Nonsteroidal Cardiotonics. 3. New 4,5-Dihydro-6-(1*H*-indol-5-yl)pyridazin-3(2*H*)-ones and Related Compounds with Positive Inotropic Activities[1]

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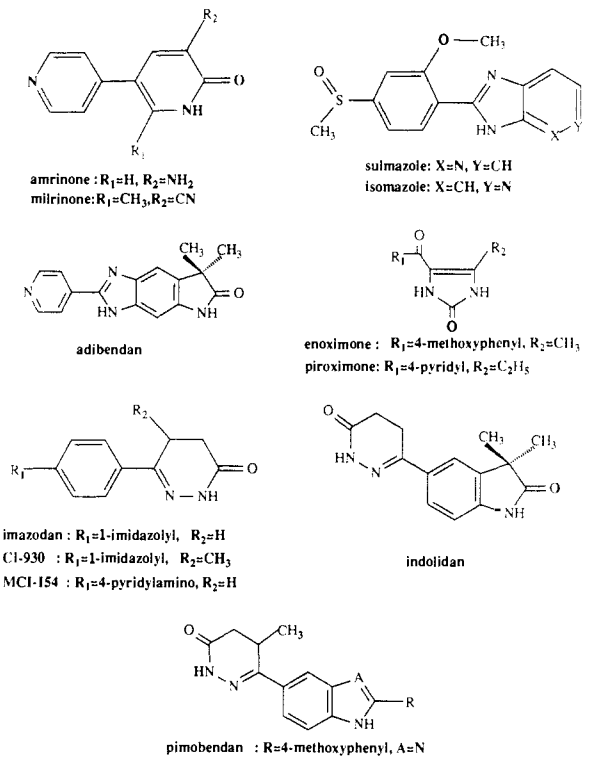
A series of substituted indolyldihydropyridazinones and related compounds 1–18 were synthesized and evaluated for positive inotropic activity. In rats, most of these indole derivatives produced a dose-related increase in myocardial contractility with little effect on heart rate and blood pressure. Compound 13, 4,5-dihydro-5-methyl-6-(2-pyridin-4-yl-1*H*-indol-5-yl)pyrazin-3(2*H*)-one (BM 50.0430), was further investigated in cats. The increase in contractility in this animal model was not mediated via stimulation of β-adrenergic receptors. After oral administration of 1 mg/kg to conscious dogs, compound 13 and pimobendan were still active after 6.5 h. However, the cardiotonic effect of 13 was at least 2-fold that of pimobendan after this period of time. The structural requirements necessary for optimal cardiotonic activity within this novel class of indole derivatives are a heterocyclic aromatic ring in position 2, a hydrogen or a methyl group in position 3, and a dihydropyridazinone ring system in position 5 of the indole.

Since the development of amrinone[2] and sulmazole[3] as nonsteroidal, noncatecholamine, cardiotonic drugs in 1978, enormous efforts have been made worldwide to find safer drugs for the treatment of congestive heart failure (CHF). Prototypical classes of nonsteroidal, noncatecholamine, cardiotonic drugs are 5-aryl-2(1*H*)-pyridones, such as amrinone[2] and milrinone,[4] pyridoimidazoles, such as sulmazole[3] and isomazole,[5] pyrrolobenzimidazolones[1,6] and related compounds, such as adibendan,[1,7] 4(5)-(het)aroyl-2,3-dihydro-2(1*H*)-imidazolones, such as enoximone[8] and piroximone,[9] and a still growing number of 6-(het)aryl-4,5-dihydro-3(2*H*)-pyridazinones, including compounds such as imazodan,[10] CI-930,[10] MCI-154,[11] pimobendan,[12] indolidan,[13] and bemoradan[14] (Chart I).

In addition to their positive inotropic properties, these novel compounds show vasodilatory effects on the peripheral vasculature. The pharmacological mechanisms of the above mentioned drugs appear to be similar and are partly mediated via inhibition of cardiac phosphodiesterases.[15,16] However, sulmazole,[17] isomazole,[18] pimobendan,[19] adibendan,[20] and MCI-154[21] may also produce an increase in myofibrillar Ca^{2+} sensitivity. In continuation of our efforts to find nonsteroidal, nonsympathomimetic drugs for the treatment of CHF, we synthesized several novel indolyldihydropyridazinones and related compounds and studied their positive inotropic effects in rats, cats, and conscious dogs. The most promising compound was 4,5-dihydro-5-methyl-6-(2-pyridin-4-yl-1*H*-indol-5-yl)-pyridazin-3(2*H*)-one (Chart I, 13, BM 50.0430).

Chart I



Chemistry

The preparation of the indolyldihydropyridazinones and related compounds followed standard synthetic methods.[22] Usually, a known, suitably substituted aniline derivative was subjected to diazotization and reduction to a phenylhydrazine derivative, which was then condensed with ketones to phenylhydrazones and subsequently cyclized to the indole ring system (Scheme I).

We usually converted the aniline derivatives directly to the hydrazones in a one-pot synthesis without isolation of any intermediate. The hydrazones commonly precipitated from the reaction mixture and were used as crude products in the last step. However, in some cases it proved to be better to isolate the hydrazine derivatives prior to the condensation with the ketones. This was actually necessary, when the ketones were not miscible with the aqueous acidic solution resulting after the reduction of the di-

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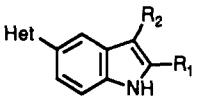
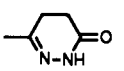
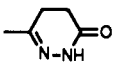
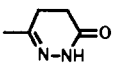
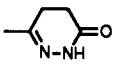
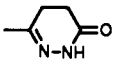
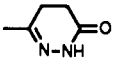
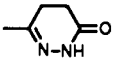
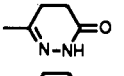
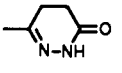
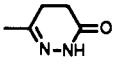
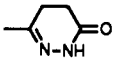
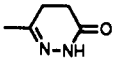
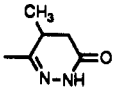
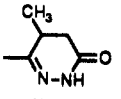
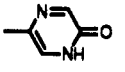
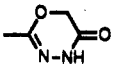
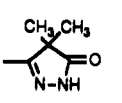
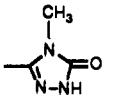
0022-2623/90/1833-2870$02.50/0

Table I. Structures and Properties of Indolyldihydropyridazinones and Related Compounds



no.	R_1	R_2	Het	% yield[a]	mp,[b] °C	recrystn solvent	formula
1	$COOC_2H_5$	H		25	235–7	$C_2H_5OC_2H_5$	$C_{15}H_{15}N_3O_3$
2	4-pyridyl	H		57	314–6	CH_2Cl_2/CH_3OH	$C_{17}H_{14}N_4O$
3	3-pyridyl	H		50	298–301	C_2H_5OH	$C_{17}H_{14}N_4O$
4	4-pyridazinyl	H		18	357–61	c	$C_{16}H_{13}N_5O$
5	4-thiazolyl	H		41	307–9	CH_3OH	$C_{15}H_{12}N_4OS$
6	phenyl	H		45	270–5	c	$C_{18}H_{13}N_3O$
7	4-methoxyphenyl	H		45	262–4	c	$C_{19}H_{17}N_3O_2$
8	4-(methylthio)phenyl	H		12	256–8	dioxane	$C_{19}H_{13}N_3OS$
9	2-hydroxyphenyl	H		13	238–40	$C_2H_5OH/C_2H_5OC_2H_5$	$C_{18}H_{15}N_3O_2$
10	4-pyridyl	CH_3		24	334–9	CH_3OH	$C_{18}H_{18}N_4O$
11	4-pyridyl	C_2H_5		65	318–21	CH_3OH	$C_{19}H_{18}N_4O$
12	4-pyridyl	$(CH_3)_2CH$		41	311–3	CH_3OH	$C_{20}H_{20}N_4O$
13	4-pyridyl	H		68	301–3	CH_2Cl_2/CH_3OH	$C_{18}H_{18}N_4O$
14	4-pyridyl	CH_3		59	294–7	CH_2Cl_2/CH_3OH	$C_{19}H_{18}N_4O$
15	4-pyridyl	H		30	>300	CH_3OH	$C_{17}H_{12}N_4O$
16	4-pyridyl	H		12	273–7	c	$C_{18}H_{12}N_4O_2$
17	4-pyridyl	H		16	>300	c	$C_{18}H_{18}N_4O$
18	4-pyridyl	H		19	380–7	C_2H_5OH	$C_{18}H_{13}N_5O$

[a] Yields are not optimized. [b] Melting points are uncorrected. [c] Purification by column chromatography (elution solvent, CH_2Cl_2/CH_3OH 10:1, v/v).

azonium salt. On the other hand, the ethyl indole-2-carboxylate derivative 1 was prepared via the reaction of 4,5-dihydro-6-(4-hydrazinophenyl)pyridazin-3(2*H*)-one with ethyl 2-methylacetoacetate and subsequent hydro-

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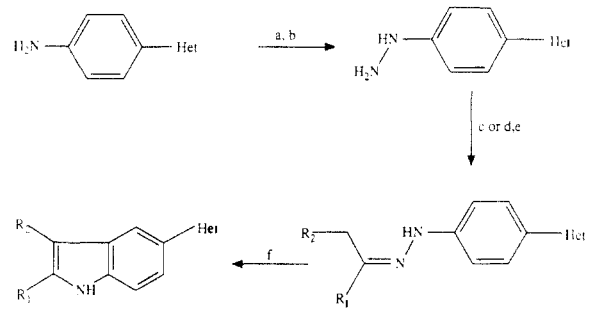
Scheme I[a]



[a] (a) $NaNO_2$/HCl; (b) $SnCl_2 \cdot 2H_2O$/concentrated HCl; (c) $R_1COCH_2R_2$; (d) $CH_3COCHCH_3COOC_2H_5$; (e) KOH; (f) PPA/Δ.

Table II. Pharmacological Data of Compounds 1–18, Milrinone, and Pimobendan in Anesthetized Rats

no.	n[a]	rat iv $ED_{1.5}$,[b] mg/kg	max,[c] mHg/s	dose,[d] mg/kg
1	2	1.50	2.30	3.0
2	5	0.04	3.10	1.0
3	2	2.50	2.00	3.0
4	4	0.02	2.50	0.1
5	4	0.26	2.50	1.0
6	2	*e*	0.70	3.0
7	2	*e*	1.30	3.0
8	2	*e*	0.70	3.0
9	4	1.04	2.20	3.0
10	4	0.08	2.90	0.3
11	2	1.10	1.90	3.0
12	2	*e*	0.80	3.0
13	8	0.02	2.30	0.2
14	4	0.02	2.90	1.0
15	4	0.15	3.40	3.0
16	4	0.70	2.70	3.0
17	4	0.25	2.20	1.0
18	4	*e*	0.40	3.0
milrinone	6	0.15	3.40	10.0
pimobendan[f]	4	1.31	2.00	3.0

[a] Number of rats. [b] $ED_{1.5}$ is the effective dose (mg/kg) required to produce an increase in dP/dt by 1500 mmHg/s from that of the control. $ED_{1.5}$ was calculated by log–linear regressions (dP/dt at a LVP of 50 mmHg) and is given as log means. [c] Max is the maximum increase in dP/dt (mmHg/s) from that of the control. dP/dt was recorded in mmHg/s and converted to mHg/s in the table. [d] Dose (mg/kg) at which the maximum increase in dP/dt was achieved. [e] Values not obtained. [f] Due to the bad solubility of pimobendan, the values probably do not represent the real potency of pimobendan after iv administration.

lyzation of the intermediate to the corresponding hydrazone of ethyl pyruvate, which was finally cyclized to the desired indole 1 (Scheme I). The final cyclization of all hydrazones to the indole ring system was always performed under acidic conditions. Among several acidic catalysts, best results were usually obtained in polyphosphoric acid. All physical data are summarized in Table I.

Table III. Pharmacological Data of Compounds 13, Milrinone, and Pimobendan in Anesthetized Cats Pretreated with 0.3 mg/kg Desacetylmetipranolol

no.	n[a]	cat iv $ED_{1.5}$,[b] mg/kg	max,[c] mHg/s	dose,[d] mg/kg
13	6	0.007	2.20	0.1
milrinone	4	0.04	3.40	0.1
pimobendan[e]	4	0.6	2.90	10.0

[a] Number of cats. [b] $ED_{1.5}$ is the effective dose (mg/kg) required to produce an increase in dP/dt by 1500 mmHg/s from that of the control. $ED_{1.5}$ was calculated by log–linear regressions (dP/dt at a LVP of 50 mmHg) and is given as log means. [c] Max is the maximum increase in dP/dt (mmHg/s) from that of the control. dP/dt was recorded in mmHg/s and converted to mHg/s in the table. [d] Dose (mg/kg) at which the maximum increase in dP/dt was achieved. [e] Due to the bad solubility of pimobendan, the values probably do not represent the real potency of pimobendan after iv administration.

Pharmacology

Anesthetized rats and cats and conscious dogs were preparated for recording dP/dt, blood pressure (BP), and heart rate (HR). Dose–response curves were performed for all compounds 1–18 by iv injection of incremental doses.

In rats, 0.01–3 mg/kg of tested compounds usually led to a dose-related increase in dP/dt with little effect on HR and BP. The effective dose required to produce an increase in dP/dt by 1500 mmHg/s ($ED_{1.5}$) was taken for comparison from the dose–response curves (Table II).

In the 2-(4-pyridyl)indole series, compound **13** was the most potent derivative ($ED_{1.5}$ = 0.02 mg/kg). Substitution of the methyl group by hydrogen in the pyridazinone ring resulted in a slightly less potent compound **2** ($ED_{1.5}$ = 0.04 mg/kg). This observation is a common fact in positive inotropic drugs derived from dihydropyridazinones and was already published in the case of CI-914[10] and indolidan[13] and their methyl derivatives. Additional introduction of a methyl group in position 3 of the indole ring (**10**, $ED_{1.5}$ = 0.08 mg/kg) did not effectively reduce the cardiotonic potency of the parent compound **13**. However, more bulky alkyl groups such as ethyl and isopropyl in position 3 dramatically decreased the potency of these substances as seen in the series **2**, **11**, and **12**. Whereas ethyl derivative **11** still showed an $ED_{1.5}$ value of 1.1 mg/kg, isopropyl derivative **12** did not reach the $ED_{1.5}$ up to the highest dose of 3 mg/kg.

To further check the influence of the pyridazinone ring, we synthesized another four heterocyclic ring systems **15**–**18** quite similar to the pyridazinones. Compounds **15**–**17** produced a dose-related increase in dP/dt starting between 0.01 and 0.1 mg/kg. However, the $ED_{1.5}$ values were almost 10–30 times higher than that for the most potent dihydropyridazinone **13**. Surprisingly *N*-methyltriazolone derivative **18** showed no cardiotonic effects at all. We finally substituted the pyridyl group in position 2 of the indole ring by phenyl derivatives, different het-

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erocycles and an ester group. Among the 2-phenylindoles **6–9**, only 4-methoxyphenyl and 2-hydroxyphenyl derivatives **7** and **9** showed weak positive inotropic effects of $ED_{1.5} > 3.0$ and 1.0 mg/kg, respectively. Especially the $ED_{1.5}$ value of **7** is worth noting, since this compound is very similar to pimobendan, although the positive inotropic effects of the latter are very weak in our animal model.

In contrast to the phenyl derivatives, the pyridazinyl- and thiazolylindoles **4** and **5** produced a strong increase in dP/dt at very low doses ($ED_{1.5}$ = 0.02 and 0.26 mg/kg). Compound **4** was even slightly more potent than the corresponding pyridyl compound **13**. Encouraged by the positive inotropic effects of this novel heterocyclic ring system in our rat model after iv administration, we chose **13** for further evaluation, since this compound showed the best relationship in regard to pharmacological data and costs of production. We next injected **13** in anesthetized, open-chest cats, pretreated with 0.3 mg/kg desacetylmetipranolol (DAM). The inotropic effect of **13** was not blocked by a prior dose of DAM, which indicates that this compound is not acting via direct stimulation of β-adrenergic receptors or indirectly by release of catecholamines. Intravenous doses of 0.001–0.1 mg/kg of **13** produced a dose-related increase in cardiac contractile force and a decrease in blood pressure as well as a slight decrease in heart rate. The effective dose that increased dP/dt by 1500 mmHg/s ($ED_{1.5}$) was 0.01 mg/kg (Table III).

Since oral activity is of paramount importance, we further investigated **13** after oral administration in conscious dogs. Due to the close structural similarity of **13** and pimobendan, we included this compound along with milrinone in our study. The dogs were given a single dose of 1 mg/kg po of each compound suspended in methylcellulose. At this dose, **13**, pimobendan, and milrinone, when orally given, seem to be almost equiactive with the maximum increase in contractility being about 2000 mmHg/s. The positive inotropic activity of **13** and pimobendan was still evident 6.5 h after administration, **13** being considerably more active after this period of time. In contrast, the positive inotropic effect of milrinone disappeared within 4 h (Figure 1).

Conclusions

We have prepared several new indolyldihydropyridazinones and related compounds and demonstrated that some candidates within this series of compounds possess potent positive inotropic activity. In general, we found in our study that a 4-pyridyl ring in position 2, a hydrogen or a methyl group in position 3, and a dihydropyridazinone ring system in position 5 of the indole are structural requirements for potent inotropic activity. A methyl group in the dihydropyridazinone ring increases the cardiotonic effect. One of the most active compounds, **13**, was further investigated in anesthetized cats where contribution of β-receptors to the cardiotonic effect was ruled out by prior administration of desacetylmetipranolol. Compound **13** (1 mg/kg) produced a pronounced positive inotropic effect in conscious dogs after oral administration. Even after 6.5 h, this increase in myocardial contractility was more pronounced than with the structurally similar compound pimobendan. On the basis of these results, further pharmacological studies were carried out and these are reported elsewhere.[23,24]

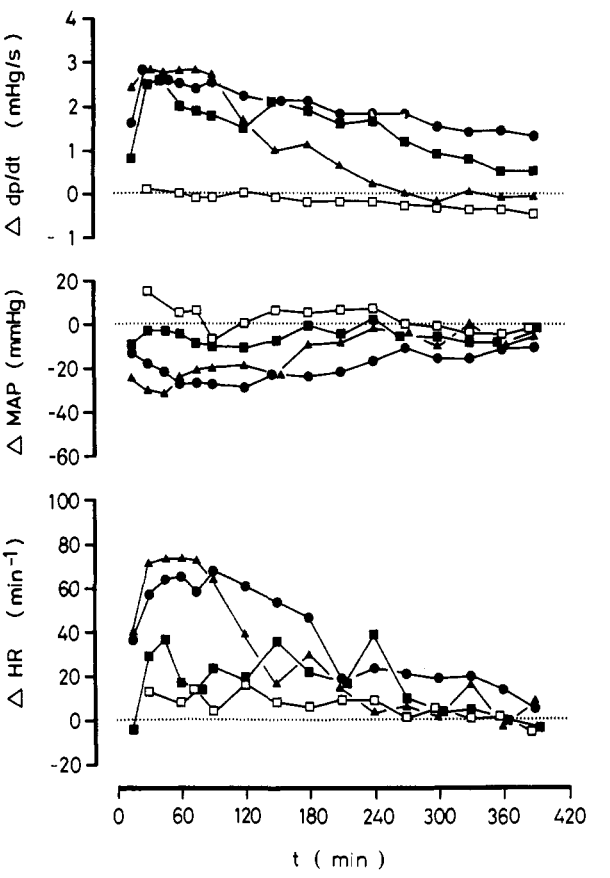

Figure 1. Effect of **13** (●, n = 8), milrinone (▲, n = 5), pimobendan (■, n = 5), and placebo (□, n = 5) on left ventricular dP/dt, mean atrial pressure, and heart rate in conscious dogs. The dose was 1 mg/kg po suspended in methylcellulose. dP/dt was recorded in mmHg/s and converted to mHg/s in the figure.

Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. The identity of all compounds was confirmed by ^{1}H NMR (300 MHz, Varian XL-300, solvent Me_2SO-d_6, TMS = 0 ppm), mass spectra (Finnigan MAT 312, data system SS300), and combustion analysis, which were provided by the Analytical Department of the Boehringer Mannheim Research Laboratories. All reactions were followed by TLC carried out on Merck F 254 silica gel plates. All aniline derivatives used in the following preparation procedures were synthesized according to literature methods: 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one,[25] 6-(4-aminophenyl)-4,5-dihydro-5-methylpyridazin-3(2*H*)-one,[25,26] 5-(4-aminophenyl)pyrazin-2(1*H*)-one,[27] 2-(4-aminophenyl)-1,6-dihydro-1,3,4-oxadiazin-5(4*H*)-one,[28] 5-(4-aminophenyl)-4,4-dimethylpyrazol-3(4*H*)-one,[28] and 5-(4-aminophenyl)-4-methyl-1,2,4-triazol-3(4*H*)-one.[28]

Preparation of 4,5-Dihydro-5-methyl-6-(2-pyridin-4-yl-1*H*-indol-5-yl)pyridazin-3(2*H*)-one (13). Method A (a). A 10.2 g (0.05 mol) sample of 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone[25,26] was mixed with 100 mL of 2 *N* hydrochloric acid and cooled to −2–0 °C and 3.5 g (0.051 mol) of sodium nitrite in 10 mL of water was added dropwise. After 30

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min, 28 g (0.124 mol) of tin(II) chloride dihydrate in 20.5 mL of concentrated hydrochloric acid was dropped into the solution at the same temperature. After 1 h, 6.05 g (0.05 mol) of 4-acetylpyridine was added and the mixture was stirred overnight at room temperature. The precipitate was isolated by suction, washed with water, again suspended in water, and adjusted to pH 8 to liberate the free base. The precipitate was isolated, dried, and extracted with three 75-mL portions of warm methanol/methylene chloride 1:1. The organic phases were combined and the solvent was evaporated to yield 10.4 g (65%) of 4-acetylpyridine [4-(2,3,4,5-tetrahydro-5-methyl-3-oxo-6-pyridazinyl)phenyl]hydrazone as crude product.

(**b**). A 6.0 g (18.7 mmol) sample of the above crude product and 100 g of polyphosphoric acid were heated under nitrogen at 120 °C for 2 h. After being poured into ice/water, the precipitate was isolated by suction, again suspended in water, and adjusted to pH 8 to liberate the free base. The precipitate was isolated and recrystallized from methanol/methylene chloride to yield 3.8 g (68%) of pure product: mp 301–3 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.13–1.15 (d, 3 H, CH_3), 2.23–2.29 (m, 1 H, CH), 2.66–2.74 (m, 1 H, CH), 3.47–3.52 (m, 1 H, C*H*CH_3), 7.24 (1 H, H-3 indole), 7.46–7.49 (1 H, H-7 indole), 7.72–7.76 (1 H, H-6 indole), 7.82–7.84 (2 H, pyridine), 7.99 (1 H, H-4 indole), 8.62–8.64 (2 H, pyridine), 10.78 (1 H, NH), 11.89 (1 H, NH); MS m/e 304 (M^+).

According to the above mentioned method A, the following compounds were prepared.

4,5-Dihydro-6-(2-pyridin-4-yl-1*H*-indol-5-yl)pyridazin-3-(2*H*)-one (2). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 4-acetylpyridine yielded 57% of pure product: mp 314–6 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.43–2.48 (t, 2 H, CH_2), 2.99–3.05 (t, 2 H, CH_2), 7.25 (1 H, H-3 indole), 7.45–7.48 (1 H, H-7 indole), 7.70–7.73 (1 H, H-6 indole), 7.82–7.84 (2 H, pyridine), 7.95 (1 H, H-4 indole), 8.62–8.65 (2 H, pyridine), 10.82 (1 H, NH), 11.95 (1 H, NH); MS m/e 290 (M^+).

4,5-Dihydro-6-(2-pyridin-3-yl-1*H*-indol-5-yl)pyridazin-3-(2*H*)-one (3). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 3-acetylpyridine yielded 50% of pure product: mp 298–301 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.43–2.49 (t, 2 H, CH_2), 2.99–3.05 (t, 2 H, CH_2), 7.08 (1 H, H-3 indole), 7.44–7.46 (1 H, H-7 indole), 7.46–7.51 (1 H, pyridine), 7.65–7.69 (1 H, H-6 indole), 7.93 (1 H, H-4 indole), 8.20–8.24 (1 H, pyridine), 8.51–8.53 (1 H, pyridine), 9.11 (1 H, pyridine), 10.74 (1 H, NH), 11.52 (1 H, NH); MS m/e 290 (M^+).

4,5-Dihydro-6-(2-pyridazin-4-yl-1*H*-indol-5-yl)pyridazin-3(2*H*)-one (4). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 4-acetylpyridazine[29] yielded 18% of pure product: mp 357–61 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.45–2.50 (t, 2 H, CH_2), 3.00–3.06 (t, 2 H, CH_2), 7.44 (1 H, H-3 indole), 7.49–7.51 (1 H, H-7 indole), 7.74–7.77 (1 H, H-6 indole), 7.97 (1 H, H-4 indole), 8.01–8.03 (1 H, H-5 pyridazine), 9.23–9.25 (1 H, H-3 pyridazine), 9.74 (1 H, H-6 pyridazine), 10.77 (1 H, NH), 11.62 (1 H, NH); MS m/e 291 (M^+).

4,5-Dihydro-6-(2-thiazol-4-yl-1*H*-indol-5-yl)pyridazin-3-(2*H*)-one (5). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 4-acetylthiazole[30] yielded 41% of pure product: mp 307–9 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.42–2.47 (t, 2 H, CH_2), 2.98–3.04 (t, 2 H, CH_2), 6.79 (1 H, H-3 indole), 7.41–7.44 (1 H, H-7 indole), 7.61–7.65 (1 H, H-6 indole), 7.92 (1 H, H-4 indole), 8.05 (1 H, thiazole), 9.20 (1 H, thiazole), 10.69 (1 H, NH), 11.68 (1 H, NH); MS m/e 296 (M^+).

4,5-Dihydro-6-(3-methyl-2-pyridin-4-yl-1*H*-indol-5-yl)-pyridazin-3(2*H*)-one (10). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 4-propionylpyridine[31] yielded 24% of pure product: mp 334–9 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.44–2.50 (t, 2 H, CH_2), 2.53 (s, 3 H, CH_3), 3.03–3.09 (t, 2 H, CH_2), 7.41–7.44 (1 H, H-7 indole), 7.67–7.72 (1 H, H-6 indole and 2 H, pyridine), 7.95 (1 H, H-4 indole), 8.66–8.68 (2 H, pyridine), 10.73 (1 H, NH), 11.51 (1 H, NH); MS m/e 304 (M^+).

4,5-Dihydro-6-(3-ethyl-2-pyridin-4-yl-1*H*-indol-5-yl)-pyridazin-3(2*H*)-one (11). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 4-butyrylpyridine[31] yielded 65% of pure product: mp 318–21 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.27–1.32 (t, 3 H, CH_3), 2.44–2.50 (t, 2 H, CH_2), 2.95–3.08 (m, 2 x 2 H, CH_2CH_2 and CH_2CH_3), 7.40–7.43 (1 H, H-7 indole), 7.61–7.64 (2 H, pyridine), 7.67–7.70 (1 H, H-6 indole), 7.97 (1 H, H-4 indole), 8.66–8.68 (2 H, pyridine), 10.72 (1 H, NH), 11.47 (1 H, NH); MS m/e 318 (M^+).

4,5-Dihydro-6-(3-isopropyl-2-pyridin-4-yl-1*H*-indol-5-yl)-pyridazin-3(2*H*)-one (12). Starting from 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] and 4-(3-methylbutyryl)-pyridine[31] yielded 41% of pure product: mp 311–3 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.45–1.48 (d, 6 H, 2 CH_3), 2.44–2.50 (t, 2 H, CH_2), 3.01–3.09 (t, 2 H, CH_2), 3.35–3.48 (m, 1 H, CH), 7.40–7.43 (1 H, H-7 indole), 7.53–7.55 (2 H, pyridine), 7.61–7.65 (1 H, H-6 indole), 8.12 (1 H, H-4 indole), 8.68–8.70 (2 H, pyridine), 10.71 (1 H, NH), 11.38 (1 H, NH); MS m/e 332 (M^+).

4,5-Dihydro-5-methyl-6-(3-methyl-2-pyridin-4-yl-1*H*-indol-5-yl)pyridazin-3(2*H*)-one (14). Starting from 6-(4-aminophenyl)-4,5-dihydro-5-methylpyridazin-3(2*H*)-one[25,26] and 4-propionylpyridine[31] yielded 53% of pure product: mp 294–7 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.12–1.15 (d, 3 H, CH_3), 2.23–2.29 (1 H, CH), 2.53 (s, 3 H, CH_3), 2.65–2.75 (1 H, CH), 3.52–3.61 (m, 1 H, C*H*CH_3) 7.40–7.43 (1 H, H-7 indole), 7.66–7.68 (2 H, pyridine), 7.70–7.73 (1 H, H-6 indole), 7.97 (1 H, H-4 indole), 8.65–8.67 (2 H, pyridine), 10.75 (1 H, NH), 11.50 (1 H, NH); MS m/e 318 (M^+).

5-(2-Pyridin-4-yl-1*H*-indol-5-yl)pyrazin-2(1*H*)-one (15). Starting from 5-(4-aminophenyl)pyrazin-2(1*H*)-one[27] and 4-acetylpyridine yielded 30% of pure product: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.20 (1 H, H-3 indole), 7.47–7.50 (1 H, H-7 indole), 7.70–7.73 (1 H, H-6 indole), 7.82–7.84 (2 H, pyridine), 8.03 (1 H, pyrazine), 8.13 (1 H, pyrazine), 8.13–8.14 (1 H, H-4 indole), 8.62–8.63 (2 H, pyridine), 11.79 (1 H, NH), 12.16–12.20 (1 H, NH); MS m/e 288 (M^+).

1,6-Dihydro-2-(2-pyridin-4-yl-1*H*-indol-5-yl)-1,3,4-oxadiazin-5(4*H*)-one (16). Starting from 2-(4-aminophenyl)-1,6-dihydro-1,3,4-oxadiazin-5(4*H*)-one[28] and 4-acetylpyridine yielded 12% of pure product: mp 273–7 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.76 (s, 2 H, CH_2), 7.27 (1 H, H-3 indole), 7.47–7.50 (1 H, H-7 indole), 7.64–7.65 (1 H, H-6 indole), 7.81–7.83 (2 H, pyridine), 8.03–8.04 (1 H, H-4 indole), 8.62–8.64 (2 H, pyridine), 10.88 (1 H, NH), 11.98 (1 H, NH); MS m/e 292 (M^+).

4,4-Dimethyl-5-(2-pyridin-4-yl-1*H*-indol-5-yl)pyrazol-3-(4*H*)-one (17). Starting from 5-(4-aminophenyl)-4,4-dimethylpyrazol-3(4*H*)-one[28] and 4-acetylpyridine yielded 16% of pure product: mp > 300 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.45 (s, 6 H, 2 CH_3), 7.25 (1 H, H-3 indole), 7.42–7.88 (1 H, H-7 indole, 1 H, H-6 indole and 2 H, pyridine), 8.02 (1 H, H-4 indole), 8.62–8.63 (2 H, pyridine), 11.37 (1 H, NH), 11.83 (1 H, NH); MS m/e 304 (M^+).

4-Methyl-5-(2-pyridin-4-yl-1*H*-indol-5-yl)-1,2,4-triazol-3-(4*H*)-one (18). Starting from 5-(4-aminophenyl)-4-methyl-1,2,4-triazol-3(4*H*)-one[28] and 4-acetylpyridine yielded 19% of pure product: mp 380–7 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.28 (s, 3 H, CH_3), 7.29 (1 H, H-3 indole), 7.45–7.49 (1 H, H-6 indole) 7.57–7.59 (1 H, H-7 indole) 7.85–7.87 (2 H, pyridine), 7.92 (1 H, H-4 indole), 8.64–8.67 (2 H, pyridine), 11.70 (1 H, NH), 12.03 (1 H, NH); MS m/e 291 (M^+).

Preparation of 4,5-Dihydro-6-(2-phenyl-1*H*-indol-5-yl)-pyridazin-3(2*H*)-one (6). Method B (a). A 9.45 g (0.05 mol) sample of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] was mixed with 100 mL of 2 N hydrochloric acid and cooled to −2–0 °C and 3.5 g (0.051 mol) of sodium nitrite in 10 mL of water was added dropwise. After 30 min 28 g (0.124 mol) of tin(II) chloride dihydrate in 20.5 mL of concentrated hydrochloric acid was dropped into the solution at the same temperature. After 1 h, the precipitate was isolated by suction at 0 °C and carefully washed with 2 N hydrochloric acid and water to yield 8.7 g (72.2%) of 4,5-dihydro-6-(4-hydrazinophenyl)pyridazin-3(2*H*)-one: mp 243 °C dec (HCl salt); ^{1}H NMR (Me_2SO-d_6) δ 2.39–2.43 (t, 2 H, CH_2), 2.87–2.92 (t, 2 H, CH_2), 7.02–7.05 (2 H, phenyl), 7.64–7.67 (2 H, phenyl), 8.53 (br s, NH), 10.42 (br s, 3 H, NH_3^+), 10.73 (1 H, NH); MS m/e 204 (M^+).

(**b**). A 4.0 g (16.6 mmol) sample of the above product, 2.2 g (18.3 mmol) of acetophenone, 50 mL of ethanol, and 50 mL of water were stirred for 3 h at room temperature. The precipitate was isolated by suction, washed with water, again suspended in water, and adjusted to pH 8. The crystals were isolated and

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recrystallized from ethanol to yield 3.9 g (76.8%) of acetophenone [4-(2,3,4,5-tetrahydro-3-oxo-6-pyridazinyl)phenyl]hydrazone: mp 200–5 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.28 (s, 3 H, CH_3), 2.39–2.43 (t, 2 H, CH_2), 2.87–2.92 (t, 2 H, CH_2), 7.25–7.41 (5 H, phenyl), 7.63–7.66 (2 H, phenyl), 7.78–7.81 (2 H, phenyl), 9.44 (1 H, NH), 10.64 (1 H, NH); MS *m/e* 306 (M^+).

(c). According to method A (b) 3.0 g (10.0 mmol) of the above product was cyclized in polyphosphoric acid to yield 1.3 g (45%) of pure product: mp 270–5 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.45–2.48 (t, 2 H, CH_2), 2.98–3.05 (t, 2 H, CH_2), 6.93 (1 H, H-3 indole), 7.29–7.64 (5 H, phenyl and 1 H, H-7 indole), 7.84–7.87 (1 H, H-6 indole), 7.90 (1 H, H-4 indole), 10.70 (1 H, NH), 11.60 (1 H, NH); MS *m/e* 289 (M^+).

The following compounds were prepared according to method B (b and c).

4-Methoxyacetophenone [4-(2,3,4,5-tetrahydro-3-oxo-6-pyridazinyl)phenyl]hydrazone: yield 74%; mp 183–6 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.24 (s, 3 H, CH_3), 2.39–2.43 (t, 2 H, CH_2), 2.87–2.92 (t, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 6.93–6.96 (2 H, phenyl), 7.12–7.24 (2 H, phenyl), 7.61–7.64 (2 H, phenyl), 7.72–7.75 (2 H, phenyl), 9.42 (1 H, NH), 10.62 (1 H, NH); MS *m/e* 336 (M^+).

4,5-Dihydro-6-[2-(4-methoxyphenyl)-1*H*-indol-5-yl]-pyridazin-3(2*H*)-one (7): yield 45%; mp 262–4 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.40–2.47 (t, 2 H, CH_2), 2.95–3.09 (t, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 6.79 (1 H, H-3 indole), 7.01–7.04 (1 H, H-7 indole), 7.38–7.40 (2 H, phenyl), 7.58–7.60 (2 H, phenyl), 7.77–7.80 (1 H, H-6 indole), 7.86 (1 H, H-4 indole), 10.69 (1 H, NH), 11.55 (1 H, NH); MS *m/e* 319 (M^+).

4-(Methylthio)acetophenone [4-(2,3,4,5-tetrahydro-3-oxo-6-pyridazinyl)phenyl]hydrazone: yield 63%; mp 219–22 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.25 (s, 3 H, CH_3), 2.37–2.43 (t, 2 H, CH_2), 2.49 (s, 3 H, SCH_3), 2.85–2.93 (t, 2 H, CH_2), 7.23–7.25 (2 H, phenyl), 7.26–7.28 (2 H, phenyl), 7.62–7.65 (2 H, phenyl), 7.72–7.75 (2 H, phenyl), 9.44 (1 H, NH), 10.65 (1 H, NH); MS *m/e* 352 (M^+).

4,5-Dihydro-6-[2-[4-(methylthio)phenyl]-1*H*-indol-5-yl]-pyridazin-3(2*H*)-one (8): yield 12%; mp 256–8 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.40–2.47 (t, 2 H, CH_2), 2.52 (s, 3 H, CH_3), 2.98–3.05 (t, 2 H, CH_2), 6.90 (1 H, H-3 indole), 7.33–7.36 (2 H, phenyl), 7.38–7.41 (1 H, H-7 indole), 7.58–7.62 (1 H, H-6 indole), 7.78–7.81 (2 H, phenyl), 7.88 (1 H, H-4 indole), 10.70 (1 H, NH), 11.58 (1 H, NH); MS *m/e* 335 (M^+).

2-Hydroxyacetophenone [4-(2,3,4,5-tetrahydro-3-oxo-6-pyridazinyl)phenyl]hydrazone: yield 51%; mp 232–4 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, CH_3), 2.39–2.43 (t, 2 H, CH_2), 2.87–2.92 (t, 2 H, CH_2), 6.85–6.92 (2 H, phenyl), 7.07–7.10 (2 H, phenyl), 7.19–7.35 (1 H, phenyl), 7.55–7.85 (1 H, phenyl), 7.68–7.71 (2 H, phenyl), 9.68 (1 H, NH), 10.68 (1 H, NH), 12.55 (1 H, OH); MS *m/e* 322 (M^+).

4,5-Dihydro-6-[2-(2-hydroxyphenyl)-1*H*-indol-5-yl]-pyridazin-3(2*H*)-one (9): yield 13%; mp 238–40 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.42–2.48 (t, 2 H, CH_2), 2.98–3.04 (t, 2 H, CH_2), 6.88–6.93 (1 H, phenyl) 7.01–7.04 (1 H, H-3 indole and 1 H, phenyl), 7.12–7.18 (1 H, phenyl), 7.46–7.49 (1 H, H-7 indole), 7.57–7.61 (1 H, H-6 indole), 7.73–7.76 (1 H, phenyl), 7.89 (1 H, H-4 indole), 10.20 (1 H, NH), 10.69 (1 H, NH), 11.23 (1 H, OH); MS *m/e* 305 (M^+).

Preparation of 4,5-Dihydro-6-[2-(ethoxycarbonyl)-1*H*-indol-5-yl]pyridazin-3(2*H*)-one (1). (a). A 4.0 g (0.05 mol) sample of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one[25] was mixed with 5.1 mL of concentrated hydrochloric acid and 25 g of ice, cooled to −2–0 °C and 1.6 g (23.3 mmol) of sodium nitrite in 5 mL of water was added dropwise. After 30 min the mixture was filtered and the filtrate, simultaneously with a solution of 5.1 g of potassium hydroxide in 13 mL of water, was dropped into a mixture of 3.0 g (21 mmol) of ethyl 2-methylacetoacetate and 25 g of ice. After 30 min at 0 °C another 20 g of ice and 3.9 mL of concentrated hydrochloric acid was added, the mixture was filtered, the remaining gum was dissolved in methylene chloride and a little methanol and dried, and the solvent was evaporated. The residue was treated with diethyl ether to yield 4.7 g (74%) of ethyl pyruvate [4-(2,3,4,5-tetrahydro-3-oxo-6-pyridazinyl)-phenyl]hydrazone: mp 227–9 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.25–1.30 (t, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.39–2.44 (t, 2 H, CH_2), 2.87–2.93 (t, 2 H, CH_2), 4.17–4.25 (q, 2 H, OCH_2), 7.25–7.30 (2 H, phenyl), 7.67–7.72 (2 H, phenyl), 10.03 (1 H, NH), 10.82 (1 H, NH); MS *m/e* 302 (M^+).

(b). According to method A (b) 3.02 g (10 mmol) of the above product was cyclized in polyphosphoric acid to yield 0.71 g (25%) of pure product: mp 235–7 °C (diethyl ether); ^{1}H NMR (Me_2SO-d_6) δ 1.33–1.38 (t, 3 H, CH_3), 2.42–2.45 (t, 2 H, CH_2), 2.97–3.03 (t, 2 H, CH_2), 4.32–4.39 (q, 2 H, OCH_2), 7.20 (1 H, H-3 indole), 7.45–7.48 (1 H, H-7 indole), 7.77–7.80 (1 H, H-6 indole), 8.00 (1 H, H-4 indole), 10.75 (1 H, NH), 11.47 (1 H, NH); MS *m/e* 285 (M^+).

Pharmacological Methods. 1. Anesthetized Rat Model. Male SPF Sprague–Dawley rats (350–450 g, Charles River WIGA, 8741 Sulzfeld, FRG) were anesthetized with thiabutabarbital sodium (80–100 mg/kg ip). After tracheotomy and insertion of a cannula to maintain airway potency, a Millar Microtip manometer PR-249 was introduced into the left ventricle via the right carotid artery for recording left ventricular pressure (LVP). Arterial blood pressure (BP) was registered via a polypropylene catheter (PP 50) which had been inserted into the femoral artery and connected to a Statham Transducer P 23 Db. Change in left ventricular pressure was determined by electronic differentiation of pressure signal with a physiodifferentiator. This was regarded as an index of inotropic state.[32] To avoid the influence of changes in afterload on the rate of change of pressure over time (dP/dt), we used dP/dt_{50} (dP/dt at a LVP of 50 mmHg) instead of dP/dt_{max}, which is commonly used. Heart rate (HR) was deduced from the LVP signal by a pulse counter. All parameters were continuously recorded by a universal amplifier 47/Varioscript V 8008. All test doses of compounds 1–18 were injected in a volume of 0.5 mL/kg into the jugular vein as single bolus injection in increasing doses at an interval of 10 min. The hemodynamic parameters were always determined 10 min after application and represent "steady-state effects" and not the maximum change in hemodynamics which occurred about 1–3 min after the bolus injections.

2. Anesthetized Cat Model. Cats of both sexes were anesthetized with pentobarbitone sodium (45 mg/kg ip) and after tracheotomy respirated by a Starling pump with open air (10 mL/kg and 30 strokes/min). Anesthesia was continued by a maintenance infusion of pentobarbitone sodium at a dose of 0.1 mg/kg min. After thoracotomy, LVP and HR were recorded by means of a Millar Tip manometer (PC-350), which had been introduced into the left ventricle via the auricle. BP and dP/dt were recorded as described in rats. The animals received dextran (MW 75 000) at a dose of 10 mL/kg via a jugular vein by an injection of desacetylmetipranolol (0.3 mg/kg iv) to induce cardiovascular failure by β-blockade. The test compounds were intravenously injected at an interval of 10 min in increasing doses. Again the hemodynamic parameters obtained 10 min after the bolus injection were taken as results.

3. Oral Administration to Conscious Dogs. The dogs were instrumented as described before and a Konigsberg manometer was guided into the left ventricle. Each animal received 1 mg/kg **13**, milrinone, or pimobendan by gavage in a suspension of 1% of methylcellulose or an equivalent volume of methylcellulose as placebo for control experiments. LV dP/dt_{60}, heart rate, and blood pressure were recorded for 6.5 h after drug administration. LV dP/dt_{60} was obtained at a LVP of 60 mmHg. During the experiments, the dogs were kept in small cages, permitting only limited movement. In addition, the dogs were largely shielded from environmental effects (noise, moving people, etc.).

(32) Mason, D. T. *Am. J. Cardiol.* **1969**, *23*, 516.