Articles

7-Heteroaryl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one Derivatives with Cardiac Stimulant Activity

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A series of 7-heteroaryl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-ones was synthesized and evaluated in dogs for cardiac stimulant activity. Compounds were obtained by a palladium-catalyzed cross-coupling reaction between a heteroarylzinc chloride and a 7-iodo-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one or by cyclization of an *N*-[(2-aminophenyl)methyl]glycinate with cyanogen bromide. Compared to the parent ring system (**3**), introduction of a 2,6-dimethylpyridin-3-yl (**6**), 2,4-dimethylimidazol-1-yl (**7**), or 1,2,4-triazol-1-yl (**8**) moiety at the 7-position led to a 13–17-fold increase in positive inotropic activity (percentage increase in dP/dt_{max}) in anesthetized dogs. Potency could be further enhanced with a 9-methyl substituent (**10–12**). The most potent member of the series, 7-(2,4-dimethylimidazol-1-yl)-9-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one (**11**) (23% increase in dP/dt_{max}, 2 μg/kg), was 80 times more active than **3** and displayed a 5-fold advantage over milrinone. In conscious dogs, **6** elicited marked and sustained positive inotropic activity (decrease in QA interval) after oral administration (1 mg/kg), whereas **10–12** were 10 times more potent. **11** produced an obvious increase in cardiac contractility (20% increase in dP/dt_{max}) at low dose levels (25 μg/kg) while, after 100 μg/kg, the marked response (50% increase in dP/dt_{max}) was maintained for the whole 7-h test period. In these experiments, **11** had no effect on heart rate, and the compound also displayed exceptional selectivity for increasing the force rather than the rate of cardiac contraction (>150% increase in dP/dt_{max}) in the Starling heart–lung preparation. These studies demonstrate that the tetrahydroimidazoquinazolinone nucleus is an effective bioisostere for the 2(1*H*)-quinolinone system and that **11** displays improved cardiac stimulant activity and duration of action when compared to milrinone.

Previous reports from these laboratories have described the synthesis and inodilator properties of various 6-heteroaryl-8-methyl-2(1*H*)-quinolinone derivatives.[1-3] Many of these compounds proved to be more potent inotropic agents than milrinone, and they also displayed prolonged cardiac stimulant activity after oral administration to conscious dogs. Moreover, this novel 2(1*H*)-quinolinone series had barely any effect on heart rate, either in conscious animals or in a Starling heart–lung preparation. As a result of this favorable hemodynamic profile, UK-61,260 (**1a**) and UK-66,838 (**1b**) were selected for preclinical development studies, and the former agent is currently undergoing phase II evaluation in congestive heart failure.

Structure–activity relationships (SARs) in these 2-(1*H*)-quinolinone series[1-3] demonstrated that an appropriate 6-heteroaryl function had a beneficial effect on inotropic activity, and that potency and duration of action could be further improved by incorporation of an additional 8-methyl substituent. As part of a general program to identify novel structures with cardiac stimulant activity, several isosteric replacements for the 2(1*H*)-quinolinone ring system have been examined to determine whether similar SARs can be expressed in alternative heterocyclic systems.

This paper describes a new series of 7-heteroaryl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one derivatives (**2**)[4] (Chart I) which demonstrate marked improvement (20–80-fold) in inotropic activity over the parent ring system (**3**)[5a] and over quazinone (Ro 13-6438, **4**),[6,7] which has undergone clinical evaluation.[8] More recently, cardiac stimulant activity has been reported for RS-82856[9] (**5**), a cilostamide–anagrelide hybrid,[10,11] but comparative data are not presented in this paper.

Chemistry. Table I lists the novel 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-ones (**6–15**) which were evaluated for cardiac stimulant activity, and synthetic routes A–C are summarized in Scheme I. In route A, **6**, **9**, and **10** were obtained by a palladium-catalyzed cross-coupling reaction[12] between (2,6-dimethylpyridin-3-yl)zinc chloride and a 7-iodo-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2(1*H*)-one (**16–18**). In route B, treatment of the *N*-(phenylmethyl)glycinates (**25**, **26**, and **28**) with cyanogen bromide in ethanol under reflux provided **7**, **8**

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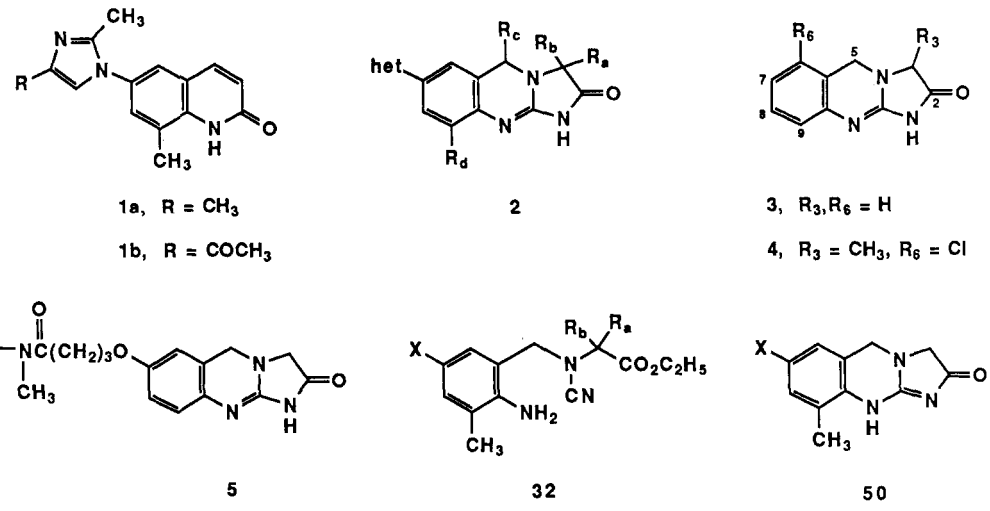
Chart I

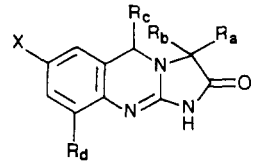


1a, R = CH_3 2 3, R_3,R_6 = H

1b, R = $COCH_3$ 4, R_3 = CH_3, R_6 = Cl

5 32 50

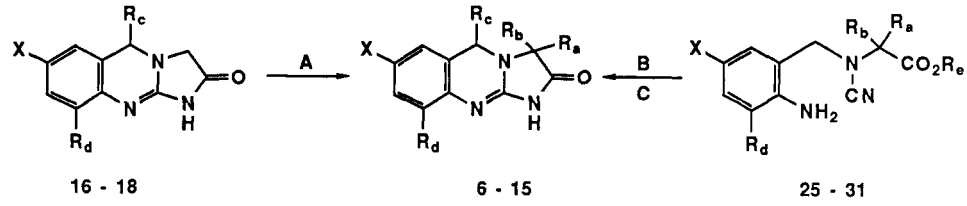
Table I. Synthetic Routes and Physicochemical Data for 1,2,3,5-Tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one Derivatives



no.	X	R_a	R_b	R_c	R_d	route	mp, °C	formula	anal.
6	2,6-dimethylpyridin-3-yl	H	H	H	H	A	330–332	$C_{17}H_{16}N_4O·0.5H_2O$	C, H, N
7	2,4-dimethylimidazol-1-yl	H	H	H	H	B	324–328	$C_{15}H_{15}N_5O·1.75H_2O$	C, H,[a] N
8	1,2,4-triazol-1-yl	H	H	H	H	B	>340	$C_{12}H_{10}N_6O·0.5H_2O$	C, H, N
9	2,6-dimethylpyridin-3-yl	H	H	CH_3	H	A	314–316	$C_{18}H_{18}N_4O·0.3H_2O$	C, H, N
10	2,6-dimethylpyridin-3-yl	H	H	H	CH_3	A	253–256	$C_{18}H_{18}N_4O$	C, H, N
11	2,4-dimethylimidazol-1-yl	H	H	H	CH_3	C	310–312	$C_{16}H_{17}N_5O$	C, H, N
12	1,2,4-triazol-1-yl	H	H	H	CH_3	B	318–320	$C_{13}H_{12}N_6O$	C, H, N
13	1,2,4-triazol-4-yl	H	H	H	CH_3	C	>360	$C_{13}H_{12}N_6O$	C, H, N[b]
14	2,4-dimethylimidazol-1-yl	CH_3	H	H	CH_3	C	263–266	$C_{17}H_{19}N_5O·0.5H_2O$	C, H, N
15	2,4-dimethylimidazol-1-yl	CH_3	CH_3	H	CH_3	C	230–233	$C_{18}H_{21}N_5O·H_2O$	C, H, N
16	I	H	H	H	H	B	323–324	$C_{10}H_8IN_3O$	C, H, N
17	I	H	H	CH_3	H	B	289–290	$C_{11}H_{10}IN_3O$	C, H, N
18	I	H	H	H	CH_3	B	280	$C_{11}H_{10}IN_3O$	C, H, N

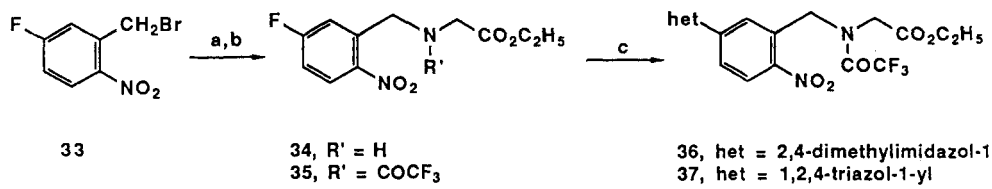
[a] H: calcd, 6.0; found, 5.0. [b] N: calcd, 29.4; found, 28.9.

Scheme I



16 - 18 6 - 15 25 - 31

Scheme II[a]



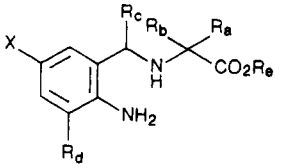
33 34, R' = H; 35, R' = $COCF_3$ 36, het = 2,4-dimethylimidazol-1-yl; 37, het = 1,2,4-triazol-1-yl

[a] Reagents: (a) $NH_2CH_2CO_2C_2H_5$, (b) $(CF_3CO)_2O$, (c) heterocycle/Na_2CO_3/DMF.

and **12** directly.[5b] Alternatively, the reaction of **27** and **29–31** with cyanogen bromide could be carried out at room temperature, the *N*-cyano intermediates (**32**) could be isolated[13] and then cyclized under reflux in an alcoholic solvent to give **11**, and **13–15** (route C). In the case of **11**, ring closure could be effected in ethanol (24 h), whereas butanol (30 h) was required for the more sterically hindered **15**. The iodo derivatives (**16–18**) required for route A were obtained by treatment of the *N*-(phenylmethyl)-glycinates (**19–21**) with iodine monochloride in acetic acid, followed by cyclization of **22–24** with cyanogen bromide (Table II).

(13) For the preparation of **11**, the structure of intermediate **32** (X = 2,4-dimethylimidazol-1-yl, R_a, R_b = H) was confirmed by spectroscopy.

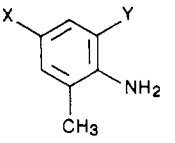
Table II. Physicochemical Data for *N*-[(2-Aminophenyl)methyl]glycinate Derivatives



no.	R_a	R_b	R_c	R_d	R_e	X	mp, °C
19[5a]	H	H	H	H	CH_2CH_3	H	oil
20[5c]	H	H	CH_3	H	CH_2CH_3	H	oil
21[26]	H	H	H	CH_3	CH_2CH_3	H	oil
22	H	H	H	H	CH_2CH_3	I	58–61
23	H	H	CH_3	H	CH_2CH_3	I	oil
24	H	H	H	CH_3	CH_2CH_3	I	64–67
25	H	H	H	H	CH_3	2,4-dimethylimidazol-1-yl	oil
26	H	H	H	H	CH_3	1,2,4-triazol-1-yl	oil
27	H	H	H	CH_3	CH_2CH_3	2,4-dimethylimidazol-1-yl	oil
28	H	H	H	CH_3	CH_2CH_3	1,2,4-triazol-1-yl	oil
29	H	H	H	CH_3	CH_2CH_3	1,2,4-triazol-4-yl	oil
30	H	CH_3	H	CH_3	CH_2CH_3	2,4-dimethylimidazol-1-yl	oil
31	CH_3	CH_3	H	CH_3	CH_3	2,4-dimethylimidazol-1-yl	oil

[a] Compounds **19–21** and **25–31** were characterized spectroscopically.

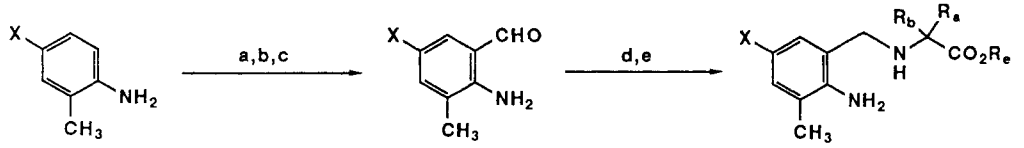
Table III. Physicochemical Data for 4-Heteroaryl-2-methylaniline Derivatives



no.	X	Y	mp, °C	formula	anal.
38[2]	2,4-dimethylimidazol-1-yl	H	118–120	$C_{12}H_{15}N_3$	C,[a] H, N
39[2]	1,2,4-triazol-1-yl	H	122–125	$C_9H_{10}N_4$	C, H, N
40[2]	1,2,4-triazol-4-yl	H	152–154	$C_9H_{10}N_4$	C, H, N
41[2]	2,4-dimethylimidazol-1-yl	Br	176–181	$C_{12}H_{14}BrN_3 \cdot 0.5H_2O$	C, H, N
42	1,2,4-triazol-1-yl	I	151–154	$C_9H_9IN_4$	C,[b] H, N
43	1,2,4-triazol-4-yl	I	211–214	$C_9H_9IN_4$	C, H, N
44[2]	2,4-dimethylimidazol-1-yl	CN	214–217	$C_{13}H_{14}N_4$	C,[c] H, N
45	1,2,4-triazol-1-yl	CN	231–233	$C_{10}H_9N_5$	C,[d] H, N
46	1,2,4-triazol-4-yl	CN	283–286	$C_{10}H_9N_5 \cdot 0.25H_2O$	C, H, N
47[2]	2,4-dimethylimidazol-1-yl	CHO	203–207	$C_{13}H_{15}N_3O \cdot 0.5H_2O$	C, H, N[e]
48[f]	1,2,4-triazol-1-yl	CHO	209–211	$C_{10}H_{10}N_4O$	
49	1,2,4-triazol-4-yl	CHO	250–252	$C_{10}H_{10}N_4O$	C, H, N

[a] C: calcd, 71.6; found, 71.0. [b] C: calcd, 36.0; found, 36.6. [c] C: calcd, 69.0; found, 68.3. [d] C: calcd, 60.3; found, 59.8. [e] N: calcd, 17.6; found, 18.2. [f] Obtained as a mixture with the intermediate imine and characterized spectroscopically.

Scheme III[a]



38 - 40 47 - 49 27 -31

[a] Reagents: (a) Br_2 or ICl, (b) CuCN or NaCN, (c) $[(CH_3)_2CHCH_2]_2AlH$, (d) $NH_2C(R_aR_b)CO_2Re$, (e) H_2/Pd or $NaBH_3CN$.

Preparation of the *N*-(phenylmethyl)glycinates (**25–31**) used in routes B and C is outlined in Schemes II and III. N-Alkylation of ethyl glycinate with **33** followed by acylation with trifluoroacetic anhydride gave **35**, which underwent regioselective nucleophilic aromatic substitution reactions[2,3] with 2,4-dimethylimidazole[14] and 1,2,4-triazole[15] to provide **36** and **37**. (See Scheme II; direct reaction between **34** and a nitrogen heterocycle was not successful.) Hydrogenation of the nitro group of **36** and **37** over Raney nickel followed by deprotection of the glycine function with sodium carbonate in methanol then afforded **25** and **26**, albeit with concomitant ester exchange.

The preparation of *N*-[(2-amino-5-heteroaryl-3-methylphenyl)methyl]glycinates **27–31** is described in Scheme III. The previously reported anilines[2] (**38–40**) were halogenated with bromine or iodine monochloride to give **41–43**, and further reaction with cuprous cyanide in 1-methyl-2-pyrrolidinone or with sodium cyanide on alumina[16] in toluene gave **44–46** (Table III). Reduction of the nitrile function with diisobutylaluminum hydride provided **47–49**, which were condensed with an appropriate

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Table IV. Inotropic Activity for Tetrahydroimidazoquinazolinone Derivatives following Intravenous and Oral Administration to Dogs

no.	% increase in dP/dt_{max}[a]	dose, μg/kg, iv	rel inotropic potency[b]	decrease in the QA interval, ms ± SEM[c] 1 h	3 h	dose, mg/kg, po
3	24	250	0.1			
4	66	250	0.3			
6	29	50	1.3	14 ± 1	15 ± 1	1.0
7	30	20	1.9	6 ± 2	10 ± 1	1.0
8	63	50	1.7			
9	50	50	1.6	13 ± 1	9 ± 1	0.125
10	30	10	2.7	15 ± 1	15 ± 2	0.125
11	23	2	7.8	5 ± 1	15 ± 1	0.1
12	76	50	3.2	8 ± 3	12 ± 1	0.125
13	24	50	0.5			
14	12	10	0.9	9 ± 2	15 ± 2	1.0
15	20	250	0.1			
milrinone	46	25	1.6	13 ± 4	7 ± 3	0.25
CI-930	100	50	1.6	-	-	-

[a] Anesthetized dog. [b] Compared to the percentage increase in dP/dt_{max} observed with 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline (50 μg/kg) in the same dog (see the Experimental Section). [c] Conscious dog (n = 4).

amino acid ester then reduced to give the *N*-(phenylmethyl)glycinates (**27–31**). Imine formation was generally carried out in toluene under Dean–Stark conditions (**27** and **29–31**), but molecular sieves in chloroform could also be used (**28**). Reduction of the imine intermediates by catalytic hydrogenation was preferred (**27**, **28**, **30**, and **31**), since sodium cyanoborohydride gave only a moderate yield when used for **29**.

SARs for Inotropic Activity. The tetrahydroimidazoquinazolinone derivatives in Table I were administered intravenously to instrumented, anesthetized dogs in order to measure positive inotropic activity (Table IV). Results are expressed as absolute percentage increases in dP/dt_{max} and also as inotropic potencies relative to the response observed with 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline in the same animals. This protocol compensates for interanimal variation and allows accurate SAR comparisons against standard agents such as milrinone and CI-930.

The results in Table IV show that the simple tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one derivatives (**3** and **4**) display relatively weak inotropic activity, but this can be markedly improved by introduction of a 7-heteroaryl substituent (**6–8**). Indeed, **7** is some 20 times more potent than **3** and shows similar inotropic activity to milrinone and CI-930. Activity within this range was maintained with the introduction of a 5-methyl group (**9**), whereas a 9-methyl substituent proved to be much more beneficial (**10** and **11**). Compound **11** is approximately 80 times more potent than **3**; it displays a 5-fold potency advantage over milrinone and is equiactive with **1a**.[2] Finally, introduction of a 3-methyl substituent into **11** reduced inotropic activity some 9-fold (**14**) which is in contrast to **4**, where a similar modification was acceptable.[17,18]

These results show that introduction of a 7-heteroaryl function into the tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one system leads to a marked increase in inotropic activity and that potency can be further enhanced by a 9-methyl substituent. The similarity in SARs between series **2** and previously reported 2(1*H*)-quinolinone derivatives[1-3] is striking and suggests that these ring systems are effective bioisosteres for each other. Superimposition

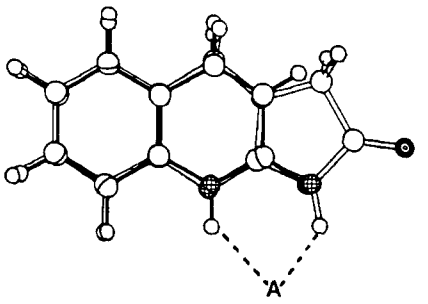

Figure 1. Superimposition of tetrahydroimidazo[2,1-*b*]-quinazolin-2(1*H*)-one and quinolin-2(1*H*)-one nuclei, and potential hydrogen-bond formation with a common acceptor site (A).

of the tetrahydroimidazoquinazolinone and quinolinone nuclei shows that, while the phenyl rings are obviously equivalent, the 1-H atoms are some 2.6 Å apart. (Figure 1). Even so, interaction with a common acceptor site (A) located approximately 2 Å from each hydrogen atom should be quite feasible, since effective hydrogen bonds need not be linear.[19] Moreover, the pK_as of the amidic functions in **3** and **1a**[2] are 10.9 ± 0.15 and 11.2 ± 0.2, respectively, and their abilities to act as hydrogen-bond donors should be roughly equivalent. Alternatively, formation of tautomer **50** may also be feasible under physiological conditions, and equivalence with the 2(1*H*)-quinolinone system would be more apparent.

Most of the compounds in Table IV were also tested in conscious dogs to determine effects on cardiac contractility (decrease in the QA interval) after oral dosing. Compound **6** elicited marked and sustained positive inotropic activity, although substantial improvements in potency were observed with **9–12**. Moreover, for all of the novel tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-ones in Table IV (except **9**), maximum increases in cardiac contractility were observed after 3 h, confirming that long duration of action is characteristic of the series. Unexpectedly, the changes in contractility observed with **6** and **10** were accompanied by a tachycardia (30–50 beats/min), although no increase in heart rate was observed with **11**, despite a similar substantial inotropic response. More detailed evaluation of **11** in conscious dogs (Figure 2) showed that a dose level as low as 25 μg/kg produced an obvious increase in cardiac contractility (approximately 20% increase in dP/dt_{max})

(17) Kienzle, F.; Kaiser, A.; Chodnekar, M. S. *Eur. J. Med. Chem.* **1982**, *17*, 547.
(18) Only antiplatelet data are reported,[17] but inotropic activity is also claimed.
(19) Baker, E. N., Hubbard, R. E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, 97.

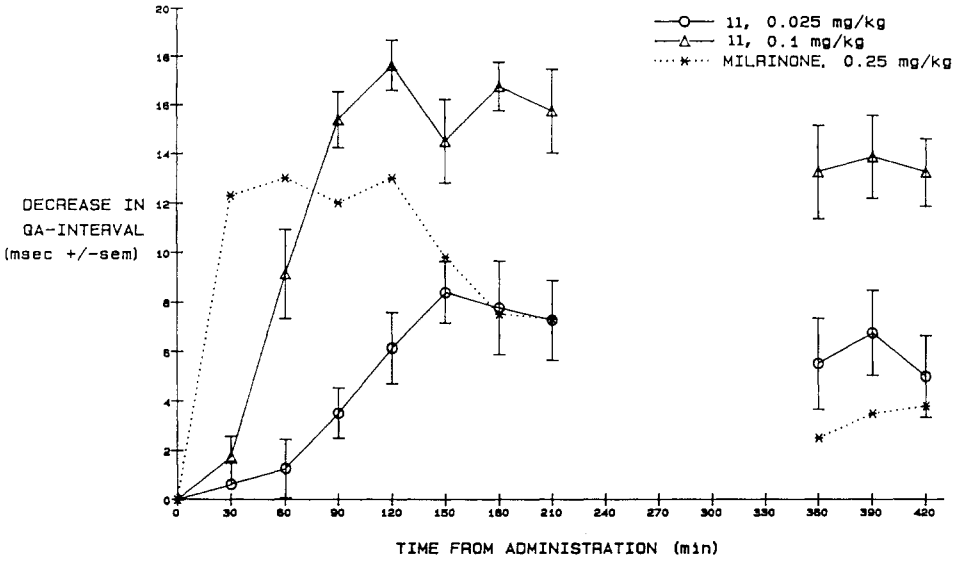

Figure 2. Effects of 11 (n = 8) and milrinone (n = 4) on the QA interval in conscious dogs following oral administration.

while after 100 μg/kg a marked response (approximately 50% increase in dP/dt_{max}) was maintained throughout the whole 7-h test period. These experiments clearly demonstrate improved oral potency and duration of action for **11** when compared to milrinone.

In order to clarify the different effects of some of the above tetrahydroimidazoquinazolinones on heart rate in the conscious dog, **7** and **10–12** were also evaluated in a Starling heart–lung preparation (Figure 3). Significantly, **11** demonstrated a marked selectivity for increasing the force of cardiac contraction (>150% increase in dP/dt_{max}) without any appreciable change in heart rate. The 9-desmethyl analogue (**7**) was only moderately less selective whereas the positive inotropic responses to **10** and **12** were accompanied by a more obvious tachycardia. These results suggest that SARs for increasing contractile force, rather than heart rate, are influenced by both the 7-heteroaryl and 9-methyl substituents, which are optimally combined in **11**. The highly selective, positive inotropic activity displayed by **11** should be particularly appropriate in the treatment of congestive heart failure since any unnecessary increases in myocardial oxygen consumption are avoided.

In summary, this paper describes SARs for a novel series of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one derivatives with cardiac stimulant properties. This program demonstrated that a combination of 7-heteroaryl and 9-methyl substituents provided optimum inotropic activity and that the imidazoquinazolinone nucleus is an effective bioisosteric replacement for the previously described 2-(1*H*)-quinolinone system. Indeed compound **11**, a direct analogue of the clinical candidate **1a**, demonstrated a particularly favorable pharmacological profile, producing marked, long-lasting, positive inotropic activity without any appreciable changes in heart rate.[20]

Experimental Section

Chemistry. Melting points were determined in a Gallenkamp apparatus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin-Elmer 257 (IR), AE1 MS 12, or VG 7070F (MS), Bruker WM250, and Nicolet QE300 (NMR) instruments and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. NMR data are reported in ppm relative to external TMS (0.0 ppm) as standard and are referenced to the solvent shift (Me_2SO-d_6, 2.49 ppm).

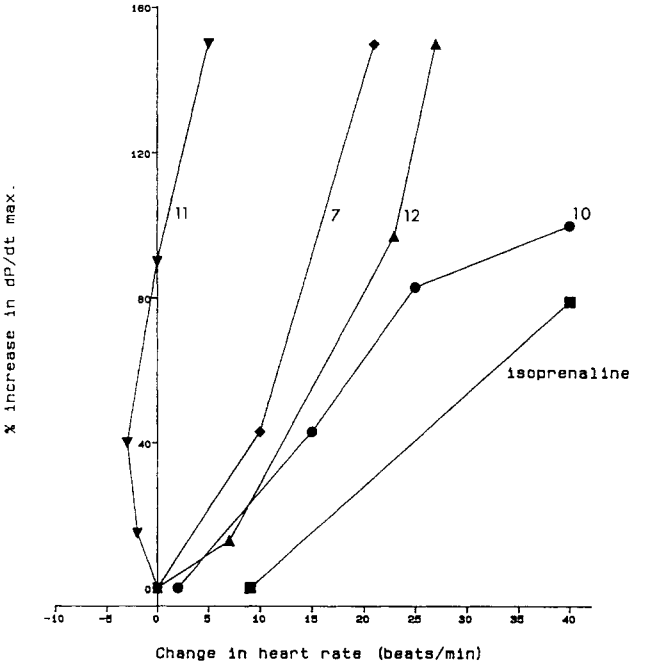

Figure 3. Effects of **7**, **10–12**, and isoprenaline on contractile force and heart rate in the dog heart-lung preparation (for dose levels see the Experimental Section).

Route A. 7-(2,6-Dimethylpyridin-3-yl)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one Hemihydrate (6). A solution of 3-bromo-2,6-dimethylpyridine (1.31 g, 7 mmol) in tetrahydrofuran (3 mL) was added dropwise to a stirred suspension of magnesium (0.187 g, 7.7 mmol) in tetrahydrofuran (4 mL) at reflux under an atmosphere of nitrogen.[21] After approximately 20% of the addition, a crystal of iodine was introduced and the remaining 3-bromo-2,6-dimethylpyridine was then added. After a further 0.5 h at reflux, the mixture was cooled to 50 °C and then treated with a solution of anhydrous zinc chloride (0.95 g, 7 mmol) in tetrahydrofuran (5 mL) followed by a mixture of **16** (0.94 g, 3 mmol) and tetrakis(triphenylphosphine)palladium (0.03 g, 0.03 mmol). The reaction was heated under reflux for 2.5 h. The mixture was evaporated and the residue was partitioned between chloroform–methanol (9:1, 100 mL) and a solution of ethylenediaminetetraacetic acid disodium

(20) Although most of the compounds in Table I are potent (μM) inhibitors of cAMP phosphodiesterase,[9b] we have not been able to establish any useful correlation with inotropic activity.

(21) Kato, T.; Yamanaka, H.; Sakamoto, T.; Shiraishi, T. *Chem. Pharm. Bull.* **1974**, *22*, 1206.

salt dihydrate (5.2 g, 14 mmol) in water (100 mL). The aqueous phase was further extracted with chloroform–methanol (9:1, 2 × 50 mL), and the combined organic phases were discarded. The aqueous phase was adjusted to pH 9 with saturated sodium carbonate solution then extracted with chloroform–methanol (9:1, 4 × 60 mL). These latter, combined extracts were dried ($MgSO_4$) and then evaporated, and the residue was chromatographed on silica by eluting with chloroform–methanol (19:1). The solid product was recrystallized from chloroform–2-propanol to give (7-(2,6-dimethylpyridin-3-yl)-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2(1*H*)-one hemihydrate (0.25 g, 28%): mp 330–332 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.36 (3 H, s), 2.43 (3 H, s), 3.81 (2 H, s), 4.54 (2 H, s), 7.01 (1 H, d), 7.10 (1 H, d), 7.18 (1 H, s), 7.21 (1 H, d), 7.43 (1 H, d) ppm. Anal. ($C_{17}H_{16}N_4O$·0.5H_2O) C, H, N.

Route B. 7-(2,4-Dimethylimidazol-1-yl)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one 1.75-Hydrate (7). A mixture of **25** (0.41 g, 1.4 mmol) and cyanogen bromide (0.159 g, 1.5 mmol) was heated under reflux in ethanol (5 mL) for 72 h. On cooling to room temperature, a precipitate formed and the resulting suspension was treated with a solution of sodium hydroxide (0.06 g, 1.5 mmol) in water (3 mL). The solid material dissolved and after 2 h at room temperature the new solid precipitate was collected and dried to give 7-(2,4-dimethylimidazol-1-yl)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-(1*H*)-one 1.75-hydrate (0.19 g, 43%): mp 324–328 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.11 (3 H, s), 2.26 (3 H, s), 3.83 (2 H, s), 4.53 (2 H, s), 7.04 (1 H, d), 7.06 (1 H, s), 7.28 (1 H, s), 7.30 (1 H, d), 10.8 (1 H, br s) ppm. Anal. ($C_{15}H_{15}N_5O$·1.75 H_2O) C, N; H: calcd, 6.0; found, 5.0.

Route C. 7-(2,4-Dimethylimidazol-1-yl)-9-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one (11). A mixture of **27** (0.75 g, 2.4 mmol) and cyanogen bromide (0.265 g, 2.5 mmol) was stirred in ethanol (5 mL) at room temperature for 1 h. The mixture was partitioned between dichloromethane (25 mL) and sodium carbonate solution (10%, 10 mL) and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with dichloromethane–methanol (19:1). A sample of the solid product (0.60 g, 73%) was recrystallized from ethyl acetate to give ethyl *N*-cyano-*N*-[[2-amino-3-methyl-5-(2,4-dimethylimidazol-1-yl)-phenyl]methyl]glycinate hemihydrate, mp 135–140 °C. Anal. ($C_{18}H_{23}N_5O_2$·0.5 H_2O) C, H, N.

This material was heated under reflux in ethanol (5 mL) for 24 h, the solvent was evaporated, and the residue was chromatographed on silica by eluting with dichloromethane–methanol (19:1). The solid product was recrystallized from ethyl acetate–methanol to give 7-(2,4-dimethylimidazol-1-yl)-9-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one (0.28 g, 54%): mp 310–312 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.04 (3 H, s), 2.18 (3 H, s), 2.26 (3 H, s), 3.85 (2 H, s), 4.46 (2 H, s), 6.86 (1 H, s), 6.99 (1 H, s), 7.07 (1 H, s) ppm. Anal. ($C_{16}H_{17}N_5O$) C, H, N.

7-Iodo-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one (16). A mixture of **22** (3.34 g, 10 mmol) and cyanogen bromide (1.11 g, 10.5 mmol) was heated in ethanol (20 mL) under reflux for 18 h. After cooling, a solution of sodium hydroxide (0.42 g, 10.5 mmol) in water (5 mL) was added and the mixture was stirred for a further 2 h. The mixture was filtered and the solid product was collected, washed with water, and dried. A sample of the solid product (2.36 g, 75%) was chromatographed on silica by eluting with chloroform–methanol (19:1), and the solid product was triturated with 2-propanol to give 7-iodo-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one, mp 323–324 °C. Anal. ($C_{10}H_8IN_3O$) C, H, N.

Ethyl *N*-[(2-Amino-5-iodophenyl)methyl]glycinate (22). Iodine monochloride (3.24 g, 20 mmol) was added to a stirred solution of **19**[5a] (4.16 g, 20 mmol) and sodium acetate (1.80 g, 22 mmol) in acetic acid (100 mL) at room temperature. After 1 h, volatile material was removed by evaporation and the residue was partitioned between chloroform (200 mL) and saturated sodium carbonate solution (50 mL). The aqueous phase was further extracted with chloroform (2 × 50 mL), and the combined organic extracts were washed with sodium thiosulphate solution (10%, 50 mL). The dried ($MgSO_4$) organic extracts were evaporated, and the oily residue was chromatographed on silica by eluting with chloroform. A sample of the solid product (4.9 g, 73%) was recrystallized from ethyl acetate–hexane to give ethyl *N*-[(2-amino-5-iodophenyl)methyl]glycinate, mp 58–61 °C. Anal. ($C_{11}H_{15}IN_2O_2$) C, H, N.

Ethyl *N*-[(5-Fluoro-2-nitrophenyl)methyl]glycinate (34). A mixture of ethyl glycinate monohydrochloride (4.18 g, 30 mmol) and triethylamine (5.6 mL, 40 mmol) in ethanol (40 mL) was heated under reflux until all the solid material entered solution. A solution of **33**[22] (2.34 g, 10 mmol) in ethanol (20 mL) was then added dropwise over 0.5 h at reflux, followed by further heating for 1 h. The cooled mixture was evaporated and the residue was partitioned between dichloromethane (100 mL) and saturated aqueous sodium carbonate solution (50 mL). The aqueous phase was further extracted with dichloromethane (2 × 50 mL), and the combined and dried ($MgSO_4$) organic extracts were evaporated to give an oil. This was chromatographed on silica by eluting with chloroform to give ethyl *N*-[(5-fluoro-2-nitrophenyl)methyl]-glycinate (1.15 g, 45%) as an oil, which was characterized spectroscopically.

Ethyl *N*-(Trifluoroacetyl)-*N*-[(5-fluoro-2-nitrophenyl)-methyl]glycinate (35). Trifluoroacetic anhydride (3.0 mL, 21 mmol) was added dropwise to a stirred solution of **34** (5.10 g, 20 mmol) and triethylamine (3.0 mL, 21 mmol) in dichloromethane (40 mL) at −70 °C under nitrogen. The mixture was warmed to room temperture and partitioned between dichloromethane (60 mL) and sodium carbonate solution (10%, 50 mL). The organic phase was dried ($MgSO_4$) and then evaporated and the oily residue was chromatographed on silica by eluting with ethyl acetate–hexane (1:9). The oily product (6.27 g, 89%) crystallized on standing for several days to afford ethyl *N*-(trifluoroacetyl)-*N*-[(5-fluoro-2-nitrophenyl)methylglycinate, mp 60–63 °C. Anal. ($C_{13}H_{12}F_4N_2O_5$) C, H, N.

Ethyl *N*-(Trifluoroacetyl)-*N*-[[2-nitro-5-(2,4-dimethylimidazol-1-yl)phenyl]methyl]glycinate (36). A mixture of 2,4-dimethylimidazole (6.25 g, 65 mmol), **35** (22.0 g, 62 mmol), and sodium carbonate (6.62 g, 62 mmol) was stirred and heated in DMF (100 mL) at 130 °C for 2 h. Volatile material was removed from the cooled mixture by evaporation and the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic phase was washed with water (2 × 25 mL), dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on silica by eluting with ethyl acetate–methanol (19:1). Trituration of the oily product with ether gave ethyl *N*-(trifluoroacetyl)-*N*-[[2-nitro-5-(2,4-dimethylimidazol-1-yl)phenyl]-methyl]glycinate (3.1 g, 12%) mp 173–176 °C. Anal. ($C_{18}H_{19}F_3N_4O_5$) C, H, N.

Methyl *N*-[[2-Amino-5-(2,4-dimethylimidazol-1-yl)-phenyl]methyl]glycinate (25). A solution of **36** (1.5 g, 3.5 mmol) in ethanol (60 mL) was hydrogenated over Raney nickel (0.15 g) at 20 psi/20 °C for 3 h. The mixture was filtered through Solkafloc and was evaporated to give an oil (1.4 g, 99%), which crystallized on trituration with ether to afford ethyl *N*-(trifluoroacetyl)-*N*-[[2-amino-5-(2,4-dimethylimidazol-1-yl)phenyl]methyl]glycinate 0.25-hydrate, mp 163–166 °C. Anal. ($C_{18}H_{21}F_3N_4O_3$·0.25 H_2O) C, H, N.

A mixture of the above product (1.4 g, 35 mmol) and anhydrous sodium carbonate (0.74 g, 7 mmol) in methanol (20 mL) was heated under reflux for 3 h. The cooled solution was evaporated and the residue was partitioned between chloroform (50 mL) and water (10 mL). The aqueous phase was extracted with chloroform (2 × 25 mL), and the combined and dried ($MgSO_4$) organic extracts were evaporated to give an oil, which was chromatographed on silica, with ethyl acetate–methanol (9:1) as eluant to give methyl *N*-[[2-amino-5-(2,4-dimethylimidazol-1-yl)phenyl]methyl]glycinate as an oil (0.41 g, 41%), which was characterized spectroscopically.

Ethyl *N*-[(2-Amino-5-(2,4-dimethylimidazol-1-yl)-3-methylphenyl)methyl]glycinate (27). A mixture of ethyl glycinate (2.2 g, 21 mmol) and **47**[2] (0.647 g, 2.8 mmol) was heated under reflux in toluene (30 mL) for 3 h in a Dean and Stark apparatus. The volatile material was evaporated and the crude imine intermediate (0.84 g) was taken up in ethanol (25 mL) and hydrogenated over 10% palladized charcoal at 25 °C/60 psi for 2.5 h. The mixture was filtered through Solkafloc and then

(22) McCord, T. J.; Crawford, C. P.; Rabon, J. A.; Gage, L. D.; Winter, J. M.; Davis, A. L. *J. Heterocycl. Chem.* **1982**, *19*, 401.

evaporated to give ethyl *N*-[[2-amino-5-(2,4-dimethylimidazol-1-yl)-3-methylphenyl]methyl]glycinate (0.75 g, 89%) as an oil, which was characterized spectroscopically.

Ethyl *N*-[[2-Amino-3-methyl-5-(1,2,4-triazol-1-yl)-phenyl]methyl]glycinate (28). A mixture of ethyl glycinate (0.38 g, 3.7 mmol), **48** (0.5 g, 2.5 mmol), and 3A molecular sieves was stirred in chloroform (10 mL) under reflux for 4 h. The cooled mixture was filtered and then evaporated and the residue was taken up in ethanol (30 mL) and hydrogenated over 10% palladized charcoal at 20 °C/60 psi for 16 h. The mixture was filtered through Solkafloc and then evaporated and the residue was chromatographed on silica by eluting with chloroform to give ethyl *N*-[[2-amino-3-methyl-5-(1,2,4-triazol-1-yl)phenyl]methyl]glycinate (0.37 g, 54%) as an oil, which was characterized spectroscopically.

Ethyl *N*-[[2-Amino-3-methyl-5-(1,2,4-triazol-4-yl)-phenyl]methyl]glycinate (29). A mixture of ethyl glycinate (5.7 g, 55 mmol) and **49** (1.62 g, 8 mmol) was heated under reflux in toluene (120 mL) in a Dean and Stark apparatus for 2.5 h. The volatile material was evaporated and the crude imine intermediate (2.35 g) was taken up in ethanol (200 mL) and was treated with sodium cyanoborohydride (5.0 g, 80 mmol) under reflux for 10 h. The cooled solution was evaporated to half-volume and then was poured into aqueous sodium carbonate solution (2%, 100 mL). The mixture was extracted with dichloromethane (3 × 200 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica by eluting with dichloromethane–ethanol (19:1) to give ethyl *N*-[[2-amino-3-methyl-5-(1,2,4-triazol-4-yl)phenyl]methyl]glycinate (1.14 g, 49%) as an oil, which was characterized spectroscopically.

4-(4-Amino-3-iodo-5-methylphenyl)-1,2,4-triazole (43). A solution of iodine monochloride (0.58 g, 3.59 mmol) in acetic acid (5 mL) was added dropwise to a stirred solution of **40** (0.50 g, 2.87 mmol) and sodium acetate (0.47 g, 5.74 mmol) in glacial acetic acid (5 mL) at room temperature. The reaction was stirred for 2 h and then poured into water and basified (5 N NaOH). The mixture was extracted with dichloromethane, the combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by elution with chloroform to give 4-(4-amino-3-iodo-5-methylphenyl)-1,2,4-triazole (0.27 g, 31%), mp 211–214 °C. Anal. ($C_9H_9IN_4$) C, H, N.

4-(4-Amino-3-cyano-5-methylphenyl)-1,2,4-triazole (46). A mixture of **43** (1.75 g, 5.8 mmol), sodium cyanide-alumina[16] (1:2, 1.07 g, 7.3 mmol), and tetrakis(triphenylphosphine)palladium (0.10 g, 0.08 mmol) in toluene (30 mL) was stirred at 75 °C for 18 h and then under reflux for 24 h. The cooled solution was partitioned between ethyl acetate and water; the aqueous phase was further extracted with ethyl acetate (2 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with chloroform. A sample of the solid product (1.09 g, 92%) was recrystallized from ethyl acetate–methanol to give 4-(4-amino-3-cyano-5-methylphenyl)-1,2,4-triazole 0.25-hydrate, mp 283–286 °C. Anal. ($C_{10}H_9N_5 \cdot 0.25H_2O$) C, H, N.

4-(4-Amino-3-formyl-5-methylphenyl)-1,2,4-triazole (49). A stirred suspension of **46** (0.39 g, 1.96 mmol) in tetrahydrofuran (20 mL) was treated with a solution of diisobutylaluminum hydride (1.5 M in toluene, 3.62 mL, 5.4 mmol) at 0 °C. The reaction was stirred at room temperature for 2.5 h and was then poured into hydrochloric acid (2 M, 25 mL). After 0.5 h, the mixture was basified with sodium carbonate solution (10%) and was extracted with dichloromethane (3 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with chloroform. The product was recrystallized from ethyl acetate–methanol to give 4-(4-amino-3-formyl-5-methylphenyl)-1,2,4-triazole (0.046 g, 12%), mp 250–252 °C. Anal. ($C_{10}H_{10}N_4O$) C, H, N.

Biology. Measurement of Inotropic Activity. (a) Anesthetized Dogs. Dogs were anesthetized with intravenous sodium pentobarbitone (Sagatal, M & B; 30–40 mg/kg) and intubated. The saphenous vein, and the femoral and carotid arteries were cannulated for compound injection and for the recording of blood pressure and left ventricular pressure (LVP), respectively. LVP was recorded with a Millar Mikso-tip catheter introduced to the left ventricle via the carotid artery. The signal was differentiated to give dP/dt_{max}, which was used as the index of cardiac contractility. Following surgery, an equilibration period of 0.75 h was allowed. All compounds were administered intravenously in saline solution (4 mL, 0.9%) 0.5 h after the standard agent, 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline (50 μg/kg). This cycle was repeated when control levels were reestablished, with a minimum of 0.5 h between compound administration. Changes in dP/dt_{max} (mmHg/s), blood pressure (mmHg), and heart rate (beats/min) were recorded, but since most compounds had little effect on the latter two parameters on acute administration, these data are not presented. Inotropic activity is presented as both a percentage increase in dP/dt_{max} and relative to 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline evaluated in the same dog. Thus

$$\text{relative inotropic potency} = \frac{\%\text{ increase in } dP/dt_{max} \text{ to drug}}{\%\text{ increase in } dP/dt_{max} \text{ to standard}} \times \frac{\text{dose standard}}{\text{dose drug}}$$

During a typical test run in which five quinolinone derivatives were evaluated, percentage increases in dP/dT_{max} recorded for 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline (50 μg/kg) were 48, 42, 45, 48, and 46%.

Dog Heart–Lung Preparation. A Starling dog heart–lung preparation was set up as previously described.[23] Cannulae were inserted via the inferior vena cava into the right atrium and via the left subclavian artery into the left ventricle to record right atrial and left intraventricular pressures respectively. These cannulae were connected via Bell and Howell pressure transducers to a Devices eight-channel pen recorder. The first derivative of left ventricular pressure (dP/dt) was recorded and the maximum value was utilized as an index of myocardial contractility. ECG (lead II) was recorded conventionally with needle electrodes. The temperature of the blood was maintained at 37 °C and was adequately oxygenated. Control values were established for left ventricular end diastolic pressure, left ventricular dP/dt_{max}, central venous pressure, circuit pressure, circuit flow, heart rate, and filling pressure. Drugs were injected via the venous inflow catheter and hemodynamic parameters were remeasured. Force/rate selectivity is expressed graphically (Figure 3) by plotting percentage increases in dP/dt_{max} against absolute increases in heart rate. All compounds were tested in two to four dogs and the dose ranges employed were as follows: 20–640 μg/kg (**7**), 20–320 μg/kg (**10**), 20–640 μg/kg (**11**) 10–320 μg/kg (**12**), 50–500 ng/kg (isoprenaline). Figure 3 is derived by drawing the best lines through the accumulated data points for increases in force and rate. All data points lie within 10% of the line for either dependent variable.

(b) Conscious Dogs.[24,25] Adult beagle dogs (Pfizer colony) were prepared, under aseptic recovery surgery, with a carotid artery loop and two subcutaneous titanium studs, designed to act as permanent ECG electrodes and placed, one each, in the dorsal neck and rump areas. Following adequate time for recovery and full wound healing, each dog was placed in a canvas support within the laboratory. A strain gauge was placed around the carotid loop, and recording leads were attached to the two electrodes. Recordings of both the arterial pulse and the ECG were made via appropriate interfacing onto a Grass polygraph. Measurements of the QA interval (the time in ms between the R wave of the ECG signal and the up-stroke of the arterial pressure pulse) were made by digital computer. To assess the activity of a test substance, recordings of the QA interval were made every 0.16 h, from 0.5 h before to up to 4 h after the oral administration, by gavage, of a solution of the test substance. Each value of the QA interval, at a given time point, represents the mean of six consecutive sets of values, each set being the mean of the values recorded in an 8-s period. Results are expressed as the change in the QA interval from the mean control (predose) value. In control animals (n = 8), changes in the QA interval of 1.5 ± 2 and 0.5 ± 1.5 ms were

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(24) Alabaster, C. T.; Henderson, C. G. *Br. J. Pharmacol.* **1982**, *76*, 251P.
(25) Cambridge, D.; Whiting, M. V. *Cardiovasc. Res.* **1986**, *20*, 444.
(26) Prepared from 2-amino-3-methylbenzaldehyde[27] by using the method described for example **28**.
(27) Black, D. St. C.; Bos Vanderzalm, C. H.; Wong, L. C. H. *Aus. J. Chem.* **1982**, *35*, 2435.

observed at 1 and 3 h, respectively, after saline administration. Decreases in the QA interval of 10, 15, and 20 ms correspond approximately to increases in dP/dt_{max} of 20, 45, and 70%, respectively. A decrease in the QA interval of 20 ms approaches the maximum change possible.

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Registry No. **3**, 50608-24-7; **4**, 105622-85-3; **6**, 108857-06-3; **7**, 108857-11-0; **8**, 108857-12-1; **9**, 108857-08-5; **10**, 108857-07-4; **11**, 108892-68-8; **12**, 108857-13-2; **13**, 108857-16-5; **14**, 108857-14-3; **15**, 108857-15-4; **16**, 108857-18-7; **17**, 108857-44-9; **18**, 108857-43-8; **19**, 50794-16-6; **20**, 58579-89-8; **21**, 121375-09-5; **22**, 108857-21-2; **23**, 108857-23-4; **24**, 108857-22-3; **25**, 108857-19-8; **26**, 121375-10-8; **27**, 121375-11-9; **27** (imine), 121375-16-4; **28**, 108857-28-9; **29**, 121393-36-0; **29** (imine), 121375-17-5; **30**, 108857-36-9; **31**, 108857-37-0; **32**, 108857-20-1; **33**, 82420-35-7; **34**, 108857-29-0; **35**, 108857-30-3; **36**, 108857-31-4; **37**, 121375-12-0; **38**, 102792-03-0; **39**, 102791-90-2; **40**, 102792-08-5; **41**, 108857-39-2; **42**, 108857-34-7; **43**, 121375-13-1; **44**, 108857-38-1; **45**, 108857-33-6; **46**, 121375-14-2; **47**, 108857-35-8; **48**, 108857-27-8; **49**, 121375-15-3; CI-930, 86798-59-6; $H_2NCH(CH_3)CO_2CH_2CH_3$, 3082-75-5; $H_2NC(CH_3)_2CO_2CH_2CH_3$, 1113-49-1; 1,2,4-triazole, 288-88-0; 3-bromo-2,6-dimethylpyridine, 3430-31-7; cyanogen bromide, 506-68-3; ethyl glycinate monohydrochloride, 623-33-6; 2,4-dimethylimidazole, 930-62-1; ethyl *N*-(trifluoroacetyl)-*N*-[[2-amino-5-(2,4-dimethylimidazol-1-yl)phenyl]methyl]glycinate, 108857-32-5; milrinone, 78415-72-2.

Supplementary Material Available: NMR spectral data (300-MHz, Me_2SO) for **19**–**31** and **48** (2 pages). Ordering information is given on any current masthead page.