15d, 107601-08-1; 15e, 115913-89-8; 15f, 115913-90-1; 16a, 118-00-3; 17, 115913-81-0; 18, 69370-84-9; 4-$(NO_2)C_6H_4CH_2CH_2OH$, 100-27-6; 4-MeC_6H_4SH, 106-45-6; 5′-*O*-trityl-3′-azido-2′,3′-dideoxyuridine, 84472-84-4; 5′-*O*-trityl-3′-azido-2′,3′-dideoxythymidine, 29706-84-1; 1-(3-cyano-3-deoxy-5-*O*-trityl-β-D-arabinofuranosyl)thymine, 115941-56-5; N^2,5′-*O*-bis(monomethoxytrityl)-2′-deoxyguanosine, 84870-95-1; 5′-*O*-(monomethoxytrityl)-3′-*O*-[phenoxy(thiocarbonyl)]-2′-deoxythymidine, 115913-91-2.

2(1*H*)-Quinolinones with Cardiac Stimulant Activity. 1. Synthesis and Biological Activities of (Six-Membered Heteroaryl)-Substituted Derivatives

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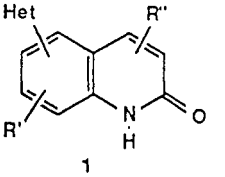
A series of (six-membered heteroaryl)-substituted 2(1*H*)-quinolinones (1) was synthesized, and structure–activity relationships for cardiac stimulant activity were determined. Most compounds were prepared by acidic hydrolysis of a heteroaryl-2-methoxyquinoline obtained by palladium-catalyzed cross-coupling methodology. Direct reaction of a pyridinylzinc reagent with a 6-haloquinolinone also proved successful. In anesthetized dogs, 6-pyridin-3-yl-2(1*H*)-quinolinone (**3**; 50 μg/kg) displayed greater inotropic activity (percentage increase in d*P*/d*t* max) than positional isomers (**2**, **4**–**6**), and potency was maintained with either mono- (**13**, **15**) or di- (**16**) alkylpyridinyl substituents. Introduction of a 4- (**24**) or 7- (**25**) methyl group into **3** reduced inotropic activity, whereas the 8-isomer (**26**) proved to be the most potent member of the series. Compound **26** and the 2,6-dimethylpyridinyl analogue (**27**) were approximately 6 and 3 times more potent than milrinone. Several quinolinones displayed positive inotropic activity (decrease in QA interval) in conscious dogs after oral administration (1 mg/kg), and **26**, **27** were again the most potent members of the series. Compound **27** (0.25, 0.5, 1.0 mg/kg po) demonstrated dose-related cardiac stimulant activity, which was maintained for at least 4 h. No changes in heart rate were observed. Compounds **3**, **4**, **26**, and **27** also selectively stimulated the force of contraction, rather than heart rate, in the dog heart–lung preparation. For a 50% increase in d*P*/d*t* max with **27**, heart rate changed by less than 10 beats/min. In norepinephrine contracted rabbit femoral artery and saphenous vein, **27** produced dose related (5×10^{-7} to 5×10^{-4} M) vasorelaxant activity. The combined cardiac stimulant and vasodilator properties displayed by **27**, coupled with a lack of effect on heart rate, should be beneficial for the treatment of congestive heart failure.

Congestive heart failure (CHF) is a major health problem[1] of increasing incidence, due to an aging population and improved treatment of other cardiovascular disorders.[2] Current therapy for CHF relies heavily on digitalis, diuretics, and vasodilators, but annual mortality rates between 30 and 50% are still commonly observed.[3] Consequently, there is strong clinical demand for improved agents, particularly those that correct the major hemodynamic derangements characteristic of CHF.[4] Over the last few years, a variety of novel inodilator agents have been described,[5] and clinical evaluation of several of these drugs is currently in progress.[6-8] Although these compounds belong to several diverse chemical series,[5] two common structural features appear to be important for inodilator activity—a cyclic carboxamide function and an appropriately positioned heteroaromatic system. These individual pharmacophores can also be expressed in the 2(1*H*)-quinolinone system (1) where a high degree of



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conformational constraint allows an accurate assessment of the optimum location of the carboxamide and heterocyclic moieties. Moreover, since the overall topography of series **1** is subtly different from milrinone and CI-930, for example, then a modified pharmacological/pharmacodynamic profile might also be expected. This paper describes our initial studies with a novel series of 2-(1*H*)-quinolinones substituted with various six-membered heteroaryl systems.[9] These compounds display marked cardiac stimulant activity, with little effect on heart rate, and may be useful for the treatment of CHF.

Chemistry. The heteroaryl 2-methoxyquinoline intermediates (Table III) required for the preparation of most of the various mono- and disubstituted 2(1*H*)-quinolinones listed in Tables I and II were synthesized following routes A, B, and C outlined in Scheme I.[10] Thus,

(1) Gillum, R. F. *Am. Heart J.* **1987**, *113*, 1043.
(2) (a) Likoff, M. J.; Spielman, S. R. *Cardiovasc. Rev. Rep.* **1985**, *6*, 1306. (b) Furberg, C. D.; Yusuf, S.; Thom, T. *J. Am. J. Cardiol.* **1985**, *55*, 45A.
(3) (a) Applefield, M. M. *Am. J. Med.* **1986**, *80* (Suppl. 2B), 73. (b) Massie, B. M.; Conway, M. *Circulation* **1987**, *75* (Suppl. IV), 11.
(4) (a) Colucci, W. S.; Wright, R. F.; Braunwald, E. *N. Engl. J. Med.* **1986**, *314*, 290. (b) Colucci, W. S.; Wright, R. F.; Braunwald, E. *N. Engl. J. Med.* **1986**, *314*, 349.
(5) For a recent review: Taylor, M. D.; Sircar, I.; Steffen, R. P. *Annu. Rep. Med. Chem.* **1987**, *22*, 85.
(6) Weber, K. T.; Ed. *Am. J. Cardiol.* **1987**, *60*, 1c.
(7) Murali, S.; Uretsky, B. F.; Valdes, A. N.; Kolesar, J. A.; Sudhakar Reddy, P. *Am. J. Cardiol.* **1987**, *59*, 1356.
(8) 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.
(9) For synthesis and in vitro studies on related derivatives: (a) Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1986**, *29*, 2427. (b) Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1986**, *29*, 2433. (c) Decker, N.; Grima, M.; Velly, J.; Marciniak, G.; Leclerc, G.; Schwartz, J. *Arzneim. Forsch.* **1987**, *37*, 1108.
(10) Campbell, S. F.; Roberts, D. A. European Patent 148,623, 1985; *Chem. Abstr.* **1986**, *104*, 19525.

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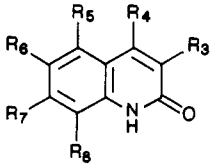
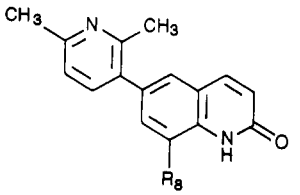
Table I. Synthetic Routes and Physicochemical Data for Heterocyclic-Substituted Quinolinone Derivatives (1)



no.	R_3	R_4	R_5	R_6	R_7	R_8	route	mp, °C	formula	anal.
2	H	H	H	pyridin-2-yl	H	H	A	258–260	$C_{14}H_{10}N_2O$	C,[a] H, N
3	H	H	H	pyridin-3-yl	H	H	B	315–318	$C_{14}H_{10}N_2O$·HCl	C, H, N
4	H	H	H	pyridin-4-yl	H	H	A	>315	$C_{14}H_{10}N_2O$·HCl	C, H, N
5	H	H	pyridin-3-yl	H	H	H	A	259–261	$C_{14}H_{10}N_2O$	C, H, N
6	H	H	H	H	pyridin-3-yl	H	A	237–239	$C_{14}H_{10}N_2O$	C, H, N
7	H	H	H	pyrimidin-2-yl	H	H	A	>310	$C_{13}H_9N_3O$	C, H, N
8	H	H	H	pyrimidin-4-yl	H	H	C	>310	$C_{13}H_9N_3O$	C, H, N
9	H	H	H	pyrimidin-5-yl	H	H	A	289–291	$C_{13}H_9N_3O$	C, H, N
10	H	H	H	pyridazin-3-yl	H	H	C	>310	$C_{13}H_9N_3O$	C,[b] H, N[c]
11	H	H	H	pyridazin-4-yl	H	H	C	285–287	$C_{13}H_9N_3O$	C, H, N
12	H	H	H	pyrazin-2-yl	H	H	C	287–289	$C_{13}H_9N_3O$	C, H, N
13	H	H	H	2-methylpyridin-3-yl	H	H	A	293–296	$C_{15}H_{12}N_2O$	C, H, N
14	H	H	H	4-methylpyridin-3-yl	H	H	A	236–237	$C_{15}H_{12}N_2O$·0.1H_2O	C, H, N
15	H	H	H	2-methylpyridin-5-yl	H	H	A	282–284	$C_{15}H_{12}N_2O$	C, H, N
16	H	H	H	2,6-dimethylpyridin-3-yl	H	H	A	280–283	$C_{16}H_{14}N_2O$·0.5H_2O	C, H, N
17	H	H	H	2-aminopyridin-5-yl	H	H	A	>300	$C_{14}H_{11}N_3O$·HCl·0.5H_2O	C, H, N
18	H	H	H	2-methoxypyridin-5-yl	H	H	D	248–252	$C_{15}H_{12}N_2O_2$	C, H, N
19	dihydro		H	pyridin-3-yl	H	H	D	180	$C_{14}H_{12}N_2O$	C, H, N
20	dihydro		H	2,6-dimethylpyridin-3-yl	H	H	E	213–215	$C_{16}H_{16}N_2O$·0.5H_2O	C, H, N
21	CN	H	H	pyridin-3-yl	H	H	B	>355	$C_{15}H_9N_3O$·0.2H_2O	C, H, N
22	NO_2	H	H	pyridin-3-yl	H	H	D	338–340	$C_{14}H_9N_3O_3$·0.5H_2O	C, H, N
23	NH_2	H	H	pyridin-3-yl	H	H	F	298–300	$C_{14}H_{11}N_3O$·0.66H_2O	C, H, N
24	H	CH_3	H	pyridin-3-yl	H	H	D	272	$C_{15}H_{12}N_2O$	C, H, N
25	H	H	H	pyridin-3-yl	CH_3	H	A	249–251	$C_{15}H_{12}N_2O$	C, H, N
26	H	H	H	pyridin-3-yl	H	CH_3	A	236–237	$C_{15}H_{12}N_2O$	C, H, N

[a] C: calcd, 75.7; found, 74.8. [b] C: calcd, 64.7; found, 65.2. [c] N: calcd, 17.4; found, 16.9.

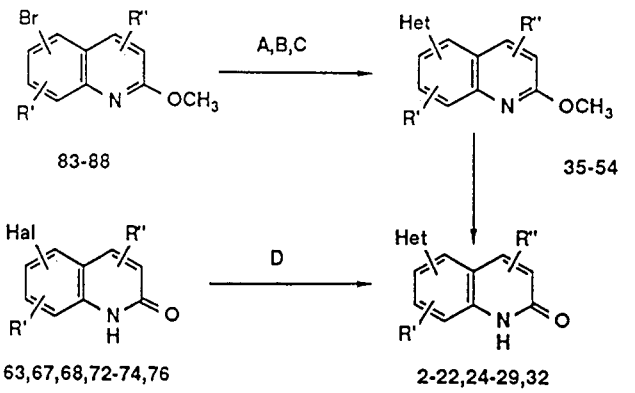
Table II. Synthetic Routes and Physicochemical Data for 8-Substituted 6-(2,6-Dimethylpyridin-3-yl)-2(1*H*)-quinolinone Derivatives



no.	R_8	route	mp, °C	formula	anal.
27	CH_3	A	256–259	$C_{17}H_{16}N_2O$	C, H, N
28	C_2H_5	D	202–204	$C_{18}H_{18}N_2O$	C, H, N
29	*i*-C_3H_7	D	188–192	$C_{19}H_{20}N_2O$	C, H, N
30	Br	G	212–215	$C_{16}H_{13}BrN_2O$	C, H, N
31	SCH_3	H	147–149	$C_{17}H_{16}N_2OS$·0.25H_2O	C, H, N
32	OCH_3	D	203–205	$C_{17}H_{16}N_2O_2$	C, H, N
33	OH	I	276–277	$C_{16}H_{14}N_2O_2$	C, H, N

treatment of a 2-methoxybromoquinoline (**83–87**) with 2 equiv of *tert*-butyllithium at −78 °C followed by addition of anhydrous zinc chloride provided the corresponding quinolinylzinc reagent. This was then coupled with an appropriate bromo heterocycle in the presence of tetrakis(triphenylphosphine)palladium as catalyst[11] to give **35, 37–40, 42, 46–53** (route A). In a complementary approach, a pyridin-3-ylzinc reagent was coupled with a 6-bromo-2-methoxyquinoline (**83, 88**) to give **36, 54** (route B). Alternatively, reaction of a (2-methoxyquinolin-6-yl)lithium reagent with a diazine followed by oxidation of the dihydro

Scheme I



intermediate[12] provided **41, 43–45** (route C). Acidic hydrolysis of these methoxyquinolines from routes A–C then gave the 2(1*H*)-quinolinone derivatives **2–17, 21, 25–27**.

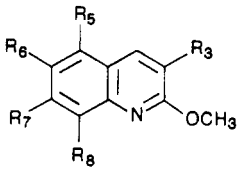
In some cases (**18, 19, 22, 24, 28, 29, 32**), direct reaction of a pyridinylzinc species with a 6-bromo- or 6-iodoquinolinone (**63, 67, 68, 72–74, 76**) was also successful[13] (route D). For these examples, 2 equiv of the pyridinylzinc reagent are required, presumably due to initial N-1 deprotonation. Moreover, since the quinolinone system is now deactivated toward cross-coupling, iodoquinolinones are preferred, since yields are higher and reaction times shorter. Under these conditions, conversion of **72, 73** to **28, 29** proceeded in over 90% yield, whereas a recent report of a similar reaction starting with 3-bromo-2(1*H*)-quinolinone gave the 3-pyridinyl derivative with only 2% conversion.[9]

(11) For related arylations of pyridine derivatives: (a) Yamamoto, Y.; Azuma, Y.; Mitoh, H. *Synthesis* **1986**, 564. (b) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936. (c) Negishi, E.; Luo, F. T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117.

(12) Van der Stoel, R. E.; Van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 116.

(13) Bell, A. S.; Roberts, D. A.; Ruddock, K. S. *Synthesis* **1987**, 843.

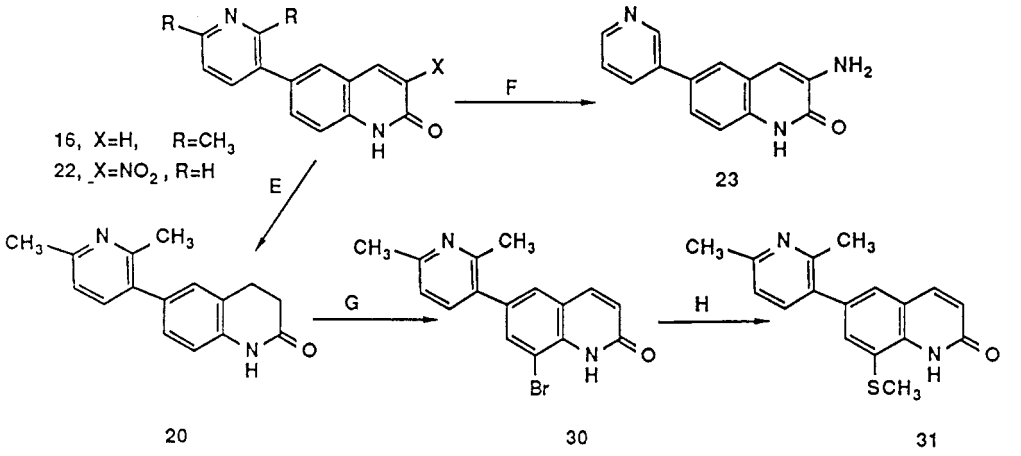
Table III. Physicochemical Data for Heteroaryl-Substituted 2-Methoxyquinoline Intermediates for Routes A–C



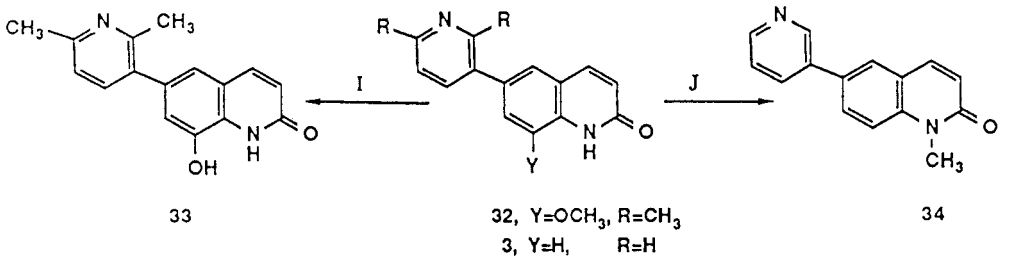
no.	R_3	R_5	R_6	R_7	R_8	mp, °C	formula	anal.
35	H	H	pyridin-2-yl	H	H	83–84	$C_{15}H_{12}N_2O$	C, H, N
36	H	H	pyridin-3-yl	H	H	93–94	$C_{15}H_{12}N_2O$	C, H, N
37[a]	H	H	pyridin-4-yl	H	H	114–115	$C_{15}H_{12}N_2O$	
38	H	pyridin-3-yl	H	H	H	74–76	$C_{15}H_{12}N_2O$	C, H, N
39	H	H	H	pyridin-3-yl	H	79–81	$C_{15}H_{12}N_2O{\cdot}0.1H_2O$	C, H, N
40	H	H	pyrimidin-2-yl	H	H	139–140	$C_{14}H_{11}N_3O$	C, H, N
41	H	H	pyrimidin-4-yl	H	H	164–165	$C_{14}H_{11}N_3O$	C, H, N
42	H	H	pyrimidin-5-yl	H	H	165–168	$C_{14}H_{11}N_3O$	C, H, N
43	H	H	pyridazin-3-yl	H	H	186–187	$C_{14}H_{11}N_3O$	C, H, N
44	H	H	pyridazin-4-yl	H	H	162–163	$C_{14}H_{11}N_3O$	C, H, N
45	H	H	pyrazin-2-yl	H	H	130–132	$C_{14}H_{11}N_3O$	C, H, N
46	H	H	2-methylpyridin-3-yl	H	H	99–101	$C_{16}H_{14}N_2O$	C, H, N
47[a]	H	H	4-methylpyridin-3-yl	H	H	oil	$C_{16}H_{14}N_2O$	
48	H	H	2-methylpyridin-5-yl	H	H	101–103	$C_{16}H_{14}N_2O$	C, H, N
49	H	H	2,6-dimethylpyridin-3-yl	H	H	88–90	$C_{17}H_{16}N_2O$	C, H, N
50	H	H	2-aminopyridin-5-yl	H	H	182–183	$C_{15}H_{13}N_3O$	C, H, N
51	H	H	pyridin-3-yl	CH_3	H	61–63	$C_{16}H_{14}N_2O$	C, H, N
52	H	H	pyridin-3-yl	H	CH_3	117–119	$C_{16}H_{14}N_2O$	C, H, N
53	H	H	2,6-dimethylpyridin-3-yl	H	CH_3	74–76	$C_{18}H_{18}N_2O{\cdot}0.33H_2O$	C, H, N
54[a]	CN	H	pyridin-3-yl	H	H	233–234	$C_{16}H_{11}N_3O$	

[a] Characterized spectroscopically.

Scheme II



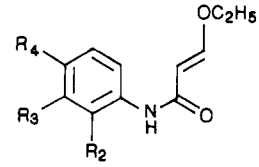
Scheme III



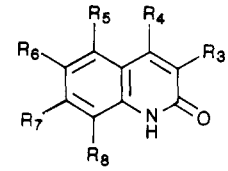
Several of the quinolinones (1) proved amenable to further chemical transformation (Schemes II and III). Catalytic hydrogenation of **16** over palladium gave **20** (route E), while stannous chloride reduction of the 3-nitroquinolinone (**22**) gave **23** (route F). Attempted 8-bromination of **16** to furnish **30** proved unsuccessful presumably due to a preferential addition–elimination sequence, which led to the 3-bromo derivative. However, bromination of **20** (Br_2/Ag_2SO_4) followed by re-aromatization (Br_2/NaOAc) provided an alternative approach to **30** (route G). Further treatment of **30** with sodium methanethiolate in the presence of cuprous iodide as catalyst gave **31** (route H). Demethylation of the 8-methoxyquinolinone (**32**) with 48% HBr gave the phenol (**33**) (route I) and alkylation of **3** with sodium hydride/dimethyl sulfate gave **34** (route J).

Most of the intermediates used in the preparation of the various quinolinones (1) are listed in Table IV, and syntheses are summarized in Scheme IV. Acylation of an appropriately substituted haloaniline (**55**) with *trans*-3-ethoxy-2-propenoyl chloride[14] provided **56–62**, which could be cyclized to quinolinones (**63**, **65**, **66**, **69–74**) on treatment

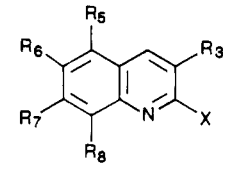
Table IV. Physicochemical Data for Intermediates Used in Routes A–D



no.	R_2	R_3	R_4	mp, °C	formula	anal.
56	H	H	I	181–182	$C_{11}H_{12}INO_2$	
57	H	Br	H	98–100	$C_{11}H_{12}BrNO_2$	C, H, N
58	H	CH_3	Br	112–115	$C_{12}H_{14}BrNO_2$	C, H, N
59	CH_3	H	Br	163–164	$C_{12}H_{14}BrNO_2$	C, H, N
60	C_2H_5	H	I	197–199	$C_{13}H_{16}INO_2$	C, H, N
61	*i*-C_3H_7	H	I	161–163	$C_{14}H_{18}INO_2$	C, H, N
62	OCH_3	H	Br	133–136	$C_{12}H_{14}BrNO_3$	C, H, N



no.	R_3	R_4	R_5	R_6	R_7	R_8	mp, °C	formula	anal.
63	H	H	H	I	H	H	260–263	C_9H_6INO	C, H, N
64[25]	H	H	H	Br	H	H	255–263	C_9H_6BrNO	C,[a] H, N
65	H	H	Br	H	H	H	251–260	C_9H_6BrNO	C, H, N
66	H	H	H	H	Br	H			
67[26]	dihydro		H	Br	H	H	170	C_9H_8BrNO	C, H, N
68[27]	H	CH_3	H	I	H	H	290	$C_{10}H_8INO \cdot 0.5H_2O$	C, H, N
69	H	H	H	Br	CH_3	H		$C_{10}H_8BrNO$	
70	H	H	CH_3	Br	H	H			
71	H	H	H	Br	H	CH_3	272–274	$C_{10}H_8BrNO$	C, H, N
72	H	H	H	I	H	C_2H_5	237–239	$C_{11}H_{10}INO$	C, H, N
73	H	H	H	I	H	$CH(CH_3)_2$	189–192	$C_{12}H_{12}INO$	C, H, N
74	H	H	H	Br	H	OCH_3	167–170	$C_{10}H_8BrNO_2$	C, H, N
75	CN	H	H	Br	H	H	308–311	$C_{10}H_5BrN_2O$	C, H, N
76	NO_2	H	H	I	H	H	279–282	$C_9H_5IN_2O_3$	C, H, N



no.	R_3	R_5	R_6	R_7	R_8	X	mp, °C	formula	anal.
77	H	H	Br	H	H	Cl	157	$C_9H_5BrClN \cdot 0.5H_2O$	C, H, N
78	H	Br	H	H	H	Cl	76–78	C_9H_5BrClN	C, H, N
79	H	H	H	Br	H	Cl	115–116	C_9H_5BrClN	C, H, N
80	H	H	Br	CH_3	H	Cl	121–123	$C_{10}H_7BrClN$	C, H, N
81	H	H	Br	H	CH_3	Cl	114–116	$C_{10}H_7BrClN$	C, H, N
82	CN	H	Br	H	H	Cl	228–230	$C_{10}H_4BrClN_2$	C, H, N
83	H	H	Br	H	H	OCH_3	92	$C_{10}H_8BrNO$	C, H, N
84	H	Br	H	H	H	OCH_3	86–87	$C_{10}H_8BrNO$	C, H, N
85	H	H	H	Br	H	OCH_3	71–72	$C_{10}H_8BrNO$	C, H, N
86	H	H	Br	CH_3	H	OCH_3	71–74	$C_{11}H_{10}BrNO$	C, H, N
87	H	H	Br	H	CH_3	OCH_3	89–91	$C_{11}H_{10}BrNO$	C, H, N
88	CN	H	Br	H	H	OCH_3	172–174	$C_{11}H_7BrN_2O$	C, H, N

[a] C: calcd, 48.2; found, 50.1

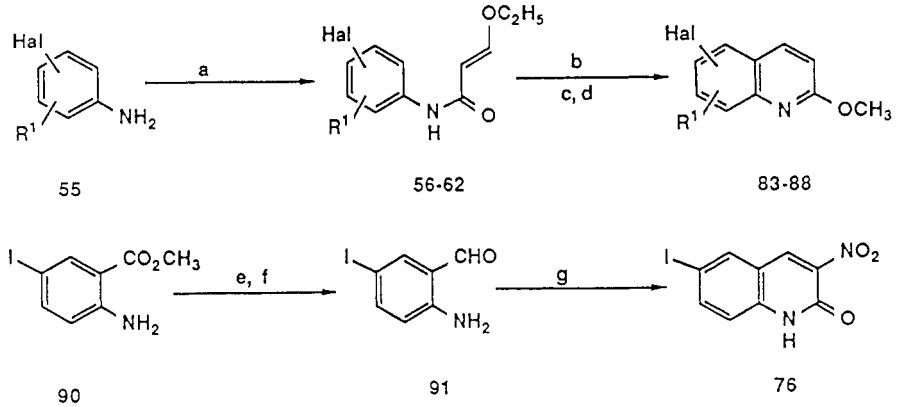
with concentrated sulfuric acid. Some quinolinones (**63**, **67**, **68**, **72–74**, **76**), were used directly in route D while others, **64–66**, **69–71**, **75**, were reacted with phosphorus oxychloride to give the 2-chloroquinolines (**77–82**). Treatment with sodium methoxide in methanol then provided the 2-methoxyquinolines (**83–88**) for routes A–C. Cyclization of propenamides (**57**, **58**) gave the isomer pairs **65**, **66** and **69**, **70**, which could not be separated directly. However, transformation to the corresponding chloroquinolines followed by HPLC purification provided pure samples of **78**, **79**, while fractional crystallization from ether gave **80**.

Regioselective 6-bromination of 3-cyano-2(1*H*)-quinolinone (**89**) gave **75** directly. Conversion of **90** to **76** could be achieved by treatment with diisobutylaluminum hydride followed by manganese dioxide oxidation and subsequent condensation of **91** with ethyl nitroacetate in the presence of piperidine.

Structure–Activity Relationships (SARs) for Inotropic Activity. All of the compounds in Tables I and II (except **12**, which proved to be insoluble) were administered intravenously to instrumented, anesthetized dogs, and changes in cardiac contractility (dP/dt max), blood

(14) Effenberger, F.; Hartmann, W. *Chem. Ber.* **1969**, *102*, 3260.

Scheme IV[a]



[a] Reagents: (a) $C_2H_5OCH{=}CHCOCl$; (b) H_2SO_4; (c) $POCl_3$; (d) $NaOCH_3/CH_3OH$; (e) $(i\text{-}Bu)_2AlH$; (f) MnO_2; (g) $NO_2CH_2CO_2C_2H_5$/piperidine.

Table V. Inotropic Activity for Quinolinone Derivatives (1) following Intravenous and Oral Administration to Dogs

no.	% increase in dP/dt max[a] dose: 50 μg/kg iv	relative inotropic potency[b]	decrease in QA interval,[c] ms ± SEM dose: 1 mg/kg po 1 h	3 h
2	62[d]	0.3	2[e] ± 1	1[e] ± 2
3	54	1.3	14 ± 1	7 ± 1
4	51	0.9	13 ± 3	8 ± 3
5	44	0.9	9 ± 4	4 ± 2
6	6	0.2		
7	28	0.7	4 ± 1	4 ± 1
8	38	1.2	6 ± 1	2 ± 1
9	44	1.1	3 ± 2	1 ± 2
10	32	0.7	8 ± 3	5 ± 2
11	43	1.3		
13	74	1.7		
14	21	1.3		
15	46	1.3		
16	37	1.4	6 ± 2	5 ± 2
17	30	0.8		
18	11	0.3		
19	41	1.1	10 ± 2	7 ± 1
20	32	0.8		
21	46	0.9		
22	39	0.6		
23	63	0.9		
24	39	0.7		
25	51[d]	0.2		
26	112[f]	9.0	16[g] + 3	20[g] + 3
27	43[f]	4.3	21 ± 2	19 ± 2
28	35	1.0		
29	16	0.4		
30	41	0.7		
31	20	0.5		
32	11	0.4		
33	19	<0.1		
milrinone	46[h]	1.6	13[i] ± 4	7[i] + 3
enoximone	32[d]	0.013		

[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). [d] 250 μg/kg. [e] 2 mg/kg. [f] 12.5 μg/kg. [g] 0.5 mg/kg. [h] 25 μg/kg. [i] 0.25 mg/kg.

pressure, and heart rate were recorded. In these acute experiments, none of the compounds tested had any significant effects on these latter two parameters, and these data are not presented in this paper. Changes in cardiac contractility are expressed as absolute percentage increases in dP/dt max and also as inotropic potencies relative to the response observed in the same animal with 4-[4-[2-(1,1-dioxo-2-isothiazolidinyl)ethyl]-1-piperidinyl]-6,7-dimethoxyquinazoline[15] (Table V). This protocol allows rapid establishment of preliminary SARs for inotropic activity, since use of a standard agent compensates for interanimal variation, particularly as compounds were evaluated over several months. Data for milrinone and enoximone are also presented in Table V for comparison.

Comparison of the inotropic activities of the isomeric pyridinyl-2(1*H*)-quinolinones (**2–6**) shows that incorporation of a pyridin-3-yl system at the 6-position is preferred over the isomeric structures. Alternative diazaheterocyclic systems (**8, 9, 11**) demonstrated similar inotropic activity, but none proved superior to **3**, which provided a convenient starting point for more detailed SAR studies. Incorporation of either mono- (**13–15**) or di- (**16**) alkyl substituents into the pyridinyl moiety maintained inotropic activity, but amino (**17**) or methoxy (**18**) groups were less favored. Saturation of the quinolinone 3,4-double bond was not beneficial (**19, 20**) nor was the introduction of electron-withdrawing (**21, 22**) or donating (**23**) groups at the 3-position. Incorporation of a 4- (**24**) or 7- (**25**) alkyl substituent reduced inotropic activity, whereas the 8-methyl isomer (**26**) proved to be the most potent member of the series. Activity was halved with the lutidine analogue (**27**), but even so **26, 27** still proved to be approximately 6 and 3 times more potent than milrinone. In this test system, enoximone showed only weak activity.

In view of the above results, SARs for the quinolinone 8-substituent were examined in some detail. However, elaboration of the alkyl function was detrimental (**28, 29**), as was the introduction of a variety of alternative substituents (**30–33**). In contrast to previous reports,[9] these studies highlight both the particularly beneficial effects of an 8-methyl substituent on inotropic activity and the limited steric tolerance at this position for alternative functions. These observations may support an important role for the quinolinone carboxamido function in receptor/enzyme affinity, which can be disrupted by unfavorable peri interactions between the NH unit and large 8-substituents (**29–32**) or by intramolecular hydrogen bonding (**33**). The importance of the 2(1*H*)-quinolinone system is further underlined by the weak inotropic activity displayed by the *N*-methyl derivative (**34**) or the methoxy intermediates in Table III (data not presented). Physicochemical measurements[16] gave pK_as of 6.30 and 12.50

(15) This compound has recently undergone clinical evaluation for the treatment of CHF and provides a convenient standard for relating inotropic potency in dogs to effective dose levels in humans.

(16) pK_a values were determined by spectrometry.

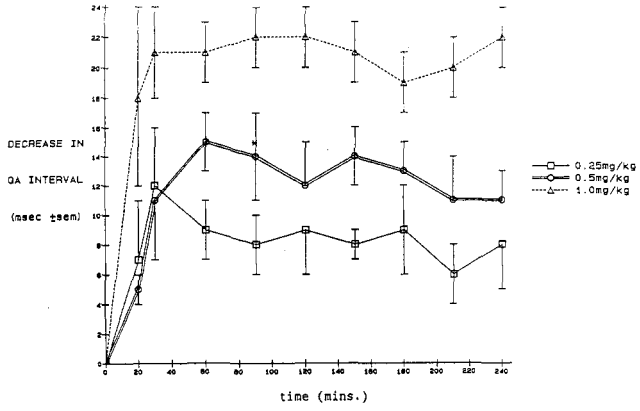


Figure 1. Effects of **27** on QA interval in conscious dogs (n = 4) following oral administration.

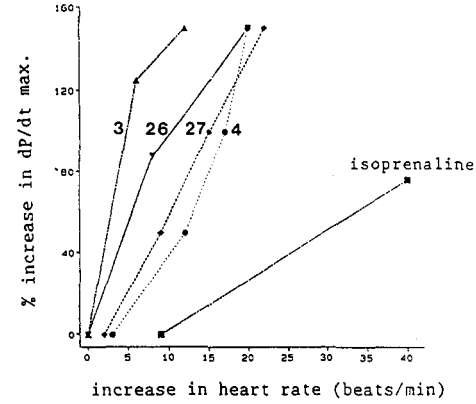


Figure 2. Effects of **3**, **4**, **26**, **27**, and isoprenaline on contractile force and heart rate in the dog heart–lung preparation (for dose levels, see the Experimental Section).

for **27**, confirming that neither protonation of the pyridine nitrogen nor ionization of the carboxamido moiety would be favored at physiological pH.

Following these preliminary SAR studies, selected quinolinone derivatives were evaluated in conscious dogs for effects on cardiac contractility (decrease in QA interval, see the Experimental Section) following oral administration (Table V). (These observed changes in QA interval are considered to reflect direct, positive inotropic effects since no increases in heart rate were detected. By contrast, under the same protocol a reflex tachycardia consistently accompanies the indirect, positive inotropic stimulation produced by arteriolar vasodilators.) Compound **2** showed poor activity, but this could be improved in the isomeric pyridine systems (**3–5**), although not with the diaza derivatives (**7–10**). At a higher dose (4 mg/kg), **7** still showed only weak activity (maximum decreases in QA interval, ca. 7 ms at 1 and 3 h post dose) but with a longer duration of action. Saturation of the quinolinone 3,4-double bond in **3** slightly reduced potency (**19**). A marked improvement in inotropic potency was noted with **26**, and activity was sustained at the 3-h timepoint, even at the lower dose level of 0.5 mg/kg. Combination of an 8-methyl substituent with a 6-lutidine moiety was also beneficial (**27**), and with this compound, marked increases in cardiac contractility were also maintained over the whole test period. More extensive studies were undertaken with **27** (Figure 1), and dose-related positive inotropism was observed following administration at 0.25, 0.5, and 1 mg/kg. The duration of action was consistently superior to milrinone (Table V), and effects were well maintained for at least 4 h after each dose. It is also important to note that, even with such obvious cardiac stimulation (a decrease in QA interval of 20 ms corresponds approximately to a 70% increase in dP/dt max), heart rate barely changed (data not shown). Such a profile is particularly appropriate for the treatment of CHF patients since excessive increases in myocardial oxygen consumption should be avoided. Moreover, **27** also relaxes both arterial and venous smooth muscle,[17] which is expected to be beneficial in reducing elevated pre- and afterload, which are characteristic hemodynamic derangements in CHF patients.

In order to confirm the marked selectivity for increasing cardiac contractility, but not heart rate, observed in the whole animal, **3**, **4**, **26**, and **27** were evaluated in the Starling dog heart–lung preparation where direct effects on these parameters can be determined in the absence of reflex sympathetic activation. By comparison with isoprenaline, all four quinolinones demonstrated a clear propensity for stimulation of cardiac contractile force rather than heart rate (Figure 2). For example, for a 50% increase in dP/dt max with **27**, heart rate changed by less than 10 beats/min.

In summary, this paper describes a novel series of 2-(1*H*)-quinolinone derivatives which produce marked positive inotropic activity in dogs after both intravenous and oral administration. Combination of an 8-methyl and 6-lutidine substituent appears to be particularly beneficial, both for inotropic potency and duration of action. These compounds (**1**) show a marked selectivity for stimulating the force of contraction rather than heart rate, and direct vasodilator activity is also displayed. Such a profile should be particularly appropriate for the treatment of CHF patients.

Experimental Section

Chemistry. Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. Spectroscopic data for all compounds were recorded on Perkin-Elmer 257 (IR), AEI MS 12 or VG 7070F (MS), and Perkin-Elmer R12B, 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. 8-Methyl-6-pyridin-3-yl-2(1*H*)-quinolinone (26). (a) *tert*-Butyllithium (8 mL of a 2 M solution in pentane, 16 mmol) was added dropwise to a stirred solution of 6-bromo-2-methoxy-8-methylquinoline (2.0 g, 8 mmol) in THF (20 mL) at −70 °C under nitrogen. After 0.17 h, the mixture was treated with a solution of anhydrous zinc chloride (1.09 g, 8 mmol) in THF (10 mL), and the resulting solution was warmed to 0 °C. A solution containing 3-bromopyridine (0.76 mL, 8 mmol) and tetrakis(triphenylphosphine)palladium (0.05 g, 0.04 mmol) in THF (10 mL) was then added, and the mixture was heated under reflux for 2 h. The reaction mixture was cooled, concentrated, and treated with chloroform (100 mL), and a solution of ethylenediaminetetraacetic acid disodium salt dihydrate (6.0 g, 16.1 mmol) in water (100 mL). The aqueous phase was further extracted with chloroform (3 × 50 mL). The combined, dried ($MgSO_4$) extracts were concentrated, and the oily residue chromatographed on silica, eluting with ethyl acetate. The solid product was recrystallized from hexane to afford 2-methoxy-8-methyl-6-pyridin-3-ylquinoline (**52**) (1.12 g, 56%), mp 117–119 °C. Anal. ($C_{16}H_{14}N_2O$) C, H, N.

For the preparation of **50**, 2 equiv of the quinolinylzinc reagent were required.

(b) A stirred solution of the above product (1.07 g 4.3 mmol) in hydrochloric acid (6 M, 10 mL) was heated under reflux for 2.5 h. The cooled solution was basified to pH 9 (2 M NaOH), extracted with chloroform–methanol (9:1, 4 × 100 mL); then, the combined extracts were dried ($MgSO_4$) and evaporated. The solid

(17) Compound **27** produces dose related (5×10^{-7} to 5×10^{-4} M) relaxation of norepinephrine contracted rabbit femoral artery and saphenous vein.

product was recrystallized from ethyl acetate–methanol to give 8-methyl-6-pyridin-3-yl-2(1*H*)-quinolinone (0.63 g, 62%), mp 236–237 °C. Anal. ($C_{15}H_{12}N_2O$), C, H, N.

Route B. 6-Pyridin-3-yl-2(1*H*)-quinolinone Hydrochloride (3). (a) *tert*-Butyllithium (8.8 mL of a 1.7 M solution in pentane, 15 mmol) was added dropwise to a stirred solution of 3-bromopyridine (0.73 mL, 7.5 mmol) in THF (15 mL) at <–90 °C under nitrogen. After being stirred for 0.17 h, a solution of anhydrous zinc chloride (1.03 g, 7.5 mmol) in THF (12 mL) was added slowly, and the mixture was allowed to warm to 0 °C over 0.17 h. 2-Methoxy-6-bromoquinoline (1.17 g, 5 mmol) and tetrakis(triphenylphosphine)palladium (0.04 g, 0.035 mmol) were added in one portion, and the mixture was heated under reflux for 6 h. The reaction mixture was cooled, poured into a solution of ethylenediaminetetraacetic acid disodium salt dihydrate (5.60 g, 15 mmol) in water (100 mL), and basified to pH 9 (2 M NaOH), and the aqueous phase extracted with dichloromethane (3 × 80 mL). The dried ($MgSO_4$) extracts were evaporated, and the solid residue was chromatographed on silica, eluting with ethyl acetate–hexane (1:1). The product was recrystallized from hexane to afford 2-methoxy-6-pyridin-3-ylquinoline (**36**) (0.34 g, 29%), mp 93–94 °C. Anal. ($C_{15}H_{12}N_2O$) C, H, N.

(b) A stirred solution of 2-methoxy-6-pyridin-3-ylquinoline (0.25 g, 1.06 mmol) in hydrochloric acid (6 M, 7 mL) was heated under reflux for 4.5 h. The cooled solution was concentrated, and the solid residue was recrystallized from methanol to provide 6-pyridin-3-yl-2(1*H*)-quinolinone hydrochloride (0.195 g, 71%), mp 315–318 °C. Anal. ($C_{14}H_{10}N_2O$·HCl) C, H, N.

Route C. 6-Pyrimidin-4-yl-2(1*H*)-quinolinone 0.25-Hydrate (8). (a) *n*-Butyllithium (2.7 mL of a 1.5 M solution in hexane, 4 mmol) was added dropwise to a stirred suspension of 2-methoxy-6-bromoquinoline (0.95 g, 4 mmol) in ether (5 mL) at –70 °C under nitrogen. When all the solid material had dissolved, a solution of pyrimidine (0.32 g, 4 mmol) in ether (1 mL) was added dropwise, and the resulting solution was allowed to warm to room temperature. Saturated ammonium chloride solution (5 mL) was added, the aqueous phase was extracted with chloroform (3 × 10 mL), and the dried ($MgSO_4$) extracts were evaporated. The residual oil was taken up in acetone and was treated dropwise with a solution of potassium permanganate (0.63 g, 4 mmol) in acetone until the purple color persisted. The mixture was filtered through Solkafloc and then evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate–hexane (1:1). The resultant solid was recrystallized from ethyl acetate to give 2-methoxy-6-pyrimidin-4-ylquinoline (**41**) (0.54 g, 57% mp 164–165 °C. Anal. ($C_{14}H_{11}N_3O$), C, H, N.

(b) The above methoxy compound (0.48 g, 2 mmol) in 48% aqueous hydrobromic acid (3 mL) was heated at 100 °C for 0.75 h. The mixture was cooled, basified (Na_2CO_3 solution) and extracted with chloroform (4 × 50 mL). Solid material was collected from the aqueous phase and combined with the dried ($MgSO_4$) organic layers; then, the whole was evaporated and the residue was chromatographed on silica by eluting with chloroform–methanol (19:1). The solid product was triturated with ethyl acetate to yield 6-pyrimidin-4-yl-2(1*H*)-quinolinone 0.25-hydrate (0.34 g, 74%) mp >310 °C. Anal. ($C_{13}H_9N_3O$·0.25H_2O) C, H, N.

Intermediate isomers (**43**, **44**) were prepared by a similar, but nonregioselective, route and were separated by chromatography on silica by eluting with ethyl acetate. Oxidation of the dihydropyrazine intermediate to **45** was carried out by passing a stream of dry air through the reaction mixture for 0.5 h at –70 °C and then for a further 1 h as the mixture was warmed to room temperature.

Route D. 6-(2,6-Dimethylpyridin-3-yl)-8-ethyl-2(1*H*)-quinolinone (28). A solution of 3-bromo-2,6-dimethylpyridine[18] (1.31 g, 7 mmol) in THF (5 mL) was added to Mg turnings (0.187 g, 7.7 mmol) and a catalytic amount of iodine in THF (5 mL) under reflux under an atmosphere of nitrogen. The mixture was heated under reflux for 1 h and then cooled, and a solution of anhydrous zinc chloride (0.95 g, 7 mmol) in THF (8 mL) was added followed by tetrakis(triphenylphosphine)palladium (0.04 g, 0.035 mmol) and 8-ethyl-6-iodo-2(1*H*)-quinolinone (0.90 g, 3 mmol). The mixture was heated under reflux for 2 h and concentrated, and the residue was partitioned between chloroform–methanol (9:1, 50 mL) and a solution of ethylenediaminetetraacetic acid disodium salt dihydrate (5.2 g, 14 mmol) in water (50 mL). The aqueous layer was separated and extracted further with chloroform–methanol (20:1) to give 6-(2,6-dimethylpyridin-3-yl)-8-ethyl-2-(1*H*)-quinolinone (0.80 g, 96%), mp 202–204 °C. Anal. ($C_{18}H_{18}N_2O$) C, H. N.

Route E. 3,4-Dihydro-6-(2,6-dimethylpyridin-3-yl)-2-(1*H*)-quinolinone Hemihydrate (20). A stirred solution of **16** (3.30 g, 13 mmol) in ethanol (200 mL) was hydrogenated over a 10% Pd/C catalyst (0.90 g) at 60 °C (60 psi) for 48 h. The catalyst was removed by filtration through Solkafloc, the filtrate was evaporated, and the residue was recrystallized from ethyl acetate to give 3,4-dihydro-6-(2,6-dimethylpyridin-3-yl)-2(1*H*)-quinolinone hemihydrate (2.50 g, 74%), mp 213–215 °C. Anal. ($C_{16}H_{16}N_2O$·0.5H_2O), C, H, N.

Route F. 3-Amino-6-pyridin-3-yl-2(1*H*)-quinolinone 0.66-Hydrate (23). Stannous chloride dihydrate (1.27 g, 5.6 mmol) was added to a stirred solution of 3-nitro-6-pyridin-3-yl-2(1*H*)-quinolinone (0.30 g, 1.1 mmol) in ethanol (10 mL), and the mixture was heated under reflux for 1.5 h and then cooled. The mixture was partitioned between chloroform (100 mL) and aqueous sodium carbonate solution (50 mL) and filtered, the layers were separated, and the aqueous phase was further extracted with chloroform–methanol (9:1, 2 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the solid product was triturated with hot 2-propanol to give 3-amino-6-pyridin-3-yl-2(1*H*)-quinolinone 0.66-hydrate (0.093 g, 33%), mp 298–300 °C. Anal. ($C_{14}H_{11}N_3O$·0.66H_2O) C, H, N.

Route G. 8-Bromo-6-(2,6-dimethylpyridin-3-yl)-2(1*H*)-quinolinone (30). (a) Bromine (0.46 mL, 9 mmol) was added to a stirred solution of 3,4-dihydro-6-(2,6-dimethylpyridin-3-yl)-2(1*H*)-quinolinone (1.5 g, 6 mmol) and silver sulfate (1.4 g, 4.5 mmol) in sulfuric acid (98%, 25 mL) at room temperature. After being warmed at 50 °C for 16 h, the cooled mixture was poured onto ice (100 g) and neutralized to pH 7 (5 M NaOH solution). Chloroform (100 mL) was then added, the phases were separated, and the aqueous phase was further extracted with chloroform (2 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and a sample of the solid residue (1.9 g) was recrystallized from ethyl acetate–methanol to afford 8-bromo-3,4-dihydro-6-(2,6-dimethylpyridin-3-yl)-2(1*H*)-quinolinone, characterized spectroscopically.

(b) Bromine (0.33 mL, 6.5 mmol) was added to a stirred suspension of the above product (1.9 g) and sodium acetate (1.06 g, 13 mmol) in acetic acid (20 mL) at room temperature. After being warmed at 100 °C for 18 h, the cooled solution was evaporated, and the residue was partitioned between sodium carbonate solution (10%, 50 mL) and chloroform (100 mL). The aqueous phase was further extracted with chloroform (3 × 100 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The solid residue was chromatographed on silica by eluting with chloroform, and the product was recrystallized from ethyl acetate–methanol to give 8-bromo-6-(2,6-dimethylpyridin-3-yl)-2(1*H*)-quinolinone (0.55 g, 29%), mp 212–215 °C. Anal. ($C_{16}H_{13}BrN_2O$) C, H, N.

Route H. 6-(2,6-Dimethylpyridin-3-yl)-8-(methylthio)-2-(1*H*)-quinolinone 0.25-Hydrate (31). A solution of sodium methanethiolate (15 mL of a 2.0 M solution in methanol, 30 mmol) was added at room temperature to a solution of the product from route I (0.50 g, 1.5 mmol) and cuprous iodide (0.15 g, 0.8 mmol) in *N*-methyl-2-pyrrolidinone (12 mL). After being heated at 160 °C for 48 h, the cooled mixture was diluted with chloroform (100 mL) and water (50 mL). The aqueous phase was further extracted with chloroform (2 × 100 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residual oil was chromatographed on silica by eluting with chloroform, and the product was recrystallized from ethyl acetate to give 6-(2,6-dimethylpyridin-3-yl)-8-(methylthio)-2(1*H*)-quinolinone 0.25-hydrate (0.04 g, 9%), mp 147–149 °C. Anal. ($C_{17}H_{16}N_2OS$·0.25H_2O) C, H, N.

Route I. 6-(2,6-Dimethylpyridin-3-yl)-8-hydroxy-2(1*H*)-quinolinone (33). A mixture of 6-(2,6-dimethylpyridin-3-yl)-8-methoxy-2(1*H*)-quinolinone (0.15 g, 0.54 mmol) and 48% aqueous HBr (5 mL) was heated under reflux for 19 h. The mixture was diluted with water (20 mL), basified to pH 7 (5 M NaOH solution), and extracted with chloroform (3 × 50 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the solid residue was

(18) (a) Talik, T.; Talik, Z.; Ban-Oganowska, H. *Synthesis* **1974**, 293. (b) Kato, T.; Yamanaka, H.; Sakamoto, T.; Shirashi, T. *Chem. Pharm. Bull.* **1974**, *22*, 1206.

recrystallized from ethyl acetate to give 6-(2,6-dimethylpyridin-3-yl)-8-hydroxy-2(1*H*)-quinolinone (0.132 g, 93%), mp 276–277 °C. Anal. ($C_{16}H_{14}N_2O_2$) C, H, N.

Route J. 1-Methyl-6-pyridin-3-yl-2(1*H*)-quinolinone 0.25-Hydrate (34). A stirred solution of 6-pyridin-3-yl-2(1*H*)-quinolinone (0.40 g, 1.8 mmol) in DMF (2 mL) was treated at room temperature with sodium hydride (0.095 g of a 50% dispersion in mineral oil, 2 mmol) for 1 h. A solution of dimethyl sulfate (0.126 g, 1 mmol) in DMF (2 mL) was then added, and the mixture was stirred for 1.5 h. The mixture was concentrated, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined, dried ($MgSO_4$) extracts were evaporated, and the residue was chromatographed on silica by eluting with chloroform. The product was triturated with ether to give 1-methyl-6-pyridin-3-yl-2(1*H*)-quinolinone 0.25-hydrate (0.19 g, 43%), mp 124–125 °C. Anal. ($C_{15}H_{12}N_2O{\cdot}0.25H_2O$) C, H, N.

6-Bromo-8-methyl-2(1*H*)-quinolinone (71). (a) *trans*-3-Ethoxy-2-propenoyl chloride (0.74 g, 5.5 mmol) was added to a stirred solution of 4-bromo-2-methylaniline (0.93 g, 5 mmol) in pyridine (10 mL) at 0 °C. After 0.5 h, water (40 mL) was added, and the solid material was collected, washed with water (30 mL), and dried. The product was then recrystallized from ethyl acetate to afford *trans*-*N*-(4-bromo-2-methylphenyl)-3-ethoxy-2-propenamide (**59**) (1.3 g, 92%), mp 163–164 °C. Anal. ($C_{12}H_{14}BrNO_2$), C, H, N.

Intermediates (**60–62**) were prepared similarly whereas for **56–58**, 2 equiv of the aniline were employed; pyridine was not required, and ether was used as solvent.

(b) *trans*-*N*-(4-Bromo-2-methylphenyl)-3-ethoxy-2-propenamide (2.0 g, 7 mmol) was added portionwise with stirring to 98% sulfuric acid at room temperature. After 16 h, the solution was poured onto ice (100 g), and the solid product (1.50 g) was recrystallized from ethyl acetate–methanol to give 6-bromo-8-methyl-2(1*H*)-quinolinone, mp 272–274 °C. Anal. ($C_{10}H_8BrNO$) C, H, N.

6-Bromo-3-cyano-2(1*H*)-quinolinone (75). A suspension of 3-cyano-2(1*H*)-quinolinone (13.3 g, 78 mmol) in acetic acid (130 mL) was treated at room temperature with a solution of bromine (4.1 mL, 80 mmol) in acetic acid (10 mL). After being heated under reflux for 4 h, the mixture was cooled, and the solid product was collected and washed with ethanol to give 6-bromo-3-cyano-2(1*H*)-quinolinone (14.63 g, 75%). A sample was recrystallized from methanol, mp 308–311 °C. Anal. ($C_{10}H_5BrN_2O$) C, H, N.

6-Bromo-2-chloro-3-cyanoquinoline (82). A suspension of 6-bromo-3-cyano-2(1*H*)-quinolinone (142 g, 570 mmol) in phosphorus oxychloride (500 mL) was heated under reflux for 1.5 h. The mixture was evaporated, the residue was suspended in chloroform (400 mL), and the resulting slurry was poured onto ice. The suspension was neutralized with aqueous ammonia solution (S.G. 0.88), and the layers were separated. The aqueous phase was further extracted with chloroform (2 × 150 mL), and the combined, dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica by eluting with toluene, and the product was recrystallized from ethyl acetate to give 6-bromo-2-chloro-3-cyanoquinoline (80 g, 52%), mp 228–230 °C. Anal. ($C_{10}H_4BrClN_2$) C, H, N.

2-Methoxy-6-bromoquinoline (83). A solution of 2-chloro-6-bromoquinoline[19] (4.0 g, 16.5 mmol) in methanol (20 mL) was heated under reflux with sodium methoxide [from sodium (0.5 g, 22 mmol) and methanol (20 mL)] for 16 h. The mixture was evaporated, and the residue partitioned between water (20 mL) and chloroform (100 mL). The aqueous phase was extracted with chloroform (2 × 30 mL), and the dried ($MgSO_4$) extracts were evaporated to leave a solid, which on recrystallization from petroleum ether (bp 60–80 °C) gave 2-methoxy-6-bromoquinoline (3.0 g, 76%), mp 92 °C. Anal. ($C_{10}H_8BrNO$) C, H, N.

6-Iodo-3-nitro-2(1*H*)-quinolinone (76). (a) Diisobutylaluminium hydride (210 mL of a 1.5 M solution in THF, 315 mmol) was added to a stirred solution of methyl 2-amino-5-iodobenzoate[20] (28.0 g, 101 mmol) in THF (100 mL) at −30 °C under nitrogen. The mixture was warmed to room temperature, stirred for 16 h, and treated with methanol (35 mL). Ethyl acetate (500 mL) was then added, the mixture was filtered, and the filtrate was evaporated. The residue was chromatographed on silica by eluting with chloroform–methanol (49:1) to give 2-amino-5-iodobenzyl alcohol (19.0 g, 76%), mp 125 °C. Anal. (C_7H_8INO) H, N; C: found, 34.4; calcd, 33.8.

(b) Manganese dioxide (0.044 g, 0.5 mmol) was added to a stirred solution of 2-amino-5-iodobenzyl alcohol (0.125 g, 0.5 mmol) in dichloromethane (10 mL), and then the mixture was stirred for a further 6 h at room temperature. An additional portion of manganese dioxide (0.044 g, 0.5 mmol) was then added, and stirring was continued for 16 h. The mixture was then filtered, the filtrate was evaporated, and the residue was chromatographed on silica by eluting with ethyl acetate to give 2-amino-5-iodobenzaldehyde hemihydrate (**91**) (0.1 g, 81%), mp 105 °C. Anal. ($C_7H_6INO{\cdot}0.5H_2O$) C, H; N: found, 6.1; calcd, 5.5.

(c) A stirred mixture of 2-amino-5-iodobenzaldehyde (2.0 g, 8 mmol), ethyl nitroacetate (4.2 g, 32 mmol), and piperidine (0.7 g, 8.2 mmol) was heated in 1,2-dimethylbenzene (100 mL) under reflux for 1.5 h. The cooled solution was evaporated, and the solid residue was recrystallized from chloroform–2-propanol to afford 6-iodo-3-nitro-2(1*H*)-quinolinone (1.14 g, 45%), mp 279–282 °C. Anal. ($C_9H_5IN_2O_3$) C, H, N.

4-Iodo-2-prop-2-ylaniline.[21] Iodine monochloride (12.9 mL, 257 mmol) was added at room temperature to a stirred solution of 2-prop-2-ylaniline (27.0 g, 200 mmol) and sodium acetate (16.4 g, 200 mmol) in acetic acid (250 mL). After 1 h, volatile material was removed in vacuo, and the residue was partitioned between ethyl acetate (200 mL) and sodium carbonate solution (10%, 50 mL). The dried ($MgSO_4$) organic layer was evaporated, and the residue was chromatographed on silica by eluting with hexane to give 4-iodo-2-prop-2-ylaniline (38.0 g) as an unstable oil, which was characterized spectroscopically. 4-Iodo-2-ethylaniline was prepared similarly from 2-ethylaniline.

Biology. Measurement of Inotropic Activity. (a) Anesthetized Dogs. Dogs were anesthetized with intravenous sodium pentabarbitone (Sagatal, M & B; 30–40 mg/kg) and intubated. The saphenous vein, 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 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

$$\text{relative inotropic potency} = \left(\frac{\%\text{ increase in } dP/dt \text{ max to drug}}{\%\text{ increase in } dP/dt \text{ max to standard}}\right)\left(\frac{\text{dose standard}}{\text{dose drug}}\right)$$

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.[22] 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 8-channel pen recorder. The first derivative of the

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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. Temperature of the blood was maintained at 37 °C and 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 left venous inflow catheter, and haemodynamic 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. All compounds were tested in two to four dogs, and dose ranges employed were **3**, **4** (100–800 μg), **26** (50–400 μg), **27** (5–640 μg), and isoprenaline (50–500 ng). Figure 2 is derived by drawing the best line through the accumulated data points for increases in force and rate. All data points lie within 7% from the line for either dependent variable.

(b) Conscious Dogs.[23,24] 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 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 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 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 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 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 QA interval of 20 ms approaches the maximum change possible.

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Registry No. **2**, 99470-75-4; **3**, 99470-74-3; **3**·HCl, 99455-04-6; **4**, 99470-76-5; **4**·HCl, 115514-65-3; **5**, 99471-02-0; **6**, 99470-99-2; **7**, 99470-82-3; **8**, 99470-79-8; **9**, 99470-83-4; **10**, 99470-81-2; **11**, 99470-84-5; **12**, 99470-84-5; **13**, 99470-93-6; **14**, 99470-77-6; **15**, 99470-92-5; **16**, 99470-91-4; **17**, 99454-94-1; **18**, 99471-32-6; **19**, 99471-41-7; **20**, 99471-49-5; **21**, 99470-85-6; **22**, 99455-03-5; **23**, 99471-44-0; **24**, 99471-35-9; **25**, 99471-04-2; **26**, 99470-89-0; **27**, 99470-97-0; **28**, 99471-38-2; **29**, 99471-39-3; **30**, 99454-99-6; **31**, 99471-59-7; **32**, 99471-40-6; **33**, 99471-63-3; **34**, 99471-47-3; **35**, 99455-43-3; **36**, 99455-20-6; **37**, 99455-44-4; **38**, 99455-31-9; **39**, 99455-34-2; **40**, 99455-48-8; **41**, 113656-42-1; **42**, 99455-47-7; **43**, 99465-02-8; **44**, 99465-01-7; **45**, 113656-43-2; **46**, 99455-24-0; **47**, 99455-46-6; **48**, 99455-23-9; **49**, 99455-21-7; **50**, 99455-26-2; **51**, 99455-37-5; **52**, 99454-91-8; **53**, 99455-28-4; **54**, 99455-51-3; **56**, 99465-20-0; **57**, 99465-18-6; **58**, 99465-19-7; **59**, 99465-17-5; **60**, 99465-21-1; **61**, 99465-22-2; **62**, 99465-23-3; **63**, 99455-01-3; **64**, 1810-66-8; **65**, 99465-09-5; **66**, 99465-10-8; **67**, 3279-90-1; **68**, 75793-88-3; **69**, 99465-12-0; **70**, 99465-11-9; **71**, 99465-08-4; **72**, 99465-13-1; **73**, 99465-14-2; **74**, 99465-15-3; **75**, 99465-03-9; **76**, 113659-91-9; **77**, 1810-71-5; **78**, 99455-13-7; **79**, 99455-15-9; **80**, 99455-16-0; **81**, 99455-14-8; **82**, 99465-04-0; **83**, 99455-05-7; **84**, 99455-06-8; **85**, 99455-08-0; **86**, 99455-09-1; **87**, 99471-77-9; **88**, 99455-49-9; **91**, 99471-71-3; I-*p*-$C_6H_4NH_2$, 540-37-4; Br-*m*-$C_6H_4NH_2$, 591-19-5; 5-bromo-2-methoxypyridine, 13472-85-0; 8-bromo-3,4-dihydro-6-(2,6-dimethylpyridin-3-yl)-2(1*H*)-quinolinone, 99471-56-4; *trans*-3-ethoxy-2-propenoyl chloride, 99471-66-6; 4-bromo-2-methylaniline, 583-75-5; 4-bromo-3-methylaniline, 6933-10-4; 4-iodo-2-ethylaniline, 99471-67-7; 4-iodo-2-prop-2-ylaniline, 76842-13-2; 4-bromo-2-methoxyaniline, 59557-91-4; 3-cyano-2(1*H*)-quinolinone, 36926-82-6; methyl 2-amino-5-iodobenzoate, 77317-55-6; 2-amino-5-iodobenzyl alcohol, 53279-83-7; 2-prop-2-ylaniline, 643-28-7; 2-ethylaniline, 578-54-1; 4-bromopyridazine, 115514-66-4.

Supplementary Material Available: 300-MHz NMR spectra in DMSO are available to **3**, **20**, **27**, and **30** (4 pages). Ordering information is given on any current masthead page.

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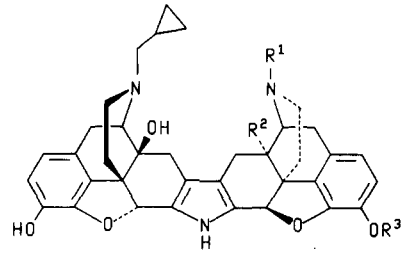
Additions and Corrections

1988, Volume 31

P. S. Portoghese,* H. Nagase, A. W. Lipkowski, D. L. Larson, and A. E. Takemori: Binaltorphimine-Related Bivalent Ligands and Their κ Opioid Receptor Antagonist Selectivity.

Page 837. The correct structure for compounds **10** and **11** is



10: $R^1 = CH_2CH(CH_2)_2$; R^2 = OH; R^3 = Me
11: $R^1 = CH_3$; $R^2 = R^3$ = H