2(1*H*)-Quinolinones with Cardiac Stimulant Activity. 3. Synthesis and Biological Properties of 6-Imidazol-1-yl Derivatives

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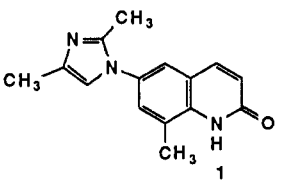
A series of 6-imidazol-1-yl-8-methyl-2(1*H*)-quinolinones was synthesized and evaluated for cardiac stimulant activity in dogs. The majority of compounds were prepared from an appropriate 6-imidazol-1-yl-2(1*H*)-quinolinone precursor or by sulfuric acid catalyzed cyclization of an *N*-(4-heteroarylphenyl)-3-ethoxypropenamide. Introduction of a range of 5-substituents into 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (1) reduced inotropic activity in anesthetized dogs (percentage increase in dP/dt_{max}) although replacement of the 2-methyl group by iodo (**10**) or cyano (**11**) substituents was well tolerated. The 2-methyl-4-chloro (**15**) and 2-methyl-4-(methylthio) (**22**) derivatives displayed similar potency to **1** (40–50% increase in dP/dt_{max}, 10–12.5 μg/kg) and these compounds were 3–5 times more potent than milrinone. Introduction of iodo (**14**), cyano (**16**), or acetyl (**17**) substituents into the 4-position approximately halved inotropic activity. In conscious dogs, **11** (0.25 mg/kg) and **16** and **17** (0.125 mg/kg) produced similar increases in cardiac contractility (decrease in the QA interval) to **1** (0.125 mg/kg) and maximum responses were maintained for at least 3 h. Dose-related (25, 125, 250 μg/kg) cardiac stimulant activity was demonstrated by **17** and after the higher doses a marked response (approximately 30% increase in dP/dt_{max}) was still observed after 7 h, in contrast to milrinone. The substantial increases in cardiac contractility observed with **16** and **17** in the conscious dog were not accompanied by any tachycardia. These compounds also displayed an overwhelming selectivity for increasing the force of cardiac contraction (>120% increase in dP/dt_{max}) rather than heart rate (5–10 beats/min decrease) in the Starling heart–lung preparation. As a result of this beneficial pharmacological profile, 6-(4-acetyl-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**17**, UK-66,838) was selected for preclinical development studies.

Previously, the synthesis and inodilator properties of a series of 2(1*H*)-quinolinone derivatives incorporating a variety of six- and five-membered heterocyclic moieties were described.[1,2] These studies confirmed that location of the heteroaryl function at the quinolinone 6-position was preferred and that an 8-methyl substituent improved both inotropic potency and duration of action. As a result of these initial structure–activity relationship (SAR) studies, 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**1**, UK-61,260) was selected for clinical development,[3,4] and phase II evaluation in congestive heart failure patients is in progress. This compound was some 5 times more potent than milrinone as an inotropic agent and also displayed a more prolonged duration of action after oral administration to conscious dogs.[2,4] In order to extend these observations, a wider range of substituents has been introduced into the imidazolyl ring system in **1**,[5,6] and SARs for inotropic activity have been determined. As a consequence, 6-(4-acetyl-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**17**, UK-66,838) was identified with a similar overall pharmacological profile to **1** and was selected for preclinical development studies.



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Chemistry

Table I lists all of the novel 2(1*H*)-quinolinones (**2–24**) which were evaluated for cardiac stimulant activity, and synthetic routes A–L are summarized in Schemes I and II. Apart from **8**, **12**, and **14**, which were prepared by sulfuric acid catalyzed cyclization of an *N*-(4-heteroarylphenyl)-3-ethoxypropenamide (**25–27**, route G[2]), all of the compounds in Table I were synthesized from an appropriate 6-imidazol-1-yl-8-methyl-2(1*H*)-quinolinone precursor. Thus, electrophilic halogenation of **1** with *N*-chloro- or *N*-bromosuccinimide (routes A and B) or iodine monochloride (route C) gave the 5-halogeno derivatives (**2–4**). Treatment of 6-(4-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**28**) with 2 equiv of *n*-butyllithium followed by iodine provided a regioselective entry to **10** (route I). The above iodoquinolinones (**4**, **10**, and **14**) also served as versatile intermediates for the introduction of a range of alternative substituents into the imidazolyl ring system (Scheme II). Thus, treatment of **4** and **14** with sodium thiomethoxide in the presence of copper(I) chloride as catalyst gave **5** and **22**, respectively (route D), which in turn allowed access to the corresponding sulfoxides (**6** and **23**) and sulfones (**7** and **24**) following S-oxidation with *m*-chloroperbenzoic acid (routes E and F). Treatment of **14** with copper(I) chloride provided **15** (route H) while reaction of **4**, **10**, or **14** with copper(I) cyanide in the presence of palladium acetate as catalyst[7] at 175 °C gave **9**, **11**, and **16** (route J). Compound **16** was subsequently converted to the ketone derivatives (**17–20**) on treatment with an appropriate Grignard reagent (route K). Finally, a palladium-catalyzed cross-coupling reaction[8] between **10** or **14** and phenylzinc chloride gave **13** and **21**, respectively (route L).

Syntheses of the intermediates (Table II) required for the preparation of the propenamides (**25–27**) used for route G are summarized in Scheme III. Thus, reaction of 5-fluoro-2-nitrotoluene (**29**) with an appropriately substituted imidazole (**39–41**) in dimethylformamide at 120 °C

(1) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1988**, *31*, 1031.
(2) Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Morris, D. S.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1989**, *32*, 575.
(3) Ellis, P.; Henderson, C. G.; Samuels, G. M. R. *Br. J. Pharmacol.* **1987**, *91*, 392P.
(4) Alabaster, C. T.; Rance, D. J. *Br. J. Pharmacol.* **1987**, *91*, 391P.
(5) Campbell, S. F.; Roberts, D. A. European Patent 0226357, 1987.
(6) Campbell, S. F.; Morris, D. S.; Roberts, D. A. European Patent 0257918, 1988.
(7) Takagi, K.; Okamaoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayamu, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298.
(8) Negishi, E.; Luo, F.-T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117.

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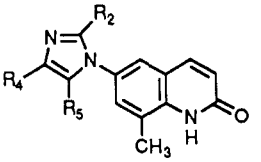
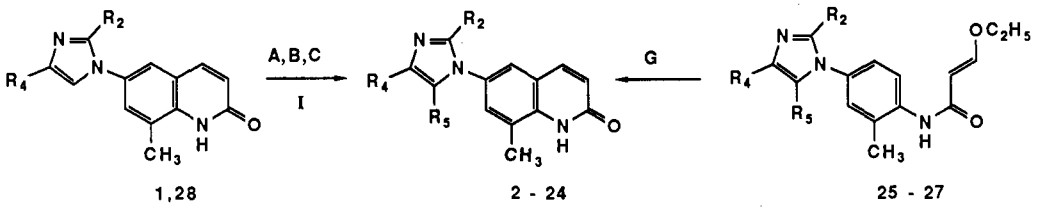
Table I. Synthetic Routes and Physicochemical Data for Imidazolylquinolinone Derivatives



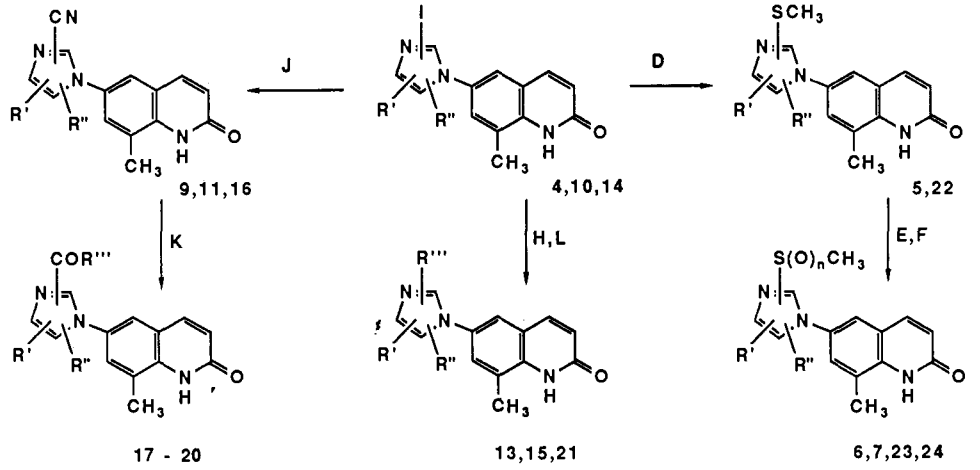
no.	R_2	R_4	R_5	route	mp, °C	formula	anal.
2	CH_3	CH_3	Cl	A	265–268	$C_{15}H_{14}ClN_3O$	C, H, N[a]
3	CH_3	CH_3	Br	B	273	$C_{15}H_{14}BrN_3O$	C, H, N
4	CH_3	CH_3	I	C	242–245	$C_{15}H_{14}IN_3O{\cdot}0.5H_2O$	C, H, N
5	CH_3	CH_3	SCH_3	D	263–265	$C_{16}H_{17}N_3OS{\cdot}0.25H_2O$	C, H, N
6	CH_3	CH_3	$SOCH_3$	E	283–285	$C_{16}H_{17}N_3O_2S{\cdot}0.33H_2O$	C, H, N
7	CH_3	CH_3	SO_2CH_3	F	276–278	$C_{16}H_{17}N_3O_3S$	C, H, N
8	CH_3	CH_3	$COCH_3$	G	240–242	$C_{17}H_{17}N_3O_2$	C, H, N
9	CH_3	CH_3	CN	J	334–337	$C_{16}H_{14}N_4O{\cdot}0.25H_2O$	C, H, N
10	I	CH_3	H	I	260	$C_{14}H_{12}IN_3O{\cdot}0.66H_2O$	C, H, N
11	CN	CH_3	H	J	302–304	$C_{15}H_{12}N_4O$	C, H, N
12	$COCH_3$	CH_3	H	G	312–314	$C_{16}H_{15}N_3O_2{\cdot}0.25H_2O$	C, H, N
13	C_6H_5	CH_3	H	L	293–295	$C_{20}H_{17}N_3O{\cdot}0.5H_2O$	C, H, N
14	CH_3	I	H	G	285–287	$C_{14}H_{12}IN_3O$	C, H, N
15	CH_3	Cl	H	H	347–350	$C_{14}H_{12}ClN_3O$	C, H, N
16	CH_3	CN	H	J	>350	$C_{15}H_{12}N_4O{\cdot}0.67H_2O$	C, H, N
17	CH_3	$COCH_3$	H	K	306–308	$C_{16}H_{15}N_3O_2{\cdot}0.17H_2O$	C, H, N
18	CH_3	COC_2H_5	H	K	261–263	$C_{17}H_{17}N_3O_2$	C, H, N[b]
19	CH_3	CO-*i*-C_3H_7	H	K	224–227	$C_{18}H_{19}N_3O_2{\cdot}0.17H_2O$	C, H, N
20	CH_3	COC_6H_5	H	K	290–293	$C_{21}H_{17}N_3O_2{\cdot}0.5H_2O$	C, H, N
21	CH_3	C_6H_5	H	L	280–282	$C_{20}H_{17}N_3O{\cdot}0.33H_2O$	C, H, N
22	CH_3	SCH_3	H	D	255	$C_{15}H_{15}N_3OS{\cdot}0.5H_2O$	C, H, N
23	CH_3	$SOCH_3$	H	E	292	$C_{15}H_{15}N_3O_2S{\cdot}1.25H_2O$	C, H, N
24	CH_3	SO_2CH_3	H	F	332–333	$C_{15}H_{15}N_3O_3S$	C, H, N

[a] N: calcd, 14.6; found, 14.1. [b] N: calcd, 14.2; found, 13.7.

Scheme I



Scheme II

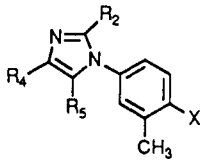


gave **30–32** with greater than 95% regioselectivity.[9] Reduction with stannous chloride then provided the anilino derivatives (**33–35**). Surprisingly, selective iodination of the imidazole ring in **34** was achieved with iodine/silver sulfate/sulfuric acid whereas reaction with bromine in acetic acid occurs ortho to the amino function.[2] Presumably, in the former case both the amino and imidazolyl systems are fully protonated and, consequently, the aromatic ring is more severely deactivated. The iodinated product 1-(4-amino-3-methylphenyl)-5-iodo-2,4-dimethylimidazole (**36**) allowed access to the corresponding 5-cyano (**37**) and 5-acetyl (**38**) derivatives by the methods of routes H and L. Finally, treatment of **33**, **35**, and **38** with *trans*-3-ethoxypropenoyl chloride provided **25–27**.

The imidazole derivatives (**39** and **40**) required for reaction with **29** were prepared from 2- and 4-methylimidazole (**42** and **43**), respectively. Thus, treament of **42**

(9) Imbach, J.-L.; Jacquier, R. *C. R. Seances Acad. Sci., Ser. 2* **1963**, *257*, 2683.

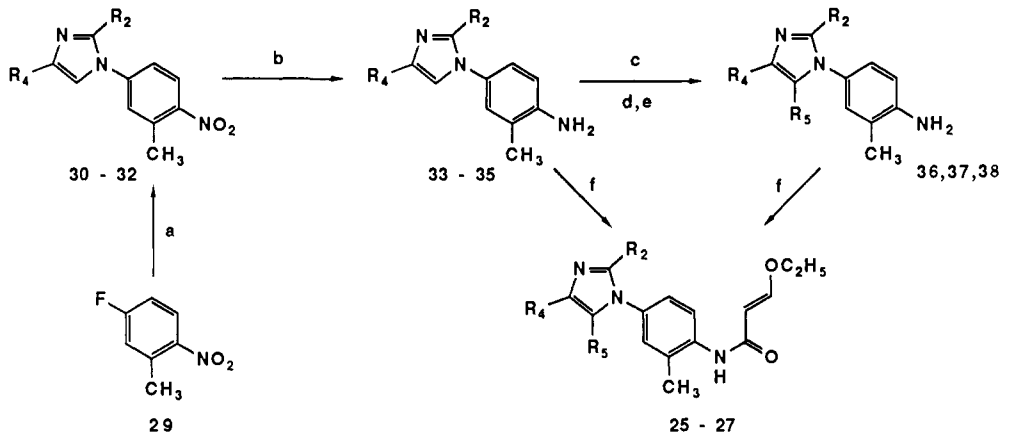
Table II. Synthetic Routes and Physicochemical Data for 1-(3-Methylphenyl)imidazole Derivatives



no.	X	R_2	R_4	R_5	mp, °C	formula	anal.
25	$NHCOCHCHOC_2H_5$	CH_3	I	H	172–174	$C_{16}H_{18}IN_3O_2$	C, H, N
26	$NHCOCHCHOC_2H_5$	$COCH_3$	CH_3	H	189–191	$C_{18}H_{21}N_3O_3$	C, H, N
27	$NHCOCHCHOC_2H_5$	CH_3	CH_3	$COCH_3$	oil[a]		
30	NO_2	CH_3	I	H	146–148	$C_{11}H_{10}IN_3O_2$	C, H, N
31[2]	NO_2	CH_3	CH_3	H	135–138	$C_{12}H_{13}N_3O_2$	C, H, N
32	NO_2	$COCH_3$	CH_3	H	157–159	$C_{13}H_{13}N_3O_3$	C,[b] H, N
33	NH_2	CH_3	I	H	crude[a]		
34[2]	NH_2	CH_3	CH_3	H	118–120	$C_{12}H_{15}N_3$	C,[c] H, N
35	NH_2	$COCH_3$	CH_3	H	157–159	$C_{13}H_{15}N_3O{\cdot}0.17H_2O$	C, H, N
36	NH_2	CH_3	CH_3	I	crude[a]		
37	NH_2	CH_3	CH_3	CN	152–154	$C_{13}H_{14}N_4{\cdot}0.33H_2O$	C, H, N
38	NH_2	CH_3	CH_3	$COCH_3$	oil[a]		

[a] Characterized spectroscopically. [b] C: calcd, 60.2; found, 59.7. [c] C: calcd, 71.6; found, 71.0.

Scheme III[a]



[a] Reagents: (a) imidazole derivative, Na_2CO_3, DMF, 120 °C; (b) $SnCl_2{\cdot}2H_2O$, C_2H_5OH; (c) Ag_2SO_4, I_2, H_2SO_4; (d) CuCN; (e) CH_3Li; (f) $C_2H_5OCH{=}CHCOCl$, pyridine.

with iodine monochloride gave the 4,5-diiodo derivative[10] (**44**), which on reaction with 2 equiv of *n*-butyllithium at −70 °C followed by quenching with water gave 4-iodo-2-methylimidazole[11] (**39**). N-1 protection of **43** using triethyl orthoformate[12] followed by regioselective 2-deprotonation (*n*-butyllithium) and acetylation (*N,N*-dimethylacetamide) gave 2-acetyl-4-methylimidazole (**40**).

SARs for Inotropic Activity. The quinolinone derivatives in Table I were administered intravenously to instrumented, anesthetized dogs in order to measure positive inotropic activity (Table III). 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[1] compensates for interanimal variation and facilitates SAR comparisons within series and against standard agents such as milrinone and CI-930.

Modification of the parent structure (**1**) by introduction of a 5-chloro substituent (**2**) approximately halved inotropic activity and this was further reduced in **3–8**. These results show that there is a very limited steric tolerance at the 5-position, possibly because the torsion angle between the imidazolyl and quinolinone ring systems is forced more toward 90° than the 30° preferred in **1**.[2] By contrast, introduction of a 2-iodo substituent was well tolerated, and **10** was some 11 times more potent than the corresponding 5-iodo analogue (**4**). An electron-withdrawing cyano group was also acceptable at the 2-position (**11**) but activity was markedly reduced with the 2-acetyl (**12**) and 2-phenyl (**13**) derivatives.

Replacement of the 4-methyl substituent in **1** was studied in some detail, and the chloro (**15**) and methylthio (**22**) analogues were essentially equipotent with the parent structure. These results suggest that the basicity of the imidazolyl 3-nitrogen atom is of little importance for inotropic activity since the estimated pK_a of **15** (approximately 4.6) would be more than 2 log units lower than that for **1**.[13] Activity was somewhat reduced with the 4-iodo (**14**), cyano (**16**), and acetyl (**17**) derivatives; elaboration of the ketone moiety was also not beneficial (**18–20**), nor was oxidation of **22** to the sulfoxide **23** or sulfone **24**. Thus, while none of the novel derivatives in Table III showed improvement over **1**, quinolinones **10**, **15**, and **22** displayed similar inotropic activity, and even some less potent members of the series (**2**, **11**, **14**, **16**, **17**, **21**) were superior to milrinone and CI-930.

(10) Vaughan, J. D.; Vaughan, V. L.; Daly, S. S.; Smith, W. A. *J. Org. Chem.* **1980**, *45*, 3108.
(11) Iddon, B. *Heterocycles* **1985**, *23*, 417.
(12) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038.
(13) The pK_a for the imidazolyl system in **1** is 7.13 ± 0.04.[2]

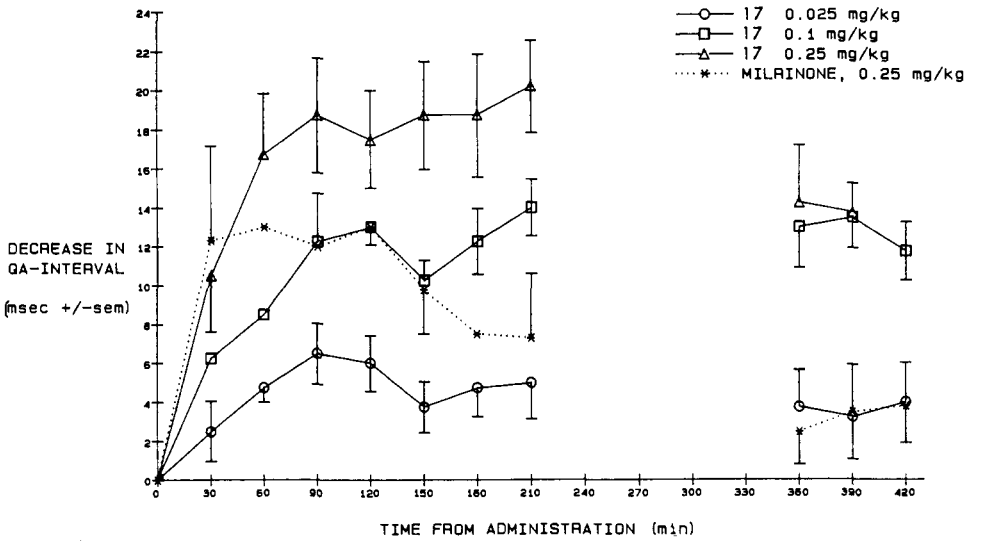


Figure 1. Effects of 17 and milrinone on the QA interval (ms ± SEM) in conscious dogs (n = 4) following oral administration.

Table III. Inotropic Activity for Quinolinone 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 QA interval, ms ± SEM[c] 1 h	3 h	dose, mg/kg, po
1[2]	40	12.5	7.6	16 ± 1	17 ± 1	0.25
2	32	10	2.9	12 ± 1	10 ± 2	0.125
3	26	50	0.7	12 ± 2	13 ± 3	2.0
4	17	50	0.5			
5	28	50	0.9			
6	7	50	0.2			
7	5	50	0.1			
8	16	50	0.4	6 ± 3	10 ± 2	2.0
9	70	50	1.1	11 ± 2	15 ± 1	1.0
10	59	10	5.7			
11	53	10	4.1	15 ± 2	15 ± 3	0.25
12	15	50	0.3			
13	15	50	0.3			
14	11	10	2.6			
15	50	10	5.6			
16	30	10	3.0	15 ± 4	15 ± 3	0.125
17	36	10	2.6	17 ± 3	19 ± 3	0.25
18	29	50	0.9			
19	24	50	0.6			
20	31	50	0.5			
21	15	10	2.4	13 ± 1	10 ± 2	0.5
22	53	10	5.0			
23	65	50	0.7			
24	25	50	0.3			
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).

Some of the compounds in Table I were also administered orally to conscious dogs and the effects on cardiac contractility (decrease in QA interval) were determined[1] (Table III). As expected, **2** was the most potent trisubstituted imidazolyl derivative evaluated, although **3**, **8**, and **9** also displayed a prolonged duration of action, albeit at higher dose levels. Compounds **11**, **16**, and **17** demonstrated a very similar profile to **1**, and in each case there was a negligible difference in activity between the 1- and 3-h time points. By contrast, milrinone elicited a maximum inotropic response after 1 h, which waned rapidly over the remainder of the experiment. More detailed studies in the conscious dog were undertaken with **17**, and dose-related (25, 125, and 250 μg/kg) decreases in the QA interval were observed (Figure 1) which were not accompanied by tachycardia (data not shown). An obvious response was apparent even at the lowest dose administered (25 μg/kg) while after the higher doses marked activity (approximately 30% increase in dP/dt_{max}) was still observed after 7 h. Indeed, **17** displayed a slightly improved duration of action over **1**, probably because plasma levels are higher after equivalent oral doses.[14]

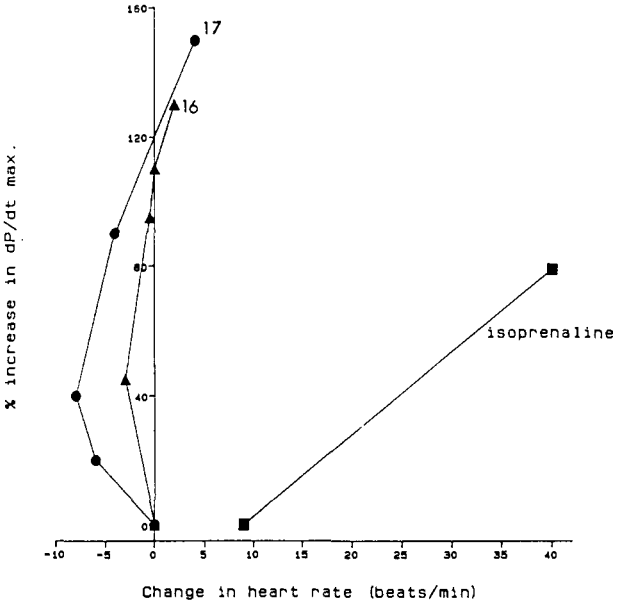


Figure 2. Effects of **16**, **17**, and isoprenaline on contractile force and heart rate in the dog heart–lung preparation (for dose levels, see the Experimental Section).

Compounds **16** and **17** were also evaluated in the Starling heart–lung preparation where marked increases in cardiac contractility were observed (>120% increase in dP/dt_{max}) without any increase in heart rate (Figure 2). Indeed, a slight bradycardia was apparent (5–10 beats/min) and it is obvious that **16** and **17** display an overwhelming selectivity for increasing the force of cardiac contraction rather than heart rate. These results are similar to previous observations for related 2(1H)-quinolinone derivatives,[1,2] and such a beneficial pharmacological profile may be particularly appropriate for the treatment of congestive heart failure.

In conclusion, these SAR studies show that substantial inotropic activity can be maintained following modification of the imidazolyl substituents in **1**, although no compound

(14) Rance, D. J. Unpublished observations.

in Table II showed improved intrinsic potency over the parent structure. However, in conscious dogs, **17** was approximately equipotent with **1** and also displayed a slightly longer duration of positive inotropic action. The marked increases in cardiac contractility observed with **17** in the conscious dog and in the heart–lung preparation were not accompanied by any increases in heart rate. As a result of this overall pharmacological profile, **17** (UK-66,838) was selected for preclinical development studies.

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), and Varian XL 100, 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.

Route A. 6-(5-Chloro-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (2). A suspension of 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**1**, 0.50 g, 2 mmol) in chloroform (20 mL) was treated with *N*-chlorosuccinimide (0.294 g, 2.2 mol) and the reaction was stirred for 48 h. The crude mixture was chromatographed on silica with chloroform–methanol (100:4) as eluant. The yellow, solid product was triturated with ether and then recrystallized from ethyl acetate to give 6-(5-chloro-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (0.50 g, 87%), mp 265–268 °C. Anal. ($C_{15}H_{14}ClN_3O$) C, H; N: calcd, 14.6; found, 14.1.

Route B. 6-(5-Bromo-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (3). *N*-Bromosuccinimide (0.374 g, 2.2 mmol) was added to a stirred suspension of 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**1**, 0.50 g, 2 mmol) in chloroform (10 mL) at room temperature. After 0.1 h, the reaction mixture was evaporated and the residue was chromatographed on silica by eluting with ethyl acetate–methanol (10:1). The solid product was recrystallized from ethyl acetate–methanol to give 6-(5-bromo-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (0.28 g, 42%), mp 273 °C. Anal. ($C_{15}H_{14}BrN_3O$) C, H, N.

Route C. 6-(2,4-Dimethyl-5-iodoimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone Hemihydrate (4). A solution of iodine monochloride (0.41 g, 2.5 mmol) in acetic acid (5 mL) was added dropwise to a stirred solution of 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**1**, 0.51 g, 2 mmol) and sodium acetate (0.33 g, 4 mmol) in acetic acid (10 mL). The mixture was stirred for 16 h and then evaporated and sodium carbonate solution (10%, 50 mL) was added followed by extraction with dichloromethane (3 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate. The solid product was recrystallized from ethyl acetate–methanol to give 6-(2,4-dimethyl-5-iodoimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone hemihydrate (0.38 g, 50%), mp 242–245 °C. Anal. ($C_{15}H_{14}IN_3O{\cdot}0.5H_2O$) C, H, N.

Route D. 6-(2-Methyl-4-(methylthio)imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone Hemihydrate (22). 6-(4-Iodo-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**14**, 1.4 g, 3.8 mmol) was added to a stirred suspension of sodium thiomethoxide (0.8 g, 11.4 mmol) and copper(I) chloride (0.45 g, 4.6 mmol) in 1-methylpyrrolidin-2-one (10 mL) and the mixture was heated under nitrogen at 140 °C. After 6 h, the cooled mixture was poured into aqueous ammonia solution (sp gr 0.880, 10 mL) and was extracted with methanol–dichloromethane (1:20, 3 × 75 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with methanol–dichloromethane (1:20). The solid product was recrystallized from ethyl acetate to give 6-(2-methyl-4-(methylthio)imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone hemihydrate (0.48 g, 44%), mp 255 °C. Anal. ($C_{15}H_{15}N_3OS{\cdot}0.5H_2O$) C, H, N.

Route E. 6-(2,4-Dimethyl-5-(methylsulfinyl)imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone 0.33-Hydrate (6). *m*-Chloroperbenzoic acid (85%, 0.3 g, 1.5 mmol) was added in portions to a stirred solution of 6-(2,4-dimethyl-5-(methylthio)-imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**5**, 0.45 g, 1.5 mmol) in chloroform (20 mL) at 0 °C. After 0.5 h, the mixture was basified to pH 10 (saturated sodium carbonate solution) and was extracted with dichloromethane (3 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with methanol–dichloromethane (1:20). The solid product was recrystallized from ethyl acetate to give 6-(2,4-dimethyl-5-(methylsulfinyl)imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone 0.33-hydrate (0.32 g, 68%), mp 283–285 °C. Anal. ($C_{16}H_{17}N_3O_2S{\cdot}0.33H_2O$) C, H, N.

Route F. 6-(2,4-Dimethyl-5-(methylsulfonyl)imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (7). *m*-Chloroperbenzoic acid (85%, 0.11 g, 0.54 mmol) was added to a stirred solution of the product from route E (0.15 g, 0.47 mmol) in chloroform (10 mL) at room temperature. After 5 h, the reaction was processed as described for route E to give 6-(2,4-dimethyl-5-(methylsulfonyl)imidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (0.05 g, 33%), mp 276–278 °C. Anal. ($C_{16}H_{17}N_3O_3S$) C, H, N.

Route G. 6-(5-Acetyl-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (8). *trans*-1-[4-(3-Ethoxypropenamido)-3-methylphenyl]-5-acetyl-2,4-dimethylimidazole (**27**, 7.1 g, 21 mmol) was added with stirring to sulfuric acid (98% w/w, 50 mL) at 0 °C. After 24 h at room temperature, the mixture was poured carefully onto ice (500 g) and the resulting solution was basified with aqueous sodium bicarbonate solution. The mixture was extracted with dichloromethane (3 × 500 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The solid residue was recrystallized from ethyl acetate–methanol to give 6-(5-acetyl-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (2.5 g, 40%) mp 240–242 °C. Anal. ($C_{17}H_{17}N_3O_2$) C, H, N.

Route H. 6-(4-Chloro-2-methylimidazol-1-yl)-8-methyl-2-(1*H*)-quinolinone 0.25-Hydrate (15). A mixture of 6-(4-iodo-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**14**, 0.20 g, 0.55 mmol) and copper(I) chloride (0.218 g, 2.20 mmol) in 1-methylpyrrolidin-2-one (1 mL) was heated at 150 °C for 24 h under nitrogen. The cooled solution was treated with ammonia (sp gr 0.880, 20 mL) and was extracted with ethyl acetate (3 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica eluting with dichloromethane–methanol (100:3). The product was recrystallized from ethyl acetate–methanol to give 6-(4-chloro-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone 0.25-hydrate (0.19 g, 13%), mp 347–350 °C. Anal. ($C_{14}H_{12}ClN_3O{\cdot}0.25H_2O$) C, H, N.

Route I. 6-(2-Iodo-4-methylimidazol-1-yl)-8-methyl-2-(1*H*)-quinolinone 0.67-Hydrate (10). *n*-Butyllithium (1.43 M in hexane, 2.94 mL, 4.2 mmol) was added dropwise to a stirred suspension of 6-(4-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**28**, 0.45 g, 1.9 mmol) in tetrahydrofuran (2.5 mL) at −70 °C under an atmosphere of nitrogen. After 0.5 h, iodine (0.51 g, 2.0 mmol) was added and the mixture was stirred for a further 0.5 h at −70 °C before warming to room temperature. Saturated ammonium chloride solution (10 mL) was added, the organic solvent was evaporated, and the residue was partitioned between water (20 mL) and dichloromethane (50 mL). The aqueous phase was further extracted with dichloromethane (2 × 50 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica by eluting with chloroform and the product was recrystallized from ethyl acetate to give 6-(2-iodo-4-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone 0.67-hydrate (0.27 g, 39%), mp 260 °C. Anal. ($C_{14}H_{12}IN_3O{\cdot}0.67H_2O$) C, H, N.

Route J. 6-(5-Cyano-2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone 0.25-Hydrate (9). A mixture of the product from route C (0.1 g, 0.26 mmol), cuprous cyanide (0.047 g, 0.52 mmol), and palladium acetate (0.01 g) in 1-methylpyrrolidin-2-one (1 mL) was stirred at 175 °C for 3 h. The cooled mixture was poured into aqueous ammonia solution (sp gr 0.880, 10 mL) and dichloromethane (50 mL) and the aqueous phase was further extracted with dichloromethane (2 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with dichloromethane–methanol (19:1). The oily product was triturated with ether to give 6-(5-cyano-2,4-dimethylimidazol-1-yl)-8-methyl-2-(1*H*)-quinolinone 0.25-hydrate (0.03 g, 42%) mp 334–337 °C. Anal. ($C_{16}H_{14}N_4O{\cdot}0.25H_2O$) C, H, N.

Route K. 6-(4-Acetyl-2-methylimidazol-1-yl)-8-methyl-2-(1*H*)-quinolinone 0.17-Hydrate (17). Methylmagnesium

bromide (3 M in diethyl ether, 1.11 mL, 3.3 mmol) was added dropwise to a stirred solution of 6-(4-cyano-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**16**, 0.15 g, 0.56 mmol) in tetrahydrofuran (25 mL) at 0 °C under an atmosphere of nitrogen. The reaction was heated under reflux for 2 h, washed with water (10 mL), and then hydrochloric acid (5 M, 10 mL) was added. The mixture was stirred at room temperature for 0.5 h, and then basified (10% sodium carbonate solution) and extracted with dichloromethane (3 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with methanol-dichloromethane (1:19). The solid product was recrystallized from ethyl acetate–methanol to give 6-(4-acetyl-2-methylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone 0.17-hydrate (0.05 g, 32%), mp 306–308 °C. Anal. ($C_{16}H_{15}N_3O_2 \cdot 0.17H_2O$) C, H, N.

Route L. 6-(4-Methyl-2-phenylimidazol-1-yl)-8-methyl-2-(1*H*)-quinolinone Hemihydrate (13). Phenyllithium [1.9 M in cyclohexane–ether (70:30), 2.4 mL, 4.48 mmol] was added dropwise to a solution of anhydrous zinc chloride (0.76 g, 5.6 mmol) in tetrahydrofuran (50 mL) and the mixture was warmed to room temperature over 1 h. A sample (0.41 g, 1.12 mmol) of the product from route I and tetrakis(triphenylphosphine)palladium (0.1 g, 0.09 mmol) were added and the reaction was heated under reflux for 1.5 h. Water (1.5 mL) was added to the cooled solution followed by a saturated solution of ethylenediaminetetraacetic acid disodium salt in water (5 mL) which had been adjusted to pH 9 with sodium carbonate solution. The mixture was extracted with dichloromethane (3 × 50 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica with methanol–dichloromethane (3:97) as eluant and the product was recrystallized from ethyl acetate to give 6-(4-methyl-2-phenylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone hemihydrate (0.16 g, 44%), mp 293–295 °C. Anal. ($C_{20}H_{17}N_3O \cdot 0.5H_2O$) C, H, N.

4-Iodo-2-methyl-1-(3-methyl-4-nitrophenyl)imidazole (30). A mixture of 5-fluoro-2-nitrotoluene (7.9 g, 50 mmol), 4-iodo-2-methylimidazole (9.0 g, 43 mmol), and sodium carbonate (4.5 g, 43 mmol) was heated with stirring in dimethylformamide (50 mL) at 120 °C for 16 h under nitrogen. The mixture was poured into water (50 mL) and was extracted with chloroform (3 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica with ethyl acetate–toluene (1:5) as eluant. The product was recrystallized from dichloromethane–hexane to give 4-iodo-2-methyl-1-(3-methyl-4-nitrophenyl)imidazole (4.0 g, 27%), mp 146–148 °C. Anal. ($C_{11}H_{10}IN_3O_2$) C, H, N.

2,4-Dimethyl-1-(3-methyl-4-nitrophenyl)imidazole[2] (**31**) and 2-acetyl-4-methyl-1-(3-methyl-4-nitrophenyl)imidazole (**32**, mp 157–159 °C. Anal. ($C_{13}H_{13}N_3O_3$) H, N; C: found, 59.7; calcd, 60.2) were prepared similarly.

1-(4-Amino-3-methylphenyl)-4-iodo-2-methylimidazole (33). Stannous chloride dihydrate (9.04 g, 40 mmol) was added portionwise to a stirred suspension of 4-iodo-1-(3-methyl-4-nitrophenyl)-2-methylimidazole (**30**, 2.75 g, 8 mmol) in absolute ethanol (50 mL) under nitrogen. After heating under reflux for 1 h, the cooled mixture was adjusted to pH 8 (2.5 M sodium hydroxide) and was extracted with chloroform (3 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica eluting with methanol–dichloromethane (1:25). The product, 1-(4-amino-3-methylphenyl)-4-iodo-2-methylimidazole (2.41 g, 96%), was characterized spectroscopically and was used without further purification.

1-(4-Amino-3-methylphenyl)-2,4-dimethylimidazole[2] (**34**) and 2-acetyl-1-(4-amino-3-methylphenyl)-4-methylimidazole 0.17-hydrate (**35**, mp 157–159 °C. Anal. ($C_{13}H_{15}N_3O \cdot 0.17\ H_2O$) C, H, N) were prepared similarly.

1-(4-Amino-3-methylphenyl)-5-iodo-2,4-dimethylimidazole (36). Silver sulfate (21.8 g, 70 mmol) and crushed iodine (35.5 g, 140 mmol) were added portionwise to a stirred solution of 1-(4-amino-3-methylphenyl)-2,4-dimethylimidazole (25.4 g, 126 mmol) in sulfuric acid (100 mL) at −10 °C. The mixture was then heated at 55 °C for 2 h, cooled, and poured onto ice (500 g). The mixture was carefully adjusted to pH 8 with ammonia solution (sp gr 0.880) and extracted with chloroform (2 × 500 mL). The combined extracts and washed with saturated sodium thiosulfate solution (200 mL), dried ($MgSO_4$), and evaporated. Trituration of the residue with ether gave 1-(4-amino-3-methylphenyl)-5-iodo-2,4-dimethylimidazole (32.25 g, 78%), which was characterized spectroscopically and was used without further purification.

1-(4-Amino-3-methylphenyl)-5-cyano-2,4-dimethylimidazole 0.33-Hydrate (37). A sample (0.33 g, 0.1 mmol) of the above product was converted by the method of route H (palladium acetate omitted) to 1-(4-amino-3-methylphenyl)-5-cyano-2,4-dimethylimidazole 0.33-hydrate (0.44 g, 60%), mp 152–156 °C. Anal. ($C_{13}H_{14}N_4 \cdot 0.33\ H_2O$) C, H, N.

5-Acetyl-1-(4-amino-3-methylphenyl)-2,4-dimethylimidazole (38). Methyllithium (1.5 M in ether, 219 mL, 328 mmol) was added dropwise to a stirred suspension of the above product (9.3 g, 41 mmol) in ether (100 mL) at −70 °C under nitrogen. The mixture was allowed to attain room temperature over 1 h and then was heated under reflux for 5 h. Water (50 mL) was added dropwise followed by hydrochloric acid (2 M, 50 mL) and the mixture was heated on a steam bath for 0.1 h. The reaction was basified to pH 9 (10% Na_2CO_3 solution) and extracted with dichloromethane (3 × 200 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with hexane–ethyl acetate (1:1 followed by 1:4). The oily product (5.6 g, 56%) was characterized spectroscopically and was used without further purification.

***trans*-1-[4-(3-Ethoxypropenamido)-3-methylphenyl]-4-iodo-2-methylimidazole (25).** A solution of *trans*-3-ethoxypropenoyl chloride (1.52 g, 1.13 mmol) in tetrahydrofuran (25 mL) was added dropwise to a stirred solution of 1-(4-amino-3-methylphenyl)-4-iodo-2-methylimidazole (2.94 g, 9.4 mmol) in anhydrous pyridine (25 mL) at −40 °C. The reaction was warmed to room temperature over 2 h, sodium carbonate solution (10%, 5 mL) was added, and the whole poured into water (50 mL) and extracted with dichloromethane (3 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with methanol–dichloromethane (1:20). The product was recrystallized from ethyl acetate to give *trans*-1-[4-(3-ethoxypropenamido)-3-methylphenyl]-4-iodo-2-methylimidazole (3.46 g, 90%), mp 172–174 °C. Anal. ($C_{16}H_{18}IN_3O_2$) C, H, N.

trans-1-[4-(3-Ethoxypropenamido)-3-methylphenyl]-2-acetyl-4-methylimidazole (**26**, mp 189–191 °C. Anal. ($C_{18}H_{21}N_3O_3$) C, H, N) and *trans*-1-[4-(3-ethoxypropenamido)-3-methylphenyl]-5-acetyl-2,4-dimethylimidazole (**27**, oil, characterized spectroscopically) were prepared similarly.

4-Iodo-2-methylimidazole (39). (a) A solution of iodine monochloride (32.5 g, 200 mmol) in dichloromethane (100 mL) was added dropwise over 1.5 h to a solution of 2-methylimidazole (8.2 g, 100 mmol) and triethylamine (20.2 g, 200 mmol) in dichloromethane (200 mL) in −70 °C under nitrogen. The reaction was stirred for 0.5 h, warmed to −30 °C, and then poured into water (200 mL). The solid product was collected and recrystallized from ethyl acetate–hexane to give 4,5-diido-2-methylimidazole (**44**, 18.5 g, 55%), which was characterized spectroscopically.

(b) *n*-Butyllithium (1.43 M in hexane, 86 mL, 123 mmol) was added dropwise to a stirred solution of the above product (20.5 g, 61 mmol) in tetrahydrofuran (300 mL) at −70 °C under nitrogen. After 0.25 h, water (20 mL) was added and the mixture warmed to room temperature over 1 h. The mixture was concentrated, water (100 mL) was added, and the solution was adjusted to pH 8 with hydrochloric acid (2 M). The aqueous phase was extracted with dichloromethane (3 × 150 mL), and then the combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica, with ethyl acetate as eluant. The solid product, 4-iodo-2-methylimidazole (9.0 g, 71%), was characterized spectroscopically.

2-Acetyl-4-methylimidazole (40). (a) 4-Methylimidazole (16.4 g, 200 mmol), triethyl orthoformate (118.4 g, 800 mmol), and *p*-toluenesulfonic acid (1.0 g) were heated at 130 °C until evolution of ethanol ceased (ca. 2 h). The volatile material was removed in vacuo and the residue was distilled under vacuum from anhydrous sodium carbonate to give 1-(diethoxymethyl)-4-methylimidazole (22.06 g, 60%), bp 126–130 °C (5 mm), which was characterized spectroscopically.

(b) *n*-Butyllithium (1.43 M in hexane, 7.7 mL, 11 mmol) was added dropwise to a stirred solution of the above product (1.84 g, 10 mmol) in tetrahydrofuran (50 mL) at −40 °C under nitrogen. After 0.5 h, *N*,*N*-dimethylacetamide (1.11 mL, 12 mmol) was

added, and the solution was warmed to room temperature and stirred for 16 h. The mixture was poured into 2 M hydrochloric acid (50 mL) and was washed with dichloromethane (2 × 50 mL). The aqueous phase was basified with sodium carbonate sodium (10%) and was extracted with dichloromethane (4 × 40 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica with ethyl acetate as eluant to give 2-acetyl-4-methylimidazole (0.47 g, 38%) mp 113–115 °C. Anal. ($C_6H_8N_2O$) 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 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. 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

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

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.[15] 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 and 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 2) by plotting percentage increases in dP/dt_{max} against absolute increases in heart rate. Compounds were tested in two to four dogs and dose ranges employed were 10–1200 μg (**16**), 5–1200 μg (**17**), and 50–500 ng (isoprenaline) Figure 2 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.[16,17] 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 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 milliseconds 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 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 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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Supplementary Material Available: NMR data are available for compounds **2–4**, **6–9**, **13**, **15**, and **17** (1 page). Ordering information is given on any current masthead page.

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