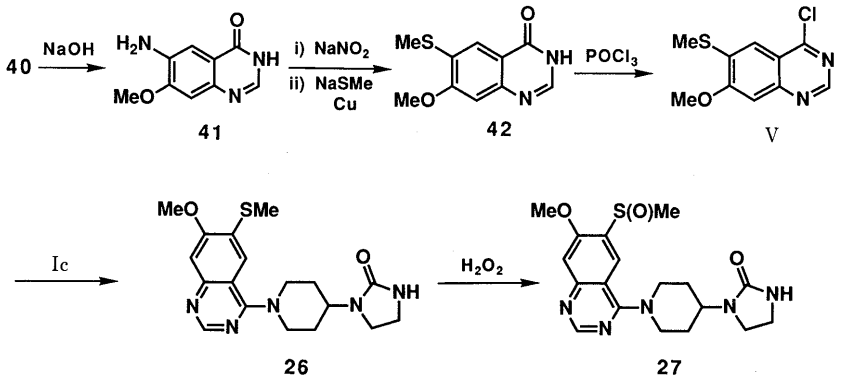


Chart 6

at 0 °C afforded **37** in 67% yield. Compound **37** reacted with $SOCl_2$, and subsequent ammonolysis with ammonia water gave **38**. Catalytic reduction of **38** afforded **39** followed by cyclization with formic acid to give the quinazolinone (**40**), which was converted to IV by reaction with $POCl_3$. Condensation of IV with Ic afforded **24**. Hydrolysis of **24** with 1 N HCl gave the 6-amino derivative **25** (Chart 5).

On the other hand, deacetylation of **40** with 1 N NaOH gave **41**. Diazotization of **41** with $NaNO_2$ and subsequent treatment with NaSMe in the presence of Cu powder gave **42** with a 32% yield. Compound **42** was converted to the chloride V which reacted with Ic to afford the 6-methylthio derivative (**26**). Oxidation of **26** with 30% H_2O_2 gave the 6-methylsulfinyl derivative **27** (Chart 6). Demethylation of **16** with trimethylsilyl iodide (TMS-I) in sulfolane gave the 6-hydroxy-7-methoxy derivative (**28**) with a 6% yield (Chart 7). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **28**, the 5-H signal of quinazoline, which observed the nuclear Overhauser effect (NOE) between the piperidine protons (δ 4.25 ppm), was found at δ 7.21 ppm. The demethylated site was confirmed by the use of the NOE which was observed between the methoxy proton (δ 3.93 ppm) and 8-H (δ 7.18 ppm) of quinazoline.

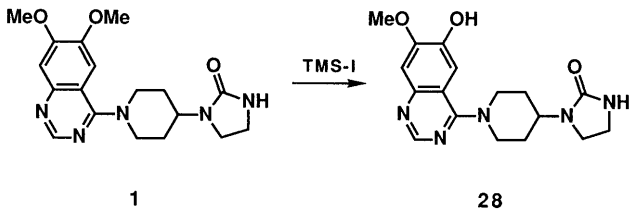


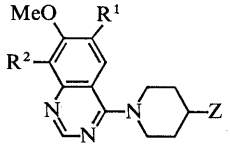
Chart 7

Biological Results Cardiotonic activities of the compounds listed in Table I were evaluated in anesthetized open chest dogs. The positive inotropic activity of the test compounds was determined by measuring percent increase in maximum dP/dt of left ventricular pressure (LV$dP/dt$ max, Δ%) after i.v. administration (1 mg/kg) of the compounds in anesthesized mongrel dogs of either sex (8—15 kg, $n=2$). The potency of cardiotonic activity of the compounds was compared with that of amrinone (1 mg/kg i.v.).[7] Relative potency was calculated as the LV$dP/dt$ max of each compound to that of amrinone (amrinone = 1) in the same dogs. The larger the relative potency, the more potent is the test compound.

The results from the experiments are summarized in Table II. As shown in Table II, the cardiotonic activity of several 6,7-dimethoxyquinazoline derivatives was more potent than that of amrinone.

With regard to the effects of the substituents of the piperidine at 4-position of the 6,7-dimethoxyquinazolines, introduction of an aromatic or a non-aromatic heterocyclic ring attained potent cardiotonic activity. Namely, the

TABLE I



Compd. No.	R^1	R^2	Z	Yield[b] (%)	mp (°C) (Crystn. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
3[a]	MeO	H	1*H*-Benzotriazol-1-yl	70	226—229 (MeOH–$CHCl_3$)	$C_{21}H_{22}N_6O_2 \cdot HCl$	59.08 (58.90)	5.43 5.46	19.69 19.75)
4	MeO	H	1,2,3,4-Tetrahydro-2-oxo-1-quinazolinyl	71	218—220 (MeOH–H_2O)	$C_{23}H_{25}N_5O_3 \cdot 1/4H_2O$	65.15 (65.15	6.06 6.09	16.52 16.43)
5[a]	MeO	H	1,2,3,4-Tetrahydro-2-oxo-3-quinazolinyl	86	230 (dec.) (MeOH–$CHCl_3$)	$C_{23}H_{25}N_5O_3 \cdot HCl \cdot 1/2H_2O$	59.41 (59.50	5.85 5.71	15.06 14.74)
6	MeO	H	3,4-Dihydro-2-oxo-2*H*-1,3-benzoxazin-3-yl	86	230—231 (MeOH–H_2O)	$C_{23}H_{24}N_4O_4$	65.70 (65.69	5.75 5.74	13.33 13.17)
7	MeO	H	2-Cyanoamino-3,4-dihydro-3-quinazolinyl	45	>300 (DMF–H_2O)	$C_{24}H_{25}N_7O_2 \cdot H_2O$	62.46 (62.80	5.90 5.58	21.24 21.23)
8	MeO	H	(1,3-Dihydro-2-oxo-2*H*-benzimidazol-1-yl)methyl	48	230—233 (MeOH–H_2O)	$C_{23}H_{25}N_5O_3 \cdot 1/2H_2O$	64.46 (64.65	6.13 5.95	16.34 16.10)
9	MeO	H	3,4-Dihydro-2,2-dioxido-1*H*-2,13-benzothiadiazin-1-yl	17	240 (dec.) (DMF)	$C_{22}H_{25}N_5O_4S$	58.01 (57.90	5.53 5.51	15.37 15.10)
10	MeO	H	3,4-Dihydro-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-3-yl	20	258 (dec.) (DMF–H_2O)	$C_{22}H_{25}N_5O_4S$	58.01 (57.83	5.53 5.61	15.37 15.46)
11	MeO	H	1,3-Dihydro-2-imino-2*H*-benzimidazol-1-yl	59	207—212 (dec.) (MeOH–H_2O)	$C_{22}H_{24}N_6O_2 \cdot H_2O$	62.54 (62.61	6.20 6.40	19.88 19.68)
12	MeO	H	3,4-Dihydro-2-ureidoquinazolin-3-yl	72	214—216 (dec.) (MeOH–H_2O)	$C_{24}H_{27}N_7O_3 \cdot 3/4H_2O$	60.68 (60.68	6.05 5.89	20.64 20.69)
13[a]	MeO	H	1*H*-Benzimidazol-1-yl	75	226—229 (MeOH–H_2O)	$C_{22}H_{23}N_5O_2 \cdot 2HCl \cdot 1/2H_2O$	56.06 (56.37	5.56 5.89	14.86 14.49)
14	MeO	H	2-Methyl-1*H*-benzimidazol-1-yl	75	220—222 (dec.) (iso-PrOH)	$C_{23}H_{25}N_5O_2 \cdot H_2O$	65.54 (65.49	6.46 6.41	16.62 16.51)
15[a]	MeO	H	2-(Methoxycarbonylamino)-3,4-dihydro-3-quinazolinyl	81	214—216 (dec.) (iso-PrOH)	$C_{25}H_{28}N_6O_4 \cdot HCl$	58.53 (58.50	5.71 5.66	16.37 16.41)
16	MeO	H	2-Oxo-1-imidazolidinyl	69	231—232 (EtOH)	$C_{18}H_{23}N_5O_3$	60.49 (60.54	6.49 6.54	19.60 16.44)
17	MeO	H	(1,2,3,4-Tetrahydro-2-oxo-3-quinazolinyl)-methyl	73	216—218 ($CHCl_3$–MeOH)	$C_{24}H_{27}N_5O_3$	66.50 (66.61	6.28 6.20	16.16 16.04)
18	MeO	H	3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl	90	196 ($CHCl_3$–MeOH)	$C_{22}H_{22}N_6O_3$	63.14 (63.22	5.30 5.18	20.09 19.80)
19[a]	MeO	H	1,2,3,4-Tetrahydro-2,4-dioxo-3-quinazolinyl	86	216—220 (MeOH)	$C_{23}H_{23}H_5O_4 \cdot HCl \cdot 2H_2O$	54.60 (54.33	5.58 5.35	13.84 13.79)
20	MeO	H	6-Chloro-1,2,3,4-tetrahydro-2,4-dioxo-3-quinazolinyl	86	287—289 (MeOH–H_2O)	$C_{23}H_{22}ClN_5O_4$	59.04 (58.78	4.74 4.82	14.97 15.00)
21[a]	MeO	H	6-Nitro-1,2,3,4-tetrahydro-2,4-dioxo-3-quinazolinyl	89	253—255 (MeOH–H_2O)	$C_{23}H_{22}N_6O_6 \cdot HCl$	53.65 (53.79	4.50 4.23	16.32 16.68)
22	MeO	H	1,3-Dihydro-2-oxo-2*H*-indol-3-ylidene	81	246—247 (MeOH)	$C_{23}H_{22}N_4O_3$	68.64 (68.72	5.51 5.85	13.92 13.76)
23[a]	MeO	H	1,3-Dihydro-2-oxo-2*H*-indol-3-yl	77	196—198 (EtOH)	$C_{23}H_{24}N_4O_3 \cdot HCl \cdot H_2O$	60.19 (59.87	5.93 5.83	12.21 12.09)
24	AcNH	H	2-Oxo-1-imidazolidinyl	[c]	267—268 (iso-PrOH)	$C_{19}H_{24}N_6O_3$	59.35 (59.17	6.30 6.76	21.85 21.57)
25	H_2N	H	2-Oxo-1-imidazolidinyl	[c]	290 (dec.) (MeOH–H_2O)	$C_{17}H_{22}N_6O_2$	59.63 (59.23	6.49 6.45	24.53 24.28)
26	MeS	H	2-Oxo-1-imidazolidinyl	[c]	228—231 (DMF–H_2O)	$C_{18}H_{23}N_5O_2S$	57.89 (57.69	6.21 6.28	18.75 18.42)
27	MeS(O)	H	2-Oxo-1-imidazolidinyl	[c]	231—234 (iso-PrOH–hex)	$C_{18}H_{23}N_5O_3S$	55.51 (55.64	5.95 5.96	17.98 17.67)
28	HO	H	2-Oxo-1-imidazolidinyl	[c]	260—263 (MeOH–H_2O)	$C_{17}H_{21}N_5O_3$	59.45 (59.08	6.18 6.38	20.38 20.12)
29	MeO	MeO	1,3-Dihydro-2-oxo-2*H*-benzimidazol-1-yl	[c]	236—238 (AcOEt)	$C_{23}H_{25}N_5O_4 \cdot 1/2H_2O$	62.15 (62.05	5.90 5.74	15.76 15.38)
30	MeO	MeO	2-Oxo-1-imidazolidinyl	64[d]	203—205 (iso-PrOH–H_2O)	$C_{19}H_{25}N_5O_4 \cdot H_2O$	56.29 (56.46	6.71 6.85	17.27 16.91)

a) As HCl salt. *b*) Yield from II. *c*) See Experimental section. *d*) Yield from IIIa.

TABLE II. Biological Activity of Quinazolinyl Piperidine Derivatives in Anesthetized Dogs ($n=2$)

Compd. No.	Cardiotonic activity		
	LVdP/dt max (Δ%)	Relative potency[a]	Duration (min)
3	77.4	1.86	52.5
4	30.0	0.60	7.5
5	53.2	2.20	>60
6	28.9	0.65	15
8	37.1	1.38	47.5
9	32.6	1.09	27.5
10	27.9	0.93	27.5
11	33.4	1.34	32.5
13	44.4	1.73	28
14	22.7	0.45	15
15	17.5	0.35	5
16	85.5	1.69	30
22	33.1	0.66	35
23	30.1	0.60	30
24	4.5	0.09	0
25	22.6	0.55	35
26	15.8	0.73	0
27	3.9	0.18	0
30	14.5	0.46	20

a) Compared to the percent increase in LVdP/dt max observed with amrinone (1 mg/kg) in the same dogs (see Experimental section).

compounds with a heteroarylpiperidine (*e.g.* **3**, **5**, **11** and **13**) exhibited potent activity as well as the compound with a non-aromatic heterocyclic ring (**16**). Insertion of methylene group between a piperidine ring and a heteroaromatic ring (*e.g.* **8**) maintained the activity.

Several known cardiotonics including **1** and **2** have a carbonyl group in the molecules.[8] While, **3** and **13**, which don't have a carbonyl group, had potent cardiotonic activity. The carbonyl group may not be important for the activity of this series.

Next, effects of the substituents at 8-position of the quinazoline were examined. Introduction of substituents at 8-position diminished the activity (**30**). Effects of the substituents at 6-position were also examined. Introduction of NHAc (**24**), NH_2 (**25**), SMe (**26**) and S(O)Me (**27**) resulted in diminished activity. The results suggest that the presence of a 6,7-dimethoxy group is essential for exhibited potent cardiotonic activity.

In conclusion, the compounds which have a piperidine bearing heterocyclic ring on the 6,7-dimethoxyquinazoline moiety exhibited generally potent positive cardiotonic activity. These compounds were not studied in depth because their poor oral activity in conscious dogs.

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. ^{1}H-NMR spectra were measured on a Varian EM-390 and a JNM-PS-100 spectrometer using tetramethylsilane (TMS) as an internal standard.

1-(1-Benzyl-4-piperidinyl)-1*H*-benzimidazole (32) A solution of **31** (2.9 g, 8.8 mmol) in 99% HCO_2H (30 ml) was refluxed for 1 h, then concentrated. They oily residue was basified to pH 10 and extracted with AcOEt. The extract was dried and concentrated to give a crystalline residue, which was mixed with Et_2O and collected by filtration to obtain **32** (2.2 g, 75%), mp 142—143 °C. *Anal.* Calcd for $C_{19}H_{21}N_3$: C, 78.31; H, 7.26; N, 14.42. Found: C, 78.51; H, 7.45; N, 14.37. IR (KBr): 1600, 1480 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.32 (1H, s, Ar-H), 7.63 (2H, m, Ar-H), 7.33 (5H, br s, benzyl), 7.20 (2H, m, Ar-H), 4.33 (1H, m, piperidine), 3.52 (2H, s, $-CH_2-$), 3.10—1.90 (8H, m, piperidine).

1-(4-Piperidinyl)-1*H*-benzimidazole (Ia) A mixture of **32** (1.5 g, 5.2 mmol), 10% Pd/C (0.15 g), MeOH (20 ml) and 1 N HCl (10 ml) was stirred for 40 h under 3 atm of H_2 at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was crystallized from MeOH–AcOEt to afford Ia·2HCl (0.97 g, 69%), mp 280—281 °C. *Anal.* Calcd for $C_{12}H_{15}N_3 \cdot 2HCl$: C, 52.57; H, 6.25; N, 15.32. Found: C, 52.86; H, 6.15; N, 15.23. IR (KBr): 1620, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6–CD_3OD) δ: 9.68 (1H, s, Ar-H), 8.23—7.60 (4H, m, Ar-H), 5.10 (1H, m, piperidine), 3.90—2.18 (8H, m, piperidine).

General Procedure for the Synthesis of 6,7-Dimethoxy-4-(4-heterocyclyl-1-piperidinyl)quinazolines. 1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]methyl-1,3-dihydro-2*H*-benzimidazol-2-one (8) A mixture of II (1.1 g, 4.9 mmol), 1-(4-piperidinyl)methyl-1,3-dihydro-2*H*-benzimidazol-2-one·HCl (1.3 g, 4.9 mmol) in MeOH (30 ml) was refluxed for 2 h, then concentrated. Water was added to the residue and the mixture was extracted with AcOEt. The extract was washed with water, dried and concentrated to give crude crystals, which were recrystallized from MeOH–water to obtain **8** (1.0 g, 49%) as white crystals. IR (KBr): 1710, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.11 (1H, br s, NH), 8.66 (1H, s, Ar-H), 7.27 (1H, s, Ar-H), 7.08 (5H, br, Ar-H), 4.20 (2H, m, $-CH_2-$), 4.01, 3.99 (3H, each s, CH_3O), 3.49—1.59 (9H, m, piperidine).

6,7,8-Trimethoxy-4(3*H*)-quinazolinethione (34) A mixture of **33** (5.0 g, 21 mmol) and P_4O_{10} (7.5 g, 17 mmol) in pyridine (40 ml) was stirred for 2 h at 100 °C. Water was added to the reaction mixture and the precipitated crystals were collected by filtration. The crystals were recrystallized from dimethylformamide (DMF)–water to give **34** (4.3 g, 81%), mp 158 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.19; H, 4.92; N, 11.05. IR (KBr): 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 13.72 (1H, br, NH), 8.04 (1H, s, Ar-H), 7.77 (1H, s, Ar-H), 3.92 (3H, s, CH_3O), 3.90 (6H, s, CH_3O).

4-(3-Chloro-4-nitrophenyl)thio-6,7,8-trimethoxyquinazoline (IIIa) A mixture of **34** (15.0 g, 59 mmol), **35** (18.0 g, 94 mmol), KOH (7.5 g, 134 mmol) and (n-Bu)$_4$NBr (0.6 g) in DMF (100 ml) was stirred for 20 h at room temperature. The reaction mixture was concentrated and the residue was crystallized from MeOH–water to give IIIa (12.0 g, 50%). The crystals were used in the next reaction without further purification. An analytical sample was recrystallized from DMF–water, mp 188—189 °C. *Anal.* Calcd for $C_{17}H_{14}ClN_3O_5S$: C, 50.07; H, 3.46; N, 10.30. Found: C, 50.30; H, 3.68; N, 10.28. IR (KBr): 1605, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.83 (1H, s, quinazoline), 8.08 (1H, d, $J=9$ Hz, phenyl), 7.73 (1H, d, $J=2$ Hz, phenyl), 7.55 (1H, dd, $J=2$, 9 Hz, phenyl), 7.18 (1H, s, quinazoline), 4.16, 4.14, 4.05 (3H each, s, CH_3O).

General Procedure for the Synthesis of 6,7,8-Trimethoxy-4-(4-heterocyclyl-1-piperidinyl)quinazolines. 1-[1-(6,7,8-Trimethoxy-4-quinazolinyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (29) A mixture of IIIa (0.39 g, 1.0 mmol), Ib·HCl (0.22 g, 1.0 mmol) and Et_3N (0.30 ml, 2.2 mmol) was stirred for 2 d at 60 °C. The reaction mixture was concentrated and the residue was partitioned between $CHCl_3$ and water. The organic layer was dried over $MgSO_4$, then concentrated. The residue was purified by column chromatography (SiO_2, 20 g, 1% MeOH–$CHCl_3$) to give **29** as crystals (0.20 g, 48%) which were recrystallized from MeOH–AcOEt for analysis. IR (KBr): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.67 (1H, br s, NH), 8.70 (1H, s, Ar-H), 7.15 (1H, s, Ar-H), 7.10—6.82 (4H, m, Ar-H), 4.30 (2H, m, piperidine), 4.04, 3.96, 3.89 (3H each, s, CH_3O), 3.70—1.30 (7H, m, piperidine).

5-Acetamido-4-methoxy-2-nitrobenzoic Acid (37) NO_2BF_4 (18.0 g, 136 mmol) was added by portions to an ice-cooling solution of **36** (20.0 g, 96 mmol) in CH_3CN (100 ml), then the whole was stirred for 10 min at 0—5 °C. The reaction mixture was poured into ice-water and the precipitates were collected to give crude crystals of **37** (18.0 g, 74%) which were used in the next reaction without further purification. An analytical sample was recrystallized from DMF–water, mp 228—232 °C. *Anal.* Calcd for $C_{10}H_{10}N_2O_6$: C, 47.24; H, 3.97; N, 11.01. Found: C, 46.95; H, 4.12; N, 10.83. IR (KBr): 1700, 1680, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 13.00 (1H, br, CO_2H), 10.23 (1H, br s, NH), 8.50 (1H, s, Ar-H), 7.47 (1H, s, Ar-H), 3.98 (3H, s, CH_3O), 2.28 (3H, s, CH_3CO).

5-Acetamido-4-methoxy-2-nitrobenzamide (38) A suspension of **37** (8.0 g, 36 mmol) in $SOCl_2$ (50 ml) was stirred under reflux for 30 min. The reaction mixture was poured into a mixture of concentrated NH_4OH (200 ml) and ice (100 ml). The precipitated crystals were collected by filtration, washed with water and dried to give crude crystals which were recrystallized from DMF–water to give pure **38** (7.4 g, 93%), mp 275—278 °C. *Anal.* Calcd for $C_{10}H_{11}N_3O_5$: C, 47.43; H, 4.38; N, 16.59.

Found: C, 47.40; H, 4.44; N, 16.38. IR (KBr): 1680, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.53 (1H, br s, NH), 8.30 (1H, s, Ar-H), 7.85, 7.42 (1H, each br s, NH_2), 7.60 (1H, s, Ar-H), 3.93 (3H, s, CH_3O), 2.16 (3H, s, CH_3CO).

6-Acetamido-7-methoxy-4(3*H*)-quinazolinone (40) A suspension of **38** (8.0 g, 31 mmol) and 10% Pd/C (0.8 g) in MeOH (150 ml) was stirred for 3 h under atmospheric pressure of H_2 at 40 °C. The catalyst was filtered off and the filtrate was concentrated. HCO_2H (100 ml) was added to the residue and the mixture was stirred for 4 h at 100 °C. After removal of the solvent, the crystalline residue was recrystallized from DMF–water to afford **40** (5.5 g, 76%), mp>300 °C. *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.64; H, 4.76; N, 18.01. Found: C, 56.66; H, 4.83; N, 17.98. IR (KBr): 1700, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 9.26 (1H, br s, NH), 8.70 (1H, s, Ar-H), 7.95 (2H, br s, Ar-H, NH), 7.22 (1H, s, Ar-H), 3.96 (3H, s, CH_3O), 2.13 (3H, s, CH_3CO).

6-Acetamido-4-chloro-7-methoxyquinazoline (IV) A suspension of **40** (5.0 g, 21 mmol) in $POCl_3$ (30 ml) was stirred under reflux for 2 h. The reaction mixture was concentrated and the residue was poured into ice-water. The precipitates were collected by filtration, washed with water and dried to give crude crystals of IV (4.0 g, 74%) which were used in the next reaction without further purification. An analytical sample was recrystallized from DMF–water, mp 215 °C (dec.). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.49; H, 4.01; N, 16.69. Found: C, 52.35; H, 3.92; N, 16.63. IR (KBr): 1700, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 9.55 (1H, br s, NH), 9.05 (1H, s, Ar-H), 8.87 (1H, s, Ar-H), 7.44 (1H, s, Ar-H), 4.10 (3H, s, CH_3O), 2.21 (3H, s, CH_3CO).

1-[1-(6-Acetamido-7-methoxy-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinone (24) A mixture of IV (2.3 g, 9.1 mmol), Ic·HCl (1.9 g, 9.2 mmol) and Et_3N (3 ml) in DMF (20 ml) was stirred for 4 h at 60 °C. The reaction mixture was concentrated under reduced pressure. The residual crystalline material was mixed with water and collected by filtration to afford crude crystals of **24**. The crystals were recrystallized from MeOH–water to give **24** (2.8 g, 79%). IR (KBr): 1700, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 9.40 (1H, br s, NH), 8.72 (1H, s, Ar-H), 8.47 (1H, s, Ar-H), 7.21 (1H, s, Ar-H), 6.23 (1H, br s, NH), 4.35—1.60 (9H, m, piperidine), 3.97 (3H, s, CH_3O), 3.26 (4H, s, $-CH_2CH_2-$), 2.16 (3H, s, CH_3CO).

1-[1-(6-Amino-7-methoxy-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinone (25) A suspension of **24** (1.7 g, 4.4 mmol) in 1 N HCl (50 ml) was stirred for 4 h at 80 °C. The reaction mixture was basified with 2 N NaOH and the precipitates were collected by filtration, washed with water and dried to obtain crude crystals which were recrystallized from MeOH–water to give **25** (1.1 g, 75%). IR (KBr): 1700, 1520 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.31 (1H, br s, Ar-H), 7.02 (1H, s, Ar-H), 6.95 (1H, s, Ar-H), 6.20 (1H, br s, NH), 5.35 (2H, br, NH_2), 4.20—1.52 (9H, m, piperidine), 3.90 (3H, s, CH_3O), 3.24 (4H, s, $-CH_2CH_2-$).

6-Amino-7-methoxy-4(3*H*)-quinazolinone (41) A solution of **40** (1.5 g, 6.4 mmol) in 1 N NaOH (50 ml) was stirred for 15 h at 90 °C. The reaction mixture was neutralized with 1 N HCl and precipitates were collected by filtration, washed with water and dried to give crude crystals which were recrystallized from DMF–water to afford **41** (0.8 g, 65%), mp 289—291 °C. *Anal.* Calcd for $C_9H_9N_3O_2$: C, 56.53; H, 4.75; N, 21.97. Found: C, 56.50; H, 4.98; N, 21.72. IR (KBr): 1680, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.71 (1H, s, NH), 7.80 (1H, s, Ar-H), 7.26 (1H, s, Ar-H), 7.00 (1H, s, Ar-H), 5.24 (2H, br, NH_2), 3.93 (3H, s, CH_3O).

7-Methoxy-6-methylthio-4(3*H*)-quinazolinone (42) A solution of **41** (4.3 g, 25 mmol) in 30% HBF_4 (30 ml) was stirred for 15 min at 5 °C. $NaNO_2$ (1.7 g, 25 mmol) was added by portions and the mixture was stirred for 30 min at the same temperature, then NaSMe (3.5 g, 50 mmol) and Cu powder (4.0 g) were added to the mixture which was stirred for 15 min at room temperature. After removal of Cu powder by filtration, the filtrate was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ then concentrated. The residue was recrystallized from MeOH–water to afford **42** (1.6 g, 32%), mp 295 °C (dec.). *Anal.* Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.54; N, 12.60. Found: C, 53.78; H, 4.71; N, 12.80. IR (KBr): 1680, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 12.10 (1H, br s, NH), 8.02 (1H, s, Ar-H), 7.72 (1H, s, Ar-H), 7.12 (1H, s, Ar-H), 4.00 (3H, s, CH_3O), 2.48 (3H, s, CH_3S).

4-Chloro-7-methoxy-6-methylthioquinazoline (V) In a manner similar to that described for IV, the reaction of **42** (4.5 g, 20 mmol) with $POCl_3$ (15 ml) gave V (4.2 g, 86%), mp 167—168 °C. *Anal.* Calcd for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.64. Found: C, 50.23; H, 3.65; N, 11.51. IR (KBr): 1600, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.91 (1H, s, Ar-H), 7.66 (1H, s, Ar-H), 7.43 (1H, s, Ar-H), 4.07 (3H, s, CH_3O), 2.59 (3H, s, CH_3S).

1-[1-(7-Methoxy-6-methylthio-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinone (26) The procedure described for **8** was followed, using V (1.3 g, 5.4 mmol), Ic·HCl (1.3 g, 6.3 mmol) and Et_3N (1.7 ml, 12.0 mmol) in DMF (20 ml). Crude **26** was recrystallized from DMF–water to give pure **26** (1.0 g, 50%). IR (KBr): 1700, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.53 (1H, s, Ar-H), 7.44 (1H, s, Ar-H), 7.18 (1H, s, Ar-H), 6.25 (1H, br s, NH), 4.45—1.62 (9H, m, piperidine), 3.98 (3H, s, CH_3O), 3.33 (4H, s, imidazolidinone), 2.53 (3H, s, CH_3S).

1-[1-(7-Methoxy-6-methylsulfinyl-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinone (27) A mixture of 30% H_2O_2 (5.0 ml) and **26** (1.1 g, 2.9 mmol) in 50% AcOH (30 ml) was stirred for 15 min at room temperature. The reaction mixture was neutralized with 2 N NaOH, then extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residual oil was purified by column chromatography (SiO_2, 60 g, 4% MeOH–$CHCl_3$). The product was crystallized from iso-PrOH–hexane to give **27** (0.6 g, 53%). IR (KBr): 1680, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.60 (1H, s, Ar-H), 8.17 (1H, s, Ar-H), 7.31 (1H, s, Ar-H), 6.24 (1H, br s, NH), 4.48—1.60 (9H, m, piperidine), 4.02 (3H, s, CH_3O), 3.39 (4H, s, imidazolidinone), 2.82 (3H, s, $S(O)CH_3$).

1-[1-(6-Hydroxy-7-methoxy-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinone (28) A mixture of **16** (1.8 g, 5.0 mmol) and TMS-I (2.9 ml) in sulfolane (10 ml) was stirred for 1 h at 100 °C. The reaction mixture was cooled, acidified with 1 N HCl. AcOEt was added to a mixture and extracted with water. The water layer was neutralized with 1 N NaOH and extracted with $CHCl_3$. Usual work-up of the extract gave crystals, which were recrystallized from MeOH–water to afford **28** (0.1 g, 1%). IR (KBr): 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 9.86 (1H, br s, OH), 8.48 (1H, s, 2-H), 7.21 (1H, s, 5-H), 7.18 (1H, s, 8-H), 6.20 (1H, br s, NH), 4.25—1.62 (9H, m, piperidine), 3.93 (3H, s, CH_3O), 3.30 (4H, s, imidazolidinone). NOE 17% CH_3O (δ 3.93)→8-H (δ 7.18), 16% 5-H (δ 7.21)→piperidine protons (δ 4.25).

Cardiotonic Activity Adult mongrel dogs (8—15 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and artificially respirated. In order to maintain anesthesia, sodium pentobarbital was continuously infused (4 mg/kg/h). A Millar catheter tip pressure transducer was introduced into the left ventricle *via* the right carotid artery for measuring left ventricular blood pressure. Another transducer was inserted into the femoral artery for measuring arterial blood pressure. LV$dP/dt$ max was calculated as the maximum rate of rise in left ventricular blood pressure. The cardiotonic activity of the compounds was determined by measuring percent increase in LV$dP/dt$ max. Heart rate was triggered by the arterial pressure signals. The test compounds were dissolved or suspended in water, and administered *via* the femoral vein. The cardiovascular effects of a test compound was compared with those of amrinone. Relative potency was calculated as the ratio of the LV$dP/dt$ max of each compound to that of amrinone in the same dogs. In order to exclude the influence of the previously administered drug, each compound was administered after recovery of the cardiovascular variables.

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