78-39-7; $C_2H_5C(OC_2H_5)_3$, 78-39-7; $ClCOCH_2CO_2C_2H_5$, 36239-09-5; $NH(CH_2)_2OH$, 141-43-5; (±)-$NHCH(C_2H_5)CH_2OH$, 13054-87-0; $NHCH(C_2H_5)CH_2OH$, 5856-62-2; $NHCH(C_2H_5)CH_2OH$, 5856-63-3; (S)$NHCH(i\text{-}C_3H_7)CH_2OH$, 2026-48-4; $NHC(CH_3)_2CH_2OH$, 124-68-5; (±)-$NHCH_2CH(CH_3)OH$, 1674-56-2; (±)-$NHCH_2CH(C_6H_5)OH$, 1936-63-6; aziridine, 151-56-4; 2-methylaziridine, 75-55-8; *N*-(5-cyano-1,3-dimethyl-1*H*-pyrazo-4-yl)propanamide, 111770-09-3; 1,3-Dimethyl-4-nitro-1*H*-pyrazole-5-carboxamide, 78208-58-9; *N*-(5-aminocarbonyl)-1,3-dimethylpyrazol-4-yl) acetamide, 89239-25-8.

Imidazole–Pyridine Bioisosterism: Comparison of the Inotropic Activities of Pyridine- and Imidazole-Substituted 6-Phenyldihydropyridazinone Cardiotonics

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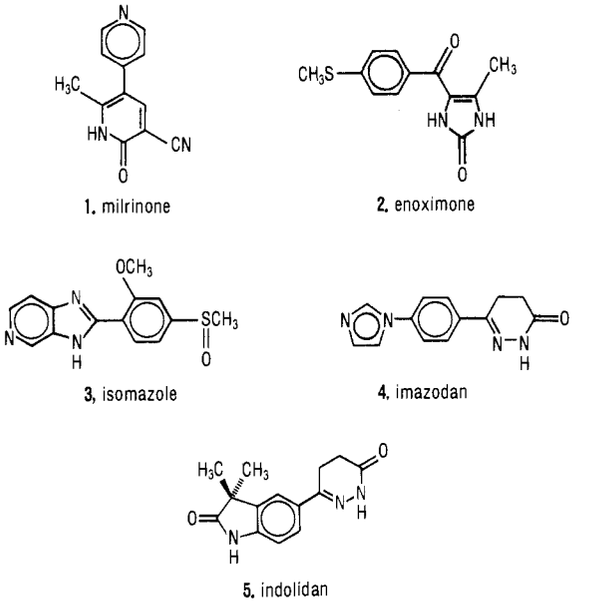
We previously reported the structure–activity relationships (SAR), molecular structure, pharmacology, and molecular pharmacology of indolidan (LY195115), a potent and long-acting dihydropyridazinone cardiotonic. Our 6-phenyldihydropyridazinone SAR studies revealed the critical nature of the substituent at the para position of the phenyl ring. An acetamido substituent provided potent cardiotonic activity and we hypothesized that this may relate to the ability of the acetamide carbonyl to function as a hydrogen-bond acceptor. To further address this question, we prepared **15** (4,5-dihydro-6-[4-(3-pyridinyl)phenyl]-3(2*H*)-pyridazinone), the 3-pyridyl analogue of imazodan. As is the case with imazodan, this (pyridylphenyl)dihydropyridazinone possesses a nitrogen three atoms removed from the phenyl ring, but the molecular framework through which it is attached to the phenyldihydropyridazinone moiety is altered. After iv administration to pentobarbital-anesthetized dogs, inotropic ED_{50} values of **15**, imazodan, and the parent compound, 4,5-dihydro-6-phenyl-3(2*H*)-pyridazinone, were 19.4, 50.1, and 6330 μg/kg, respectively. Thus, **15** is over 2-fold more potent than imazodan and 326-fold more potent than the parent, unsubstituted compound. These data, as well as data obtained with other congeners, are consistent with the hypothesis that a suitably oriented hydrogen-bond-acceptor site contributes to the high degree of inotropic potency observed with these dihydropyridazinone cardiotonics.

During the past decade there has been a resurgence of interest in development of agents for treatment of congestive heart failure (CHF).[1,2] Traditional pharmacological therapy, including digitalis and diuretics, has been supplemented with use of vasodilators to alleviate the excessive vascular tone that characterizes this disease state.[3,4] The long-term benefit of preload and afterload reduction in CHF patients has recently been confirmed with the demonstration that a combination of hydralazine and isosorbide dinitrate resulted in a decrease in mortality.[5] Moreover, the pathophysiological role of the renin–angiotensin cascade in CHF is now well-appreciated, and captopril has been approved for CHF therapy on the basis of its favorable effects on exercise tolerance.[6] Effects of the angiotensin converting enzyme inhibitor enalapril on mortality was recently addressed in a long-term, multicenter clinical trial and the drug prolonged survival in severely ill CHF patients.[7]

Several representatives of a class of cardiotonics that simultaneously express inotropic and vasodilator activities have been studied clinically. These include milrinone, enoximone, imazodan, isomazole, and indolidan (LY195115, Chart I).[8,9] Use of this class of drugs, which

Chart I



appear to exert their pharmacological effects via inhibition of a specific isozyme of phosphodiesterase,[10,11] has resulted in considerable controversy. These compounds have been studied primarily in severely ill CHF patients who are refractory to established therapy, and although they produce hemodynamic and functional improvements, mortality has been high in the small, uncontrolled clinical studies published to date. There is concern that these

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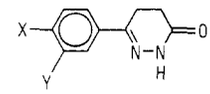
Table I. Physical Properties and Cardiovascular Profiles[a] of Dihydropyridazinone Cardiotonics



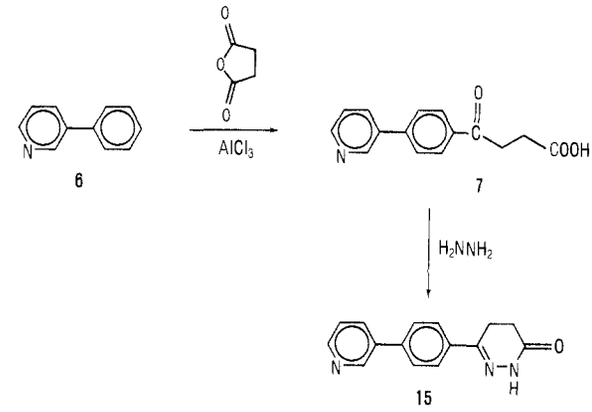
no.	X	Y	formula[b]	mp, °C	recryst solvent	ED_{50} for contractility, μg/kg iv	% increase in HR	% decrease in MAP	*n*
13	H	H	$C_{10}H_{10}N_2O$	150–152[c]	EtOH	6,330 ± 306	39.1 ± 4.0	24.9 ± 3.2	3
14	C_6H_5	H	$C_{16}H_{14}N_2O$	237–238[d]	THF/hex	513 ± 108	18.8 ± 0.7	20.9 ± 3.8	3
15	3-C_5H_4N	H	$C_{15}H_{13}N_3O$	227–228	MeOH	19.4 ± 3.3	7.5 ± 2.7	12.7 ± 3.7	3
16	4-C_5H_4N	H	$C_{15}H_{13}N_3O$	210–211	THF/MeOH/hex	146 ± 36	19.1 ± 3.0	29.9 ± 2.5	3
4	imidazol-1-yl	H	$C_{13}H_{12}N_4O$	213–214[e]	EtOH	50.1 ± 17	16.9 ± 1.5	28.4 ± 4.0	3
17[f]	$NHCOCH_3$	H	$C_{12}H_{13}N_3O_2$			11.3 ± 7.4	8.8 ± 1.5	15.1 ± 2.5	3
18[g]	$NHCOCH_2CH_2$		$C_{13}H_{13}N_3O_2$			3.2 ± 1.0	13.2 ± 2.1	16.1 ± 2.7	4
19[g]	$NHCH_2CH_2CH_2$		$C_{13}H_{15}N_3O$			257 ± 108	37 ± 12	12 ± 4	3

[a] ED_{50} values in anesthetized dogs were determined by linear regression analysis and are reported as the mean ± SEM of experimental values. Heart rate and mean arterial blood pressure values are the percent changes recorded at the inotropic ED_{50} values. Control values were as follows: contractility, 50-g tension; heart rate (HR), 127 ± 3 beats/min; mean arterial blood pressure (MAP), 99 ± 3 mmHg. [b] C, H, N analyses were within 0.4% of theory. [c] Literature mp 153–155 °C (ref 31). [d] Literature mp 241–242 °C (ref 29). [e] Literature mp 206–207 °C (ref 32). [f] Prepared as described in ref 26. [g] Prepared as described in ref 14.

agents may increase the incidence of sudden death and/or hasten progression of the underlying disease state.[12,13] However, this issue will be resolved only by large, well-controlled, double-blind clinical trials, and several such studies are currently in progress.

We previously reported the structure–activity relationships (SAR), molecular structure, pharmacology, and molecular pharmacology of indolidan (Chart I), one of the most potent and long-acting representatives of this class of cardiotonics.[14–18] Our 6-phenyldihydropyridazinone SAR studies revealed the critical nature of the substituent at the para position of the phenyl ring. An acetamido or acetamido-like substituent provided potent cardiotonic activity, and we hypothesized that this may relate to the ability of the acetamide carbonyl to function as a hydrogen-bond acceptor.[14,15] To further address this question, we prepared 4,5-dihydro-6-[4-(3-pyridinyl)phenyl]-3-(2*H*)-pyridazinone (**15**, Scheme I), the 3-pyridyl analogue of imazodan.[19–21] As is the case with imazodan, this (pyridylphenyl)dihydropyridazinone possesses a nitrogen three atoms removed from the phenyl ring, but the molecular framework through which it is attached to the phenyldihydropyridazinone moiety is altered. In this paper we describe the synthesis and inotropic activities of **15** and its congeners.

Scheme I



In addition to testing the role of hydrogen bonding in maximizing potency in this class of cardiotonics, we thought it worthwhile to explore imidazole–pyridine bioisosterism in design of new cardiovascular drugs.[22] Imidazole–pyridine bioisosterism has been previously investigated, particularly in the development of thromboxane synthetase inhibitors.[23–25]

Results and Discussion

Chemistry. The synthesis of the 3-pyridylphenyl analogue **15** was straightforward (Scheme I): Reaction of 3-phenylpyridine with succinic anhydride in the presence of aluminum chloride catalyst furnished the γ-keto acid **7** in low yield (23%). The reaction was slow and inefficient because of complexation of the phenylpyridine by the Lewis-acid catalyst; this deactivated the compound toward electrophilic substitution. Construction of the dihydropyridazinone moiety was completed by hydrazine cyclization of keto acid **7** in refluxing ethanol to afford **15** in 66% yield.

To examine if the beneficial effects of the putative hydrogen-bond-acceptor site were regiospecific, we prepared

(12) Recent evidence suggests that milrinone does not increase the incidence of sudden death: Ludmer, P. L.; Baim, D. S.; Antman, E. M.; Gauthier, D. F.; Rocco, M. B.; Friedman, P. L.; Colucci, W. S. *Am. J. Cardiol.* **1987**, *59*, 1351.
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(15) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824.
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(18) Kauffman, R. F.; Crowe, V. G.; Utterback, B. G.; Robertson, D. W. *Mol. Pharmacol.* **1986**, *30*, 609.
(19) Evans, D. B.; Potoczak, R. E.; Steffen, R. P.; Burmeister, W. E.; McNish, R. W.; Schenden, J. A.; Kaplan, H. R. *Drug. Dev. Res.* **1986**, *9*, 143.
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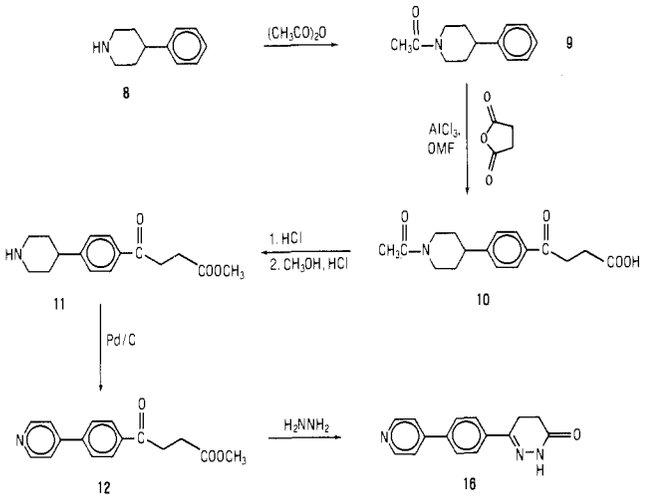
(21) For clinical studies, see: Terris, S.; Bourdillon, P. D. V.; Cheng, D.; Latts, J.; Olsen, S.; Nicklas, J.; Pitt, B. *Am. J. Cardiol.* **1986**, *58*, 596. Jafri, S. M.; Burlew, B. S.; Goldberg, A. D.; Rogers, A.; Goldstein, S. *Am. J. Cardiol.* **1986**, *57*, 254.
(22) For a review, see: Lipinski, C. M. *Annu. Rep. Med. Chem.* **1986**, *21*, 27.
(23) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287.
(24) Johnson, R.; Nidy, E. G.; Aiken, J. W.; Crittenden, N. J.; Gorman, R. R. *J. Med. Chem.* **1986**, *29*, 1461 and references cited therein.
(25) Wright, W. B.; Press, J. B.; Chan, P. S.; Marsico, J. W.; Haug, M. F.; Lucas, J.; Tauber, J.; Tomcufcik, A. S. *J. Med. Chem.* **1986**, *29*, 523.

Scheme II



16, the 4-pyridyl analogue of **15** (Scheme II). A more circuitous route was required for the synthesis of **16** because 4-phenylpyridine was completely unreactive under typical Friedel–Crafts conditions. To enable phenyl ring acylation, the skeleton of the pyridine ring was incorporated into the precursor 4-phenylpiperidine (**8**) in hydrogenated form. The sequence began by N-acylation of **8** with acetic anhydride to form **9**. Friedel–Crafts reaction of this compound with succinic anhydride in the presence of an aluminum chloride–DMF melt as described by Thyes[26] provided keto acid **10** in 53% yield. Hydrolysis of the acetyl protecting group (86%) and esterification with methanol/hydrogen chloride (80%) provided compound **11**; esterification was necessary to enhance solubility of the compound during the subsequent aromatization reaction. Aromatization was performed at this stage because of the anticipated difficulty of aromatizing the piperidine ring without concomitant aromatization of the dihydropyridazinone ring. Reaction of **11** with 5% Pd/C, using the hydrogen acceptor 1,1-diphenylethene as a solvent, provided aromatized product **12** following purification by flash chromatography. Synthesis of **16** was completed by hydrazine cyclization in refluxing ethanol (71%). Physical properties and structures of compounds employed in this study are summarized in Table I.

Pharmacology. We examined inotropic activities of these compounds after intravenous administration to open-chested, pentobarbital-anesthetized dogs; a Walton-Brodie strain-gauge arch was used to monitor right ventricular contractility. ED_{50} values were determined by linear regression analysis, and data are summarized in Table I and Figure 1. We investigated inotropic activity of the parent, unsubstituted compound **13**, 4,5-dihydro-6-phenyl-3(2*H*)-pyridazinone, to determine the actual magnitude of substituent-induced increases in inotropic potency. Despite the fact that this compound is the fundamental structural unit of a number of cardiotonics including indolidan, imazodan, and pimobendan, its inotropic activity has never been published. This compound possessed intrinsic activity, but was impotent (Figure 1); administration of 6.33 mg/kg, iv was required to increase contractility by 50%. Moreover, inotropic effects were relatively nonselective in that heart rate was increased by 39% and blood pressure was decreased by 25% at the inotropic ED_{50} (Table I). The 4-acetamidophenyl compound **17**, which was previously studied by Thyes and co-workers[26] as an inhibitor of platelet aggregation, was an extremely potent inotrope, and the iv ED_{50} was 11.3 μg/kg (Figure 1). Thus, the 4-acetamido moiety produced a remarkable 560-fold increase in potency, and **17** is among the most potent examples of this class of cardiotonics that exert their cardiovascular effects by means of phosphodiesterase inhibition. This substituent also rendered **17** more selective in that only a 9% positive chronotropic response was observed at the inotropic ED_{50} (Table I).

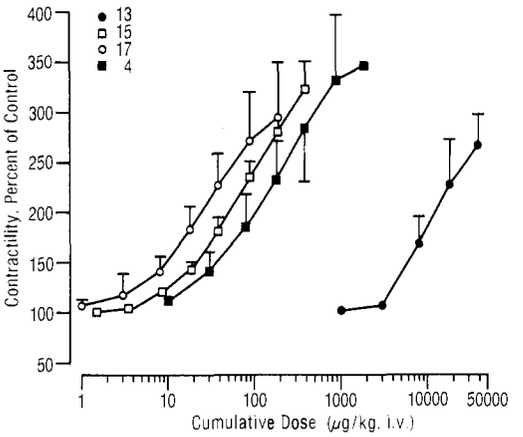


Figure 1. Dose-dependent effects of **13**, **15**, **17**, and imazodan (**4**) on myocardial contractility in pentobarbital-anesthetized dogs. Drugs were administered at 5-min intervals and peak responses recorded. Each drug was studied in a separate group of animals. Each point is the mean ± SEM of experimental values. Symbols without error bars indicate that errors fell within the area of the symbols. Control (base-line) values were as follows: contractility, 50-g tension; heart rate (HR), 127 ± 3 beats/min; mean arterial blood pressure (MAP), 99 ± 3 mmHg.

The precise molecular reasons for this profound substituent-induced increase in potency are difficult to dissect experimentally. The σ_P of the acetamido substituent is 0.00; hence electronic effects of the acetamido substituent are not responsible for the dramatic effects on inotropic potency. Although steric effects (MR = 14.93) or effects on lipophilicity (π = −0.97) may be important, they do not represent complete explanations since other sterically demanding, hydrophilic substituents such as methylsulfonyl did not increase inotropic potency to the extent observed with the acetamido substituent.[27] One notable feature of the acetamido substituent is the presence of the hydrogen-bond-acceptor site three atoms removed from the phenyl moiety in the form of the carbonyl oxygen. We have previously demonstrated the importance of the carbonyl group in structurally related inotropes.[14] ED_{50} values for the analogues **18** and **19** were 3.2 and 257 μg/kg, respectively (Table I). The potent dihydropyridazinone cardiotonic imazodan also possesses a similarly positioned hydrogen-bond-acceptor group in the form of N-3 of the imidazole moiety (Chart I).

To further probe the hydrogen-bond hypothesis, we synthesized the 3-pyridylphenyl compound **15** (Scheme I and Table I). This agent retains the suitably oriented hydrogen-bond-acceptor site of imazodan and **17**, but dramatically alters the molecular framework through which this moiety is tethered to the phenyldihydropyridazinone.

The 3-pyridylphenyl compound proved to be a potent inotrope, with an ED_{50} of 19.4 μg/kg, iv (Table I and Figure 1). With this drug, increases in contractility were rapid in onset, maximal in less than 1 min, and associated with only modest tachycardia. The compound decreased mean

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(27) Robertson, D. W.; Hayes, J. S., unpublished observations.

arterial blood pressure by 12.7% at its inotropic ED_{50}, an expression of the vasodilator activities that characterize this class of cardiotonics.[28] After administration of 0.5 mg/kg of **15**, contractility was increased to more than 300% of control values (Figure 1); 60 min postadministration contractility was still at 200% of control values (data not shown), suggesting that inotropic effects of the drug are long-lived. Imazodan was studied for comparative purposes, and its ED_{50} was 50.1 μg/kg (Figure 1), revealing that the pyridine-derived compound was approximately 2-fold more potent than the imidazole-containing drug. Compound **15** tended to have less pronounced effects on heart rate and blood pressure than imazodan (Table I). Thus, in 6-(phenyl)dihydropyridazinone cardiotonics, an imidazole or 3-pyridyl moiety at the 4-position of the phenyl ring are bioisosteric, but these two groups produce subtle differences in potency and profile.

The deaza analogue of **15**, biphenylyldihydropyridazinone **14** (Table I), was synthesized as described by Child and co-workers[29] and examined for inotropic activity to determine whether beneficial effects of the pyridine or imidazole rings were due simply to the presence of an aromatic nucleus at the 4-position of the phenyl ring regardless of whether a hydrogen-bond-acceptor site was present. Although **14** was more potent than the parent structure **13** (ED_{50} values = 0.51 and 6.33 mg/kg, respectively), **14** was 26-fold less potent than the pyridine analogue **15**, demonstrating the crucial nature of the pyridine ring nitrogen in maximizing inotropic potency. The regiospecificity of this 26-fold nitrogen-induced potency increase was explored with the 4-pyridylphenyl analogue **16** (Table I). The ED_{50} of **16** was 146 μg/kg after iv administration to pentobarbital-anesthetized dogs; although this agent was more potent than biphenylyldihydropyridazinone **14**, it was 7.5-fold less potent than the 3-pyridyl isomer. Thus, the presence *and* orientation of this nitrogen appear to be critical determinants of inotropic potency in this series of dihydropyridazinone cardiotonics.

Conclusions

These SAR data are consistent with the hypothesis that a hydrogen-bond-acceptor site three atoms removed from the phenyl moiety in these dihydropyridazinone cardiotonics contributes to the high degree of inotropic potency observed with **15**, indolidan, imazodan, and **17**. The acetamido substituent of **17** was found to increase inotropic potency by over 2 orders of magnitude. Although the 3-pyridyl, imidazole, and acetamido substituents may share other properties that contribute to their beneficial effects on dihydropyridazinone inotropic potency, one thread of physicochemical commonality is the presence of the hydrogen-bond-acceptor site. Moreover, the significantly decreased inotropic potency of **16** suggests that the beneficial effect of the hydrogen-bond-acceptor site on inotropic potency is regiospecific.

Another interesting aspect of this work is the demonstration that the imidazole and pyridine rings are virtually indistinguishable in this series of cardiovascular drugs. This is despite their differences in physicochemical characteristics such as size and basicity and the means by which these aromatic nuclei are tethered to the phenyldihydropyridazinone moieties. These data add to the examples of imidazole–pyridine bioisosterism that have been previously described.[23-25]

Experimental Section

Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Proton magnetic resonance (^1H NMR) spectra were obtained with a Bruker WM-270 spectrometer. Mass spectra were recorded from a Varian MAT CH-5 spectrometer. Microanalytical data were provided by the Physical Chemistry Department of the Lilly Research Laboratories; only symbols of elements analyzed are given, and they were within 0.4% of theoretical values unless indicated otherwise.

Except where noted, a standard procedure was used for product isolation. This involved quenching by addition to water, filtration, or exhaustive extraction with a solvent (washing of extract with aqueous solutions, on occasion), drying over an anhydrous salt, and evaporation of solvent under reduced pressure. Particular solvents, aqueous washes (if needed), and drying agents are mentioned in parentheses after the phrase "product isolation".

Literature methods were used to prepare compound **14** (6-[1,1'-biphenyl]-4-yl-4,5-dihydro-3(2*H*)-pyridazinone)[29] and imazodan (4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinone).[30] Compound **13** (4,5-dihydro-6-phenyl-3(2*H*)-pyridazinone) was prepared from 3-benzoylpropionic acid following the procedures described below, and the physical properties were as previously described.[31]

4-Oxo-4-[4-(3-pyridyl)phenyl]butanoic Acid (7). Aluminum chloride (13.8 g, 103 mmol) was added in portions to a solution of 3-phenylpyridine (5.0 g, 32 mmol) and succinic anhydride (3.55 g, 35 mmol) in 100 mL of 1,1,2,2-tetrachloroethane. The solution was heated to 60 °C overnight and then poured onto a mixture of ice and concentrated hydrochloric acid. The mixture was adjusted to a pH of 5–6 with 50% sodium hydroxide, which resulted in an inorganic precipitate that was filtered and discarded. The filtrate was extracted with ethyl acetate. Product isolation (brine, Na_2SO_4) and flash chromatography (silica gel, 0–5% methanol in methylene chloride gradient) provided 1.9 g (23%) of homogeneous keto acid **7**. The analytical sample was prepared by recrystallization from DMF/water: mp 225–228 °C. Anal. ($C_{15}H_{13}NO_3$) C, H, N.

4,5-Dihydro-6-[4-(3-pyridinyl)phenyl]-3(2*H*)-pyridazinone (15). Hydrazine hydrate (85%, 860 μL, 15 mmol) was added in one portion to a suspension of the keto acid **7** (1.69 g, 7 mmol) in 250 mL of absolute ethanol, and the reaction was refluxed for 12 h. The mixture was cooled to 0 °C and the resulting precipitate was filtered and recrystallized from DMF/water to provide 1.1 g (66.3%) of homogeneous **15** as a light yellow solid. The analytical sample was prepared by an additional recrystallization of a small portion from methanol: mp 227–228 °C. Anal. ($C_{15}H_{13}N_3O$) C, H. N.

1-Acetyl-4-phenylpiperidine (9). Acetic anhydride (38.1 mL, 406 mmol) was added dropwise to a solution of 4-phenylpiperidine (43.7 g, 271 mmol) in 200 mL of dry THF. After a portion of the acetic anhydride was added, a precipitate formed in this highly exothermic reaction. Sufficient DMF was added to achieve homogeneity and the reaction was cooled to 0 °C, whereupon the remaining acetic anhydride was added dropwise. After the reaction mixture was stirred overnight, product isolation (water, ethyl acetate, water, brine, Na_2SO_4) provided 57 g of homogeneous **9** as an amber oil that was used without further purification: mass spectrum (70 eV), *m/e* (relative intensity) 203 (74, M^+), 57 (100).

4-[4-(1-Acetyl-4-piperidinyl)phenyl]-4-oxobutanoic Acid (10). Dimethylformamide (43.3 mL, 551 mmol) was added dropwise to anhydrous aluminum chloride (262 g, 1.97 mol) and the exothermic reaction was then allowed to cool to 70 °C. A mixture of succinic anydride (19.7 g, 197 mmol) and **9** (40.0 g, 197 mmol) was slowly added to the aluminum chloride/dimethylformamide melt, and the reaction was maintained at 70 °C for 1 h. The reaction mixture was carefully poured onto a mixture of ice and concentrated hydrochloric acid. The resulting precipitate was filtered and recrystallized from DMF/water to afford 31.66 g (53%) of homogeneous **10** as a light-yellow powder:

(28) Kauffman, R. F.; Schenck, K. W.; Utterback, B. G.; Crowe, V. G.; Cohen, M. L. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 864.
(29) Child, R. G.; Osterberg, A. C.; Sloboda, A. E.; Tomcufcik, A. S. *J. Pharm. Sci.* **1977**, *66*, 466.
(30) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(31) Reichfelt, I.; Reissig, H.-U. *Synthesis* **1984**, 786.
(32) Sircar, I.; Bristol, J. A. U.S. Patent 4353905, Oct 12, 1982.

mp 204–205 °C. Anal. ($C_{17}H_{20}NO_4$) C, H, N.

4-[4-(4-Piperidinyl)phenyl]-4-oxobutanoic Acid Hydrochloride. A suspension of **10** (23.64 g, 78 mmol) in 200 mL of 6 N hydrochloric acid was refluxed overnight. The reaction was diluted with 500 mL of water and cooled to 0 °C. The resulting precipitate was filtered and dried to provide 17.52 g (86%) of homogeneous deacetylated product with mp 229–230 °C. Anal. ($C_{15}H_{19}NO_3$·HCl) C, H, N.

4-[4-(4-Piperidinyl)phenyl]-4-oxobutanoic Acid Methyl Ester Hydrochloride (11). 4-[4-(4-Piperidinyl)phenyl]-4-oxobutanoic acid hydrochloride (19.84 g, 66.7 mmol) was dissolved in 500 mL of methanol that had been saturated with hydrogen chloride, and the reaction mixture was stirred overnight at room temperature. A precipitate formed and was filtered to provide 16.5 g (80%) of the methyl ester **11** with mp 211–212 °C. Anal. ($C_{16}H_{21}NO_3$·HCl) C, H, N.

4-Oxo-4-[4-(4-pyridyl)phenyl]butanoic Acid Methyl Ester (12). A suspension of the free base of **11** (9.3 g, 33.8 mmol) and 5% Pd/C (9.3 g) in 100 g of 1,1-diphenylethylene was heated at 250 °C for 2 h, cooled to room temperature, and diluted with ethyl acetate. The mixture was filtered through Celite to remove catalyst, and the filtrate was washed with 500 mL of 1 N hydrochloric acid. The acid extract was basified with 5 N sodium hydroxide and then extracted with ethyl acetate. Product isolation (water, brine, Na_2SO_4) and flash chromatography (silica gel, 0–1% methanol in methylene chloride gradient) provided 2.1 g (23%) of **12** as a light-yellow solid. The analytical sample was prepared by recrystallization from acetone/hexane: mp 137–138 °C. Anal. ($C_{16}H_{15}NO_3$) C, H, N.

4,5-Dihydro-6-[4-(4-pyridinyl)phenyl]-3(2*H*)-pyridazinone (16). A mixture of keto ester **12** (1.25 g, 4.6 mmol) and hydrazine hydrate (85%, 602 μL, 10.2mmol) in 50 mL of absolute ethanol was refluxed overnight. Removal of solvent under reduced pressure, flash chromatography (silica gel, 0–5% methanol in methylene chloride gradient), and recrystallization from THF/methanol/hexanes provided 830 mg (71%) of homogeneous **16** as a light-yellow solid with mp 210–211 °C. Anal. ($C_{15}H_{13}N_3O$) C, H, N.

Pharmacological Methods. Experiments in Anesthetized Dogs. Mongrel dogs of either sex (7–14 kg) were anesthetized with sodium pentobarbital (35 mg/kg, iv). A positive-pressure pump was used to ventilate the dogs through an endotracheal tube (18 strokes/min, 20 mL/kg per stroke), and a heating pad was used to maintain body temperature at 37–38 °C. Femoral arterial blood pressure was measured through a polyethylene catheter filled with heparin solution (16 units/mL) and connected to a Statham pressure transducer. The femoral vein was cannulated for iv drug administration. Heart rate was derived by means of a cardiotachometer that was triggered by the arterial pressure pulse. A Walton-Brodie strain-gauge arch sutured to the right ventricle of the heart was used to measure cardiac contractility. Tension on the gauge was adjusted to 50 g, which corresponded to 10 mm of recorder pen deflection. Rapid iv injection of 50 mL of 5% dextran and mechanical compression of the aorta demonstrated that contractility measurements were independent of changes in preload and afterload. Subcutaneous pin electrodes provided a lead II ECG. Increasing log doses of test compounds were administered iv in volumes of 0.25–4.0 mL at 5-min intervals; no responses occurred with appropriate vehicle injections. ED_{50} values were determined by linear regression analysis and are reported as the mean ± SEM of experimental values. Each drug was studied in a separate group of animals.

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