A Novel Class of Cardiotonics. Synthesis and Pharmacological Properties of [4-(Substituted-amino)phenyl]pyridazinones and Related Derivatives

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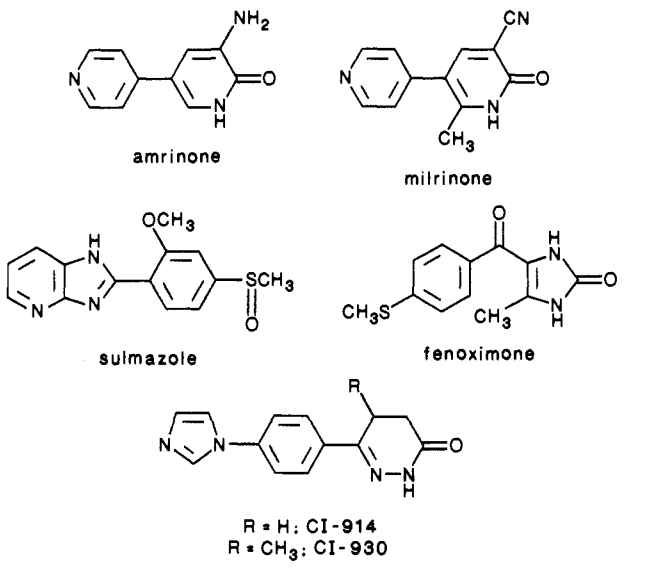
A series of [4-(substituted-amino)phenyl]pyridazinones and [4-[(substituted-methyl)amino]phenyl]pyridazinones was synthesized and evaluated for inotropic activity in vitro and for cardiohemodynamic effects in vivo. Above all, 6-[4-(4-pyridylamino)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride (**4**, MCI-154) and 6-[4-(4-pyridylamino)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride (**5**) showed extremely potent positive inotropic activity along with vasodilating activity. Regarding dP/dt_{max} (an indicator for cardiac contractility), ED_{30}'s (doses that increased dP/dt_{max} by 30%) of compounds **4** and **5** were 8.5 ± 1.9 and 4.4 ± 0.6 μg/kg, respectively, where that of amrinone was 471.9 ± 94.1 μg/kg. Structure–activity relationships of these series are presented, and a plausible model of receptor binding is discussed.

Positive inotropic agents, which enhance myocardial contractility and result in improvement of cardiac performance, have been widely used for the therapy of congestive heart failure. Currently two types of cardiotonic drugs, the cardiac glycosides (digoxin, digitoxin) and sympathomimetic agents (dopamine, dobutamine), are available to treat defective cardiac pump function. However, these agents are limited to their therapeutic use by arrhythmogenic liability and chronotopic liability, respectively. Moreover, the existing sympathomimetic agents have a disadvantage due to their lack of oral efficacy. There has existed a potential need for safer and orally effective drugs for the treatment of congestive heart failure.

Amrinone[1] was a forerunner of a series of nonsympathomimetic cardiotonic agents, and its introduction stimulated the development of several new compounds: milrinone,[2] sulmazole,[3] fenoximone,[4] CI-914,[5] and CI-930[5] (Chart I). We have also found a marked cardiotonic activity with some phenylpyridazinone derivatives,[6] and we present in this paper their synthesis and pharmacology. A pharmacological study on 6-[4-(4-pyridylamino)-phenyl]-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride (**4**, MCI-154) was briefly reported previously.[7]

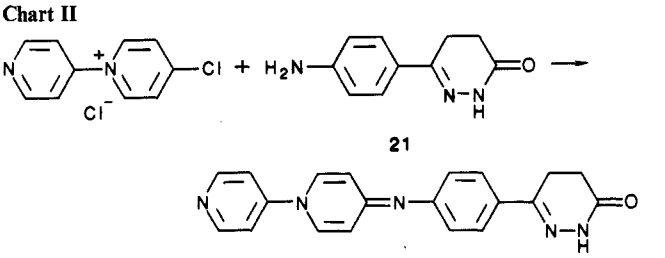
Chart I



Chemistry

[4-(Substituted-amino)phenyl]pyridazinones **1–14** listed in Table I were synthesized via the general route illustrated in Scheme I. Those compounds were all prepared by nucleophilic reaction of intermediates, (4-aminophenyl)-pyridazinones **21–29**, to the corresponding heterocyclic halides. All intermediates except for 6-(4-aminophenyl)-5-ethyl-3(2*H*)-pyridazinone (**29**) have been reported.[8-11] Compound **29** was prepared from 6-(4-aminophenyl)-4,5-dihydro-5-ethyl-3(2*H*)-pyridazinone (**26**) by dehydrogenation with sodium 3-nitrobenzene-

Chart II



Scheme I

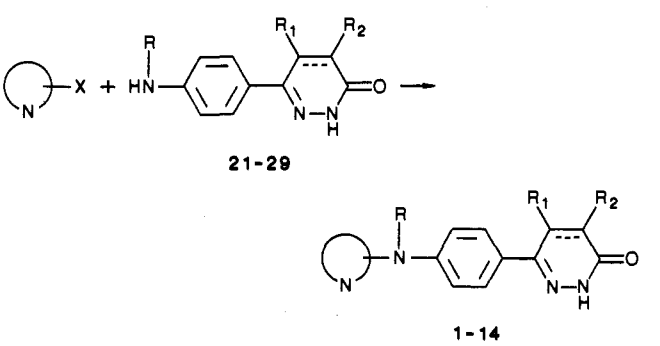


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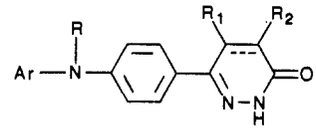
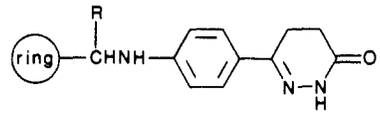
Table I. [4-(Substituted-amino)phenyl]pyridazinones



no.	Ar	R	R_1	R_2	C4–C5[a]	yield, %	mp, °C (recrystn solvent)[b]	formula[c]	ED_{15}[d] for papillary muscle contractility, μg ia	n
1	4-pyridyl	H	H	H	d	7.6	>300 (A)	$C_{15}H_{13}N_4OCl$	50 ± 6.5	2
2	4-pyridyl	H	CH_3	H	d	87.1	>300 (A)	$C_{16}H_{15}N_4OCl$	165 ± 5.1	2
3	4-pyridyl	H	C_2H_5	H	d	75.0	>300 (A)	$C_{17}H_{17}N_4OCl$	>300	2
4	4-pyridyl	H	H	H	s	64.8	>300 (B)	$C_{15}H_{15}N_4OCl$	4.1 ± 1.8	2
5	4-pyridyl	H	CH_3	H	s	68.3	270–272 (A)	$C_{16}H_{17}N_4OCl$	1.5 ± 0.8	2
6	4-pyridyl	H	C_2H_5	H	s	74.9	169–171 (A)	$C_{17}H_{19}N_4OCl$	23 ± 5.8	2
7	4-pyridyl	H	H	CH_3	s	61.6	280–281 (A)	$C_{16}H_{17}N_4OCl$	4.7 ± 1.2	2
8	2-pyridyl	H	H	H	s	27.4	>300 (C)	$C_{15}H_{15}N_4OCl$	17.5 ± 1.5	2
9	2-pyridyl	H	CH_3	H	s	71.6	157–159 (D)	$C_{16}H_{17}N_4OCl$	3.2 ± 0.6	2
10	2-pyrimidyl	H	H	H	s	29.7	>300 (E)	$C_{14}H_{14}N_5OCl$	165 ± 38	2
11	4-quinolyl	H	H	H	s	51.1	>300 (A)	$C_{19}H_{17}N_4OCl$	>300	2
12	4-pyridyl	CH_3	H	H	s	46.0	>300 (A)	$C_{16}H_{17}N_4OCl$	38 ± 9.3	2
13	4-pyridyl	CH_3	CH_3	H	s	56.8	>300 (F)	$C_{17}H_{19}N_4OCl$	18.5 ± 4.5	2
14	2-pyridyl	CH_3	H	H	s	54.2	275–276 (A)	$C_{16}H_{17}N_4OCl$	5.6 ± 1.3	2
amrinone									200 ± 43	7

[a] "s" stands for C–C saturated bond at C4–C5, "d" for C–C dehydrogenated bond. [b] A = Et_2O/MeOH; B = EtOH; C = MeOH; D = $CHCl_3$/MeOH/Et_2O; E = EtOH/H_2O; F = CH_2Cl_2/MeOH/Et_2O. [c] All compounds were analyzed within ± 0.4% of theory for C, H, and N. [d] Dose that increased developed tension by 15% in the isolated papillary muscle preparation of the dog. Values reported are either the mean ± SEM (n = 7) or the mean ± range (n = 2) of experimental values.

Table II. [4-[(Substituted-methyl)amino]phenyl]pyridazinones



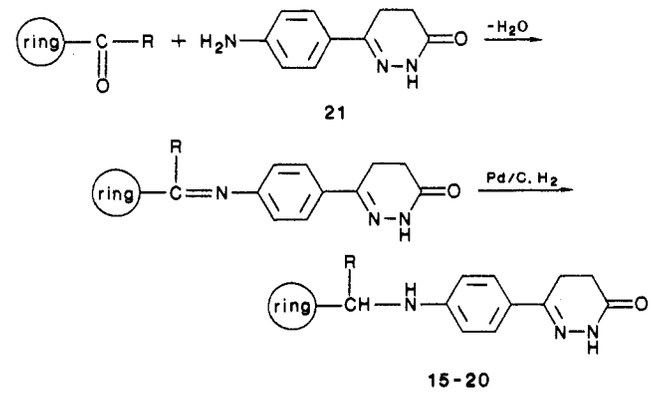
no.	ring	R	yield, %	mp, °C (recrystn solvent)[a]	formula[b]	ED_{15}[c] for papillary muscle contractility, μg ia	n
15	4-pyridyl	H	43.8	207–209 (A)	$C_{16}H_{16}N_4O$	>300	2
16	4-pyridyl	CH_3	31.8	216–217 (A)	$C_{17}H_{18}N_4O$	33 ± 5.0	2
17	3-pyridyl	H	75.3	194–196 (B)	$C_{16}H_{16}N_4O$	86 ± 33	2
18	4-quinolyl	H	66.6	210–212 (A)	$C_{20}H_{18}N_4O$	>300	2
19	phenyl	H	51.5	189–191 (A)	$C_{17}H_{17}N_3O$	NT[d]	
20	4-(dimethylamino)phenyl	H	61.9	212–214 (B)	$C_{19}H_{22}N_4O$	>300	2
amrinone						200 ± 43	7

[a] A = THF/n-hexane, B = DMF/H_2O. [b] All compounds were analyzed within ± 0.4% of theory for C, H, and N. [c] Dose that increased developed tension by 15% in the isolated papillary muscle preparation of the dog. Values reported are either the mean ± SEM (n = 7) or the mean ± range (n = 2) of experimental values. [d] Not tested.

sulfonate.[12] It was known that 4-chloropyridine was liable to dimerize to afford *N*-4′-pyridyl-4-chloropyridinium chloride[13,14] (Chart II). Therefore the order of addition of reactants to the reaction mixture as well as the presence of an appropriate quantity of triethylamine was essential to achieve a good yield of the desired products.

[4-[(Substituted-methyl)amino]phenyl]pyridazinones **15–20** listed in Table II were synthesized via the general route illustrated in Scheme II. Those compounds were all prepared by condensing 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**21**) with carbonyl compounds to form Schiff bases followed by catalytic hydrogenation.

Scheme II



Biological Results and Discussion

Compounds in Tables I and II were evaluated in the isolated dog papillary muscle for positive inotropic activities indicated by their ED_{15}'s (doses that increased developed tension by 15%).

(12) Curran, W. V.; Ross, A. *J. Med. Chem.* **1974**, *17*, 273.
(13) Wibaut, J. P.; Broekman, F. W. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 593.
(14) Wibaut, J. P.; Broekman, F. W. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 309.

The structure–activity relationships of the pyridazinone rings were examined by three types of structural change. Firstly, comparison of the potencies of the dehydrogenated pyridazinone derivatives (**1–3**) with those of the 4,5-dihydropyridazinone derivatives (**4–6**) showed that the former were less potent. Furthermore, this difference in potency of the two groups was emphasized in compounds substituted at the 5-position. Secondly, the effect of substitution at the 5-position on activity was explored. In the case of 4,5-dihydropyridazinones **4**, **8**, and **12**, the introduction of a methyl group resulted in increased potency (**5**, **9**, and **13**), whereas results from two dehydrogenated pyridazinones suggested a different trend in that series (**1** vs. **2**). Increasing the size of the 5-substituent from methyl to ethyl led to a decrease in potency with both series of pyridazinones (**1**, **4** vs. **3**, **6**). Thirdly, the influence of a methyl group at the 4-position was explored, where it was found that compound **7** was slightly less potent than the parent compound **4**. Therefore, the influence of a methyl group at position 4 does not appear as remarkable as at position 5.

Apart from variations of the pyridazinone ring, we investigated the structure–activity relationships with some variations of the 4-amino group. Replacing 4-pyridyl (**4**, **5**) with 2-pyridyl (**8**, **9**) resulted in a considerable reduction of the potency. In addition the two compounds (**10**, **11**) replaced with other heterocycles showed little activity. Previously, Schnettler et al.[4] reported the requirement of a free imidazole NH on their cardiotonics. We were interested in knowing whether a free NH connecting phenyl to pyridyl was also important in our compounds. On the methylation of the NH, a marked reduction of activity was observed, thereby suggesting some requirement for this free proton (**4**, **5**, and **8** vs. **12**, **13**, and **14**).

In Table II, test results of [4-[(substituted-methyl)-amino]phenyl]pyridazinones are listed. Compound **15** was very much less potent than the parent compound **4**. Compounds **18** and **20** showed very poor activity and compound **19** could not be tested because of its limited solubility.

Sircar et al.[15] demonstrated structure–cardiotonic activity relationships with structural changes of the pyridazinone ring such as substitutions at the 5-position and 4-position, and dehydrogenation, about the 4,5-dihydro-6-(4-heterocyclylphenyl)-3(2*H*)-pyridazinones. In the pyridazinone ring of our compounds, the observed relationships were compatible with those reported. In order to explain the marked effect of a methyl group on the 5-position, Bristol et al.[5] proposed a model with a methyl-sized lipophilic space. Our results appear to support their hypothetical model. Particuarly in the case of the dehydrogenated pyridazinone, the substitution with a methyl group at the 5-position, despite the strongly favorable effect in the 4,5-dihydropyridazinones as mentioned above, resulted in considerable reduction of the activity. From this observation it is inferred that a change in orientation of a methyl group at C-5 converted from sp^3 to sp^2, brought about steric hindrance to block the methyl group from fitting into the pocket, which is possibly narrow.

For the discussion of receptor binding, it is of interest to consider the effects of structural changes in the moiety other than the pyridazinone ring. The results described above are summarized as follows: (1) a free NH is necessary for the activity and the methylation of the NH leads to striking reduction of the activity, (2) insertion of a methylene between the NH and the heterocycles is entirely unfavorable for the activity, (3) among several heterocycles as substituents, 4-pyridyl is consistently more potent than 2-pyridyl and replacement with other heterocycles gives poor activity.

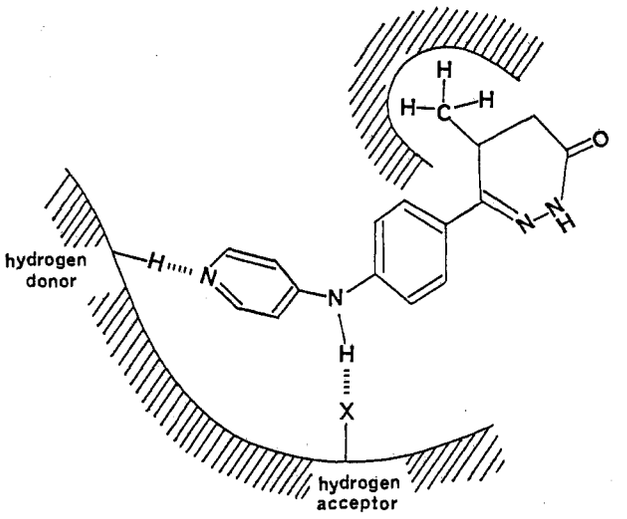


Figure 1. Hypothetical model for the interaction of the cardiotonics and a receptor. The active compounds are accommodated on the two sites of the receptor surface by means of acceptance and donation of protons.

From these observations, it is postulated that the significantly active compounds are characterized to be the compounds having the proton that can participate in the tautomerization of the pyridylamino group. Such tautomerization is known in 4-aminopyridine.[16] The significant role of a free NH was also pointed out in the case of 4-aroyl-1,3-dihydro-2*H*-imidazol-2-ones,[4] non-pyridazinone derivatives, which were less potent[7] than compound **4** or **5** and were comparable to compound **8**. In compounds **4** and **5** a geometrical configuration involving the NH donating the proton and N atom of pyridine accepting a proton is presumably appropriate for the receptor binding. The structural requirement of this moiety, as well as that of the pyridazinone ring, is suggested to be essential for the attainment of high activity. Our plausible model of interaction between drug and receptor is shown in Figure 1. This model, as depicted, makes the assumption that the concerted interaction of drug and receptor is essential for the enhancement of actvity, in addition to fitting of the methyl group into a methyl-sized pocket. This interaction takes place at the two sites, designated the proton donor site and the proton acceptor site, by a push–pull mechanism. In compound **8**, 2-pyridyl cannot contribute to this push–pull mechanism due to the improper relationship of the NH and the N atom of the pyridyl in the molecule. Thus, compound **8** is relatively less active and its activity is little affected by methylation of the NH.

Compounds that had significant inotropic potency in the isolated dog papillary muscle assay were extensively screened intravenously in anesthetized dogs, as described in the Experimental Section. Those results are given in Table III. The maximum rate of rise in left ventricular pressure (dP/dt_{max}), contractile force of right ventricle (CF), cardiac output (CO), heart rate (HR), systolic arterial blood pressure (SBP), and diastolic arterial blood pressure (DBP) were recorded. ED_{30}'s were calculated from their

(15) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.

(16) Leis, D. G.; Curran, C. *J. Am. Chem. Soc.* **1945**, *67*, 79.

Table III. Cardiohemodynamic Profile in Anesthetized Dogs

compd (n)[a]	ED_{30}[b] for dP/dt_{max},[c] μg/kg	dose, μg/kg iv	dP/dt_{max}[c]	% change CF[c]	CO[c]	HR[c]	SBP[c]	DBP[c]
amrinone (5)	472 ± 94	100	6.7 ± 1	6.5 ± 1.8	1.9 ± 1.2	1.2 ± 0.5	−5.0 ± 2.8	−4.7 ± 3.5
		300	22.3 ± 14.5	22.4 ± 4.6	15.6 ± 3.9	3.8 ± 0.6	−2.7 ± 1.6	−4.1 ± 3.3
		1000	54.8 ± 8.7	79.7 ± 10.8	36.5 ± 9.4	8.1 ± 1.5	−5.5 ± 3.6	−14.1 ± 2.3
1 (4)	22 ± 6.7	10	20.2 ± 3.9	11.0 ± 4.6	1.6 ± 3.0	1.3 ± 0.9	−3.6 ± 1.2	−7.5 ± 2.4
		30	39.6 ± 8.8	19.9 ± 3.6	5.4 ± 4.3	2.4 ± 1.8	−11.9 ± 2.5	−20.0 ± 3.8
		100	57.1 ± 18.4	33.7 ± 1.8	7.7 ± 7.9	4.2 ± 1.7	−22.3 ± 4.7	−27.6 ± 3.2
2 (2)	>1000	300	−2.2 ± 2.2	−1.1 ± 1.1	9.6 ± 6.1	−1.3 ± 0.8	0.5 ± 1.3	−0.3 ± 3.5
		1000	6.2 ± 12.2	10.5 ± 11.0	7.6 ± 0.9	5.8 ± 8.3	1.9 ± 8.1	1.4 ± 14.1
3 (2)	>1000	300	1.0 ± 1.0	2.8 ± 2.0	3.9 ± 1.4	−0.1 ± 0.7	0.4 ± 1.9	−0.9 ± 0.9
		1000	−0.9 ± 5.4	4.2 ± 0.9	8.6 ± 4.9	−2.9 ± 0.1	−5.0 ± 7.6	−9.3 ± 13.1
4 (8)	8.5 ± 1.9	3	20.9 ± 9.5	34.4 ± 5.2	12.6 ± 2.8	5.8 ± 1.7	−7.9 ± 1.8	−10.9 ± 2.0
		10	37.3 ± 7.0	56.4 ± 14.4	17.2 ± 3.5	9.9 ± 2.2	−16.1 ± 3.9	−22.0 ± 3.2
		30	69.1 ± 11.8	78.9 ± 10.2	27.7 ± 3.8	17.4 ± 5.3	−24.9 ± 3.6	−32.9 ± 3.1
5 (4)	4.4 ± 0.6	1	8.1 ± 1.6	7.9 ± 1.6	5.1 ± 1.3	3.4 ± 1.5	−4.7 ± 1.2	−7.3 ± 2.3
		3	19.5 ± 3.6	22.7 ± 6.6	11.7 ± 1.6	15.8 ± 7.8	−14.1 ± 5.0	−21.2 ± 6.3
		10	58.4 ± 7.3	61.5 ± 15.2	24.5 ± 3.9	25.1 ± 10.2	−23.6 ± 7.7	−31.4 ± 9.1
6 (2)	256 ± 143	100	20.4 ± 8.2	23.7 ± 8.2	15.2 ± 2.5	12.0 ± 10.3	−8.8 ± 0.6	−15.1 ± 2.1
		300	34.8 ± 7.5	35.7 ± 1.3	19.2 ± 1.5	22.5 ± 17.9	−11.1 ± 5.8	−18.3 ± 8.7
7 (3)	72 ± 27	30	24.2 ± 3.1	22.5 ± 4.2	10.3 ± 1.6	4.6 ± 0.4	−5.9 ± 1.6	−9.8 ± 1.6
		100	43.8 ± 10.7	52.9 ± 6.1	23.3 ± 2.6	17.3 ± 4.4	−14.6 ± 4.2	−26.1 ± 3.0
8 (3)	106 ± 36	30	16.1 ± 1.2	22.0 ± 7.6	13.9 ± 1.3	6.7 ± 0.8	−13.7 ± 2.6	−15.6 ± 2.8
		100	37.8 ± 10.7	40.5 ± 8.7	22.1 ± 0.7	16.7 ± 4.1	−27.2 ± 6.8	−25.5 ± 16.7
9 (3)	22 ± 9.8	10	19.3 ± 10.3	19.5 ± 7.1	12.7 ± 3.0	5.3 ± 2.1	−14.1 ± 3.6	−22.4 ± 6.2
		30	46.4 ± 15.5	44.4 ± 21.6	15.8 ± 4.6	8.9 ± 3.5	−17.6 ± 4.2	−31.0 ± 6.4
12 (2)	>300	100	13.6 ± 5.4	11.0 ± 0.1	5.9 ± 4.1	1.4 ± 0.4	−2.1 ± 1.7	−4.0 ± 2.6
		300	17.8 ± 7.4	20.0 ± 3.3	8.7 ± 3.8	2.7 ± 1.1	−5.8 ± 2.1	−10.3 ± 3.4
13 (2)	>100	30	11.0 ± 1.4	13.0 ± 0.5	8.9 ± 3.9	2.6 ± 0.6	−0.6 ± 3.2	−3.2 ± 3.0
		100	27.5 ± 0.5	41.2 ± 3.3	13.3 ± 3.0	22.8 ± 10.0	−5.5 ± 0.7	−13.9 ± 1.2
14 (2)	>100	30	14.3 ± 11.5	16.5 ± 10.7	13.2 ± 5.7	4.5 ± 1.7	−6.3 ± 3.4	−9.6 ± 3.7
		100	32.5 ± 21.5	37.7 ± 22.4	18.7 ± 5.6	9.5 ± 4.6	−10.5 ± 0.4	−17.8 ± 2.8
CI-914 (4)	46 ± 12	10	10.3 ± 2.1	13.8 ± 2.7	11.2 ± 0.8	3.6 ± 1.4	−4.8 ± 2.5	−8.1 ± 4.6
		30	22.3 ± 6.6	42.2 ± 12.4	26.3 ± 9.7	8.1 ± 0.9	−9.6 ± 2.7	−16.5 ± 4.7
		100	49.3 ± 5.7	83.8 ± 15.9	35.5 ± 7.1	16.1 ± 2.7	−16.9 ± 3.6	−28.3 ± 6.3

[a] "n" is the number of dogs. [b] Dose that produced 30% increase in dP/dt_{max}. Values reported are either the mean ± SEM (n = 3) or the mean ± range (n = 2) of experimental values. [c] Abbreviations used: dP/dt_{max}, maximum rate of rise in left ventricular pressure; CF, contractile force of the right ventricle; CO, cardiac output; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

dose–response (dP/dt_{max}) curves.

Relative potencies of the tested compounds on the inotropic activities after intravenous administration were almost consistent with those observed in the papillary muscle assay, except that a notable discrepancy existed in compound **9**. Consequently the structure–activity relationships in vitro were also valid in vivo. As indicated in Table III, compounds **1**, **4**, **5**, and **9** were grouped in the most effective class, more than 20 times as active as amrinone, while compounds **7** and **8** fell into another group, about 5 times the activity of amrinone. All of the rest were poorly active or almost inactive. It is especially worth noting that compound **5** is particularly potent, the increase in myocardial contractility being detected even at a dose of 1 μg/kg. It could be the most potent among the novel cardiotonics.

As regards the cardiovascular profiles of the active compounds tested, the inotropic effects were associated with a small increase in HR and decreases in SBP and DBP by their direct vasodilating effects. Oral effectiveness is essential to cardiotonic drugs. Compound **4** produced a dose-dependent increase in dP/dt_{max} after oral administration in conscious dogs.

Moreover, these beneficial effects of compound **4** were not altered by propranolol and reserpine. This indicates that these agents are not acting by direct stimulation of the β-adrenergic receptor or by release of endogenous catecholamines, allowing them to be classified as a new type of cardiotonic.

Compound **4** (MCI-154), in particular, is of continued interest. Further biochemical and pharmacological studies suggesting potential utility for the treatment of congestive heart failure are in progress, and these results will be reported in detail elsewhere.

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. NMR, IR, and mass spectra were recorded on Brucker AC-250, JASCO IR-A102, and Hitachi M-80 instruments, respectively. Elemental analyses were within 0.4% of theoretical values.

Preparation of Intermediate (4-Aminophenyl)-pyridazinones 21–29. The following eight compounds were prepared according to published procedures: 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**21**),[8,9] 6-(4-aminophenyl)-3(2*H*)-pyridazinone (**22**),[10] 6-(4-aminophenyl)-4,5-dihydro-4-methyl-3(2*H*)-pyridazinone (**23**),[9,12] 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (**24**),[12] 6-(4-aminophenyl)-5-methyl-3(2*H*)-pyridazinone (**25**),[12] 6-(4-aminophenyl)-4,5-dihydro-5-ethyl-3(2*H*)-pyridazinone (**26**),[11] 6-[4-(methylamino)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (**27**),[11] 6-[4-(methylamino)phenyl]-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (**28**).[11]

6-(4-Aminophenyl)-5-ethyl-3(2*H*)-pyridazinone (29). A mixture of NaOH (0.82 g, 19.4 mmol) in H_2O (30 mL), sodium 3-nitrobenzenesulfonate (1.45 g, 6.4 mmol), and 6-(4-aminophenyl)-4,5-dihydro-5-ethyl-3(2*H*)-pyridazinone (**26**) (1.39 g, 6.4 mmol) was heated at 110 °C for 6.5 h. After cooling and neutralization with 3 N HCl, a precipitate was collected by filtration. The crude product was chromatographed over silica gel with $CHCl_3/CH_3OH$ (50:1). After replacement of the solvent of the corresponding fraction with *n*-hexane, the recrystallized product was filtered and dried to obtain 6-(4-aminophenyl)-5-ethyl-3-(2*H*)-pyridazinone (**29**) (0.92 g, 4.27 mmol, 66.8% yield): mp 246–247 °C; ^1H NMR (Me_2SO-d_6) δ 0.99 (t, 3 H, J = 7.4 Hz), 2.44 (q, 2 H, J = 7.4 Hz), 5.36 (s, 2 H), 6.60 (d, 2 H, J = 8.4 Hz), 6.70 (s, 1 H), 7.08 (d, 2 H, J = 8.4 Hz), 12.83 (s, 1 H); IR 1670 cm^{-1}

(KBr); MS, m/e 215 (M^+) (215.25 calcd for $C_{12}H_{13}N_3O$). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 67.25; H, 6.14; N, 19.69.

Preparation of Compounds 1–14. Compounds 1–14 were all prepared by the same general method, and the procedure is exemplified by preparation of 6-[4-(4-pyridylamino)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (**5**).

6-[4-(4-Pyridylamino)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone Hydrochloride (5). 6-(4-Aminophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (**24**) (0.81 g, 3.99 mmol) was dissolved in 4 mL of *N*-methylpyrrolidone, triethylamine (0.28 mL, 2.03 mmol) was added, and then the mixture was heated to 90 °C. 4-Chloropyridine (0.60 g, 4.00 mmol) was added and the mixture was heated at 90 °C for 2 h. After the mixture was cooled on an ice bath, 50 mL of acetone was added to give a precipitate. The isolated solid was dissolved in water and alkalinized with 1 N NaOH to give a precipitate. This solid was then chromatographed over silica gel with $CHCl_3/CH_3OH$ (10:1). The residue that was obtained by the concentration to dryness of the corresponding fraction was dissolved in ethanol and was mixed with 1 N HCl/EtOH to convert into hydrochloride salt. Ether was added to the solution to deposit the purified product, which was filtered out and dried to obtain 6-[4-(4′-pyridylamino)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride (**5**) (0.863 g, 2.72 mmol, 68.3% yield): mp 249–252 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.10 (d, 3 H, J = 7.25 Hz), 2.26 (d, 1 H, J = 16.9 Hz), 2.72 (dd, 1 H, J_1 = 16.9 Hz, J_2 = 6.9 Hz), 3.4 (m, 1 H), 7.25 (d, 2 H, J = 6.75 Hz), 7.42 (d, 2 H, J = 8.5 Hz), 7.89 (d, 2 H, J = 8.5 Hz), 8.3 (d, 2 H, J = 6.75 Hz), 11.02 (s, 1 H), 11.04 (s, 1 H); IR 1640 cm^{-1} (KBr); MS, m/e 280 (M^+) (280.33 calcd for $C_{16}H_{16}N_4O$). Anal. Calcd for $C_{16}H_{16}N_4O$·HCl: C, 60.66; H, 5.41; N, 17.69. Found: C, 60.77; H, 5.49; N, 17.68.

Preparation of Compounds 15–20. Compounds **15–20** were all prepared by the same general method, and the procedure is exemplified by preparation of 6-[4-[(4-pyridylmethyl)amino]-phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (**15**).

6-[4-[(4-Pyridylmethyl)amino]phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (15). (A) In the mixture of dimethylformamide (70 mL) and toluene (150 mL) were dissolved 6-(4-aminophenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**21**) (18.8 g, 99.4 mmol), 4-pyridinecarboxaldehyde (10 mL, 104.8 mmol), and *p*-toluenesulfonic acid (20 mg, 0.12 mmol). The solution was heated on oil bath at 160 °C for 3 h with removal of water as an azeotropic mixture. The reaction mixture was then cooled and crystallized by adding ether (300 mL). The crystals were filtered and were dried to obtain the crude intermediate 6-[4-[(4-pyridylmethylidene)amino]phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (23.25 g).

(B) The above crude intermediate and 3 g of 5% Pd/C in the mixture of triethylamine (2 mL, 14.4 mmol) and dimethylformamide (200 mL) were subjected to hydrogenation at room temperature and atmospheric pressure until hydrogen uptake had ceased. Afer removal of the catalyst by filtration, water (700 mL) was added to form a precipitate, which was filtered out to separate the crude product. The crude product was then chromatographed over silica gel with $CHCl_3$/THF (2:1). Addition of *n*-hexane to the corresponding fraction afforded the purified precipitate, which was filtered and dried to obtain 6-[4-[(4-pyridylmethyl)amino]-phenyl]-4,5-dihydro-3(2*H*)-pyridazinone (**15**) (12.2 g, 43.5 mmol, 43.8% yield): mp 207–209 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.35 (t, 2 H, J = 8.25 Hz), 2.81 (t, 2 H, J = 8.25 Hz), 4.37 (d, 2 H, J = 6.25 Hz), 6.56 (d, 2 H, J = 8.5 Hz), 6.79 (t, 1 H, J = 6.25 Hz), 7.32 (d, 2 H, J = 5 Hz), 7.48 (d, 2 H, J = 8.5 Hz), 8.48 (d, 2 H, J = 5 Hz), 10.64 (s, 1 H); IR 1660 cm^{-1} (KBr); MS, m/e 280 (M^+) (280.33 calcd for $C_{16}H_{16}N_4O$). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.32; H, 5.84; N, 19.82.

Preparation of Control Compounds. Amrinone and **CI-914** were prepared according to USP 4 004 012 (1977)[17] and USP 4 353 905 (1982),[18] respectively.

Pharmacological Methods. Isolated, Blood-Perfused Papillary Muscle Preparation of the Dog. The papillary muscle preparation was similar to that described by Endoh and Hashimoto.[19] Briefly, the hearts were removed from mongrel dogs of either sex, weighing 7–12 kg, anesthetized with sodium pentobarbital (30 mg/kg iv). The preparation was essentially the anterior papillary muscle of the right ventricle taken together with the ventricular septum. The preparation was fixed to a piece of plastic plaque with a hole in which the papillary muscle was fitted at the base. The preparation was perfused at constant pressure, about 100 mmHg, through the cannulated anterior septal artery with arterial blood from a donor dog anesthetized with sodium pentobarbital (30 mg/kg iv) and heparinized (500 units/kg iv). The papillary muscle was stimulated with rectangular pulses of about 1.5 times the threshold voltage and 1 ms duration at a rate of 120 stimuli/min through bipolar electrodes placed at the base of the muscle. Tension developed by the papillary muscle was measured isometrically with a strain-gauge transducer. Test compounds were dissolved in normal saline and the solutions were injected into the anterior septal artery in a volume of 30 or 100 μL by use of a microsyringe. In each experiment, dose–response curves of a reference drug, amrinone, and of the test compounds were obtained, and ED_{15} values were calculated from the log dose–response curves.

Anesthetized Open-Chest Dog Preparation. Mongrel dogs of either sex weighing 7–15 kg were anesthetized with sodium pentobarbital (30 mg/kg iv). After tracheal intubation, artificial respiration was performed with a Harvard respirator (Model 607) using room air. A catheter connected to a pressure transducer (Nihon Kohden, MPU-0.5) was positioned in the femoral artery to measure SBP and DBP. Lead II electrocardiogram (ECG) was monitored and HR was measured with a cardiotachometer triggered by R waves of the ECG. The left chest was opened at the forth and the fifth intercostal spaces and the fifth costa was removed. The pericardium was cut to expose the heart and a Walton-Brodie strain gauge was sutured to the wall of the right ventricle to measure CF. Left ventricular pressure (LVP) was measured with a microtip catheter pressure transducer (Miller, PC-350) introduced into the left ventricle via the left carotid artery and dP/dt_{max} was obtained with an electric differentiator (Nihon Kohden, EQ-45764). All parameters were recorded on polygraphs (Nihon Kohden, RM-6000). A noncannulating probe of an electromagnetic flow meter (Nihon Kohden, MFV-1200) was placed around the ascending aorta to measure CO. Test compounds were dissolved in normal saline. The solutions of the test compounds were administered intravenously through rubber tubing inserted into the left femoral vein.

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Supplementary Material Available: ^{1}H NMR, IR and mass spectral data for compounds 1–28 (9 pages). Ordering information is given on any current masthead page.

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