Sterols. Livers were obtained from male Sprague–Dawley rats and homogenates prepared according to the method of Bucher[18] using 0.1 *M* phosphate buffer, pH 7.3, as the suspending medium except that debris was removed by centrifugation at 500g at room temperature for 5 min. Each incubation flask was made to contain 1.0 ml of supernatant, 0.1 ml of stock drug solution, cofactors as described by Holmes and Bentz,[19] and 1.0 μCi of acetate-2-^{14}C and brought to a final volume of 2.5 ml with the phosphate buffer. Stock drug solutions were prepared in 0.5 *N* NaOH solution such that 0.1 ml diluted to 2.5 ml would give the desired final concentration. An identical quantity of 0.5 *N* NaOH solution was added to each of the control flasks. Results for each experiment were obtained by averaging the data from triplicate flasks. Flasks were incubated for 1 hr in air at 37° with slow shaking (60 cpm) after which they were placed on ice and 3.0 ml of 15% KOH in 50% EtOH was added to stop the reaction. The contents of each flask were then transferred to a 15-ml glass-stoppered centrifuge tube and the flask was rinsed with 3.0 ml of the KOH solution. The reaction mixture was then saponified by heating the stoppered centrifuge tubes in a water bath at 75–80° for 1 hr.

The cooled saponification mixtures were extracted three times with 3.0 ml of hexane and the combined extracts diluted with hexane to 10.0 ml and dried (Na_2SO_4) overnight. A 5.0-ml aliquot of the dried hexane solution was added to 10.0 ml of scintillation solution (0.4% PPO in PhMe–95% EtOH, 70:30 v/v) in a standard counting vial. A sufficient number of counts were obtained to reduce the standard deviation to 1.0% or less. The data obtained were used directly to determine the % cpm from flasks which contained the test compounds relative to controls (defined as 100% incorporation).

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Antiviral Quinolinehydrazones. A Modified Free–Wilson Analysis

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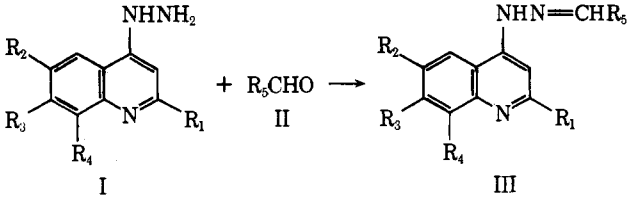
Eighty-four 4-quinolinehydrazones were synthesized and tested for antiviral activity. Thirty-nine derivatives were active against Influenza A_2 and/or Coxsackie B1 in mice at a dose of 25 mg/kg sc. Structure–activity relationships of 44 derivatives (21 inactive) were analyzed qualitatively using a modified Free–Wilson approach.

4-Quinolinehydrazones have antimalarial,[1] antimycoplasmal,[2] anticestode,[3] and tuberculostatic[4] activity. In light of their broad antiinfective profile, we elected to evaluate their effects on the replication of viruses of clinical concern.

Eighty-four 4-quinolinehydrazones (Tables I and II) were prepared by condensation of the appropriate 4-hydrazinoquinoline and aldehyde. They were tested in a unique *in vivo* antiviral screen *vs.* three viruses: Influenza A_2, Coxsackie B1, and Herpes simplex as described in the Experimental Section. Thirty-nine of the compounds were active against Influenza A_2; thirteen were active against Coxsackie B1; none was active against Herpes simplex.

Experimental Section

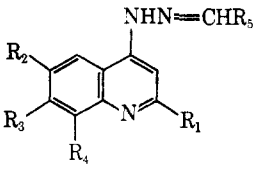
Chemistry. The compounds were prepared by refluxing equimolar amounts of 4-hydrazinoquinoline[3,5] or its HCl salt (I) and the appropriate carboxaldehyde (II) in EtOH for 1–2 hr. On cool-



I III

where R_1–R_5 are listed in Tables I and II

Table I. 4-Quinolinehydrazones Active *vs.* Influenza A_2 and/or Coxsackie B1



No.	R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	Crystn solvent	Formula[a]	Viral infections, % survivors (sc) Influenza A_2	Coxsackie B1
1	CH_3				2-$CH_3OC_6H_4$	220–223	90	EtOH	$C_{18}H_{17}N_3O$	50[b]	F[c]
2	CH_3		C_2H_5O		2,5-$(CH_3O)_2C_6H_3$	219–221	90	EtOH	$C_{21}H_{23}N_3O_3$	80[b]	F[b]
3	CH_3				4-$CH_3OC_6H_4$	210–211	90	EtOH	$C_{18}H_{17}N_3O$	80[b]	F[d]
4	CH_3	CH_3O			2-$CH_3OC_6H_4$	253	90	EtOH	$C_{19}H_{19}N_3O_2$	78[b]	70
5	CH_3	CH_3O			3-$CH_3OC_6H_4$	229	80	EtOH	$C_{19}H_{19}N_3O_2$	100[b]	100
6	CH_3	CH_3O			4-$CH_3OC_6H_4$	258	80	EtOH	$C_{19}H_{19}N_3O_2$	100[b]	90
7	CH_3		CF_3		2,4,6-$(CH_3O)_3C_6H_2$	240	90	EtOH–H_2O	$C_{21}H_{20}F_3N_3O_3$	80[b]	60
8	CH_3	CH_3O			3,4,5-$(CH_3O)_3C_6H_2$	198–200	80	EtOH–H_2O	$C_{21}H_{23}N_3O_4 \cdot H_2O$	90[b]	F[d]
9	CH_3				4-Methoxy-naphthyl	248	80	EtOH	$C_{22}H_{19}N_3O$	85[b,e]	40
10	CH_3	CH_3O			4-Methoxy-naphthyl	260	75	EtOH	$C_{23}H_{21}N_3O_2$	62	70
11	CH_3				9-Anthracenyl	288–291	70	EtOH	$C_{25}H_{19}N_3$	60	F[d]
12	CH_3				9-Ethyl-6-carbazolyl	237	80	EtOH	$C_{25}H_{22}N_4$	89	F[c]
13	CH_3	CH_3O			9-Anthracenyl	300	70	EtOH–H_2O	$C_{26}H_{21}N_3O \cdot 0.5H_2O$	40	50
14	CH_3			CH_3O	2,4,5-$(CH_3O)_3C_6H_2$	265	80	EtOH	$C_{21}H_{23}N_3O_4$	80[b]	F[c]
15	CH_3		C_2H_5O		3-Pyridyl	185	90–100	EtOH	$C_{18}H_{18}N_4O \cdot H_2O$	89	40
16	CH_3		C_2H_5O		4-Pyridyl	215	90–100	EtOH–H_2O	$C_{18}H_{18}N_4O \cdot 2H_2O$	89[b]	70
17	CH_3		C_2H_5O		C_6H_5	195	90–100	EtOH	$C_{19}H_{19}N_3O \cdot H_2O$	100	80
18	CH_3		C_2H_5O		2-ClC_6H_4	236	90–100	EtOH–H_2O	$C_{19}H_{18}ClN_3O \cdot 0.5H_2O$	80[b]	F[d]
19	CH_3		C_2H_5O		3-ClC_6H_4	290	90–100	EtOH	$C_{19}H_{18}ClN_3O \cdot H_2O$	50[b]	F[c]
20	CH_3		C_2H_5O		4-ClC_6H_4	280	90–100	EtOH	$C_{19}H_{18}ClN_3O \cdot H_2O$	70	40
21	CH_3			CH_3O	2,4,6-$(CH_3O)_3C_6H_2$	250	90	EtOH	$C_{21}H_{23}N_3O_4$	80[b]	F[c]
22	CH_3		C_2H_5O		4-FC_6H_4	235	90	EtOH	$C_{19}H_{18}FN_3O \cdot H_2O$	90[b]	F[d]
23	CH_3		C_2H_5O		2-$CH_3OC_6H_4$	243	90	EtOH	$C_{20}H_{21}N_3O_2 \cdot H_2O$	90[b]	F[d]
24	CH_3		C_2H_5O		2-$NO_2C_6H_4$	270	80	EtOH	$C_{19}H_{18}N_4O_3 \cdot H_2O$	60[b]	F[c]
25	CH_3		C_2H_5O		3-$NO_2C_6H_4$	298	90	EtOH	$C_{19}H_{18}N_4O_3 \cdot H_2O \cdot HCl$	70[b]	NT[f]
26	CH_3		C_2H_5O		4-$NO_2C_6H_4$	318	90	EtOH	$C_{19}H_{18}N_4O_3 \cdot HCl$	40[b]	F[c]
27	CH_3			CH_3O	3-$CH_3OC_6H_4$	225	80	EtOH	$C_{19}H_{19}N_3O_2$	60[b]	F[c]
28	CH_3			CH_3	4-Methoxy-naphthyl	210–212	80	EtOH	$C_{23}H_{21}N_3O$	40[b]	90
29	CH_3	CH_3			4-Methoxy-naphthyl	323	80	EtOH	$C_{23}H_{21}N_3O \cdot HCl$	50	70
30	CH_3	CH_3O			2,3-$(CH_3O)_2C_6H_3$	235	80	EtOH	$C_{20}H_{21}N_3O_3$	60[b]	F[d]
31	CH_3			CH_3O	3,4-$(CH_3O)_2C_6H_3$	120	70	EtOH–H_2O	$C_{20}H_{21}N_3O_3 \cdot H_2O$	90[b]	F[d]
32	CH_3		C_2H_5O		3-$CH_3OC_6H_4$	107	90	EtOH	$C_{20}H_{21}N_3O_2 \cdot H_2O$	40[b]	F[d]
33	CH_3		C_2H_5O		$C_6H_5CH{=}CH-$	224	70	EtOH	$C_{21}H_{21}N_3O \cdot H_2O$	90[b]	F[d]
34	CH_3		C_2H_5O		2,3-$(CH_3O)_2C_6H_3$	226	80	EtOH	$C_{21}H_{23}N_3O_3$	50[b]	F[c]
35	CH_3		C_2H_5O		2,4-$(CH_3O)_2C_6H_3$	214	80	EtOH	$C_{21}H_{23}N_3O_3$	70[b]	F[d]
36	CH_3		C_2H_5O		3,4,5-$(CH_3O)_3C_6H_2$	208	80	EtOH–H_2O	$C_{22}H_{25}N_3O_4$	100[b]	F[c]
37	CH_3		C_2H_5O		3-FC_6H_4	248	90	EtOH–H_2O	$C_{19}H_{18}FN_3O \cdot H_2O$	100[b]	F[c]
38	CH_3			CH_3O	4-$CH_3OC_6H_4$	214–216	90	EtOH–H_2O	$C_{19}H_{19}N_3O_2$	90[b]	F[d]
39	CH_3	CH_3O			2,4-$(CH_3O)_2C_6H_3$	273	90	EtOH	$C_{20}H_{21}N_3O_3$	80[b]	F[d]

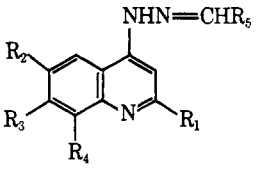
[a] All compounds were analyzed for C, H, and N and analytical results were within 0.4% of the calculated values. [b] Compound inactive po. [c] Compound inactive when tested in a group sc. [d] Compound inactive when tested singly sc. [e] Compound inactive iv and sc. [f] Not tested.

ing and diluting with H_2O the hydrazone (III) precipitated from the reaction mixture; it was collected and crystallized from the solvent indicated in Table I.

In those instances where 4-hydrazinoquinoline hydrochloride was employed, an equimolar amount of NaOAc was added to the mixture to liberate the free base for reaction. Elemental and spectral analyses of the new compounds described are consistent with the structure indicated. Melting points were determined using a Köfler block and are uncorrected.

Virology. Three compounds were randomly grouped and the

Table II. 4-Quinolinehydrazones Inactive *vs.* Influenza A_2 and Coxsackie B1



No.	R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	Crystn solvent	Formula[a]
40			Cl		3-Pyridyl	253	90	EtOH–H_2O	$C_{15}H_{11}ClN_4$
41			Cl		3-$NO_2C_6H_4$	280–282	90	EtOH	$C_{16}H_{11}ClN_4O_2$
42	CH_3			CH_3	$CH_2CH(CH_3)(CH_2)_2CH{=}C(CH_3)_2$	185–187	90–100	EtOH	$C_{21}H_{29}N_3{\cdot}C_6H_3N_3O_7$
43			Cl		$C(CH_3)CH_2COCF_3$[b]	247–249	80	EtOH	$C_{14}H_{11}ClF_3N_3O$
44		Cl		CF_3	5-Nitro-2-furyl	252	80	EtOH	$C_{15}H_8ClF_3N_4O_3$
45		Cl		CF_3	2-Pyridyl	243–245	90	EtOH	$C_{16}H_{10}ClF_3N_4$
46		Cl		CF_3	3-Pyridyl	265–268	90	EtOH	$C_{16}H_{10}ClF_3N_4$
47		Cl		CF_3	4-Pyridyl	255–257	90	EtOH	$C_{16}H_{10}ClF_3N_4{\cdot}0.5H_2O$
48		Cl		CF_3	2-FC_6H_4	251	90	EtOH	$C_{17}H_{10}ClF_4N_3$
49		Cl		CF_3	3-FC_6H_4	250–252	90	EtOH	$C_{17}H_{10}ClF_4N_3$
50		Cl		CF_3	4-FC_6H_4	242–243	90	EtOH	$C_{17}H_{10}ClF_4N_3$
51		Cl		CF_3	2-ClC_6H_4	214–216	90	EtOH	$C_{17}H_{10}Cl_2F_3N_3$
52		Cl		CF_3	3-ClC_6H_4	231–233	90	EtOH	$C_{17}H_{10}Cl_2F_3N_3$
53		Cl		CF_3	4-ClC_6H_4	245–246	90	EtOH	$C_{17}H_{10}Cl_2F_3N_3$
54		Cl		CF_3	C_6H_5	235–237	90	EtOH	$C_{17}H_{11}ClF_3N_3$
55		Cl		CF_3	6-Methyl-2-pyridyl	283	90	EtOH	$C_{17}H_{12}ClF_3N_4$
56		Cl		CF_3	3,4,5-$(CH_3O)_3C_6H_2$	285	70	EtOH	$C_{20}H_{17}ClF_3N_3O_3$
57	CH_3				3,4,5-$(CH_3O)_3C_6H_2$	228–230	80	EtOH–H_2O	$C_{20}H_{21}N_3O_3$
58			Cl		9-Ethyl-6-carbazolyl	262–265	80	EtOH	$C_{24}H_{19}ClN_4$
59	CH_3		CF_3		9-Ethyl-6-carbazolyl	208–210	90	EtOH	$C_{26}H_{21}F_3N_4$
60	CH_3		C_2H_5O		2-Pyridyl	218–220	90	EtOH	$C_{18}H_{18}N_4O$
61	CH_3		C_2H_5O		6-Methyl-2-pyridyl	220–223	90	EtOH	$C_{19}H_{20}N_4O{\cdot}H_2O$
62	CH_3				3,4-$(CH_3O)_2C_6H_3$	206–207	90	EtOH	$C_{19}H_{19}N_3O_2$
63	CH_3		C_2H_5O		2-FC_6H_4	202–205	90	EtOH	$C_{19}H_{18}FN_3O$
64	CH_3				3-$CH_3OC_6H_4$	190–192	90	EtOH–H_2O	$C_{18}H_{17}N_3O$
65	CH_3				2,3-$(CH_3O)_2C_6H_3$	276	90	EtOH	$C_{19}H_{19}N_3O_2$
66	CH_3				2,4-$(CH_3O)_2C_6H_3$	250	90	EtOH	$C_{19}H_{19}N_3O_2$
67	CH_3				2,5-$(CH_3O)_2C_6H_3$	258	90	EtOH	$C_{19}H_{19}N_3O_2$
68	CH_3			CH_3O	2-$CH_3OC_6H_4$	280	90	EtOH	$C_{19}H_{19}N_3O_2$
69	CH_3				2,4,5-$(CH_3O)_3C_6H_2$	252	90	EtOH	$C_{20}H_{21}N_3O_3$
70	CH_3	CH_3O			9-Ethyl-6-carbazolyl	270	70	EtOH–H_2O	$C_{26}H_{24}N_4O$
71	CH_3	CH_3O			2,5-$(CH_3O)_2C_6H_3$	277	90	EtOH	$C_{20}H_{21}N_3O_3$
72	CH_3			CH_3O	2,3-$(CH_3O)_2C_6H_3$	275	90	EtOH	$C_{20}H_{21}N_3O_3$
73	CH_3			CH_3O	2,4-$(CH_3O)_2C_6H_3$	298–300	90	EtOH	$C_{20}H_{21}N_3O_3$
74	CH_3			CH_3O	2,5-$(CH_3O)_2C_6H_3$	283	90	EtOH	$C_{20}H_{21}N_3O_3$
75	CH_3			CH_3O	3,4,5-$(CH_3O)_3C_6H_2$	239	80	EtOH	$C_{21}H_{23}N_3O_4$
76	CH_3		C_2H_5O		4-$(CH_3)_2NC_6H_4$	285	70	EtOH	$C_{21}H_{24}N_4O{\cdot}H_2O$
77	CH_3			CH_3O	4-Methoxy-2-naphthyl	262	70	EtOH–H_2O	$C_{23}H_{21}N_3O_2$
78	CH_3			CH_3O	9-Anthracenyl	302	70	EtOH	$C_{26}H_{21}N_3O{\cdot}0.5H_2O$
79	CH_3			CH_3O	9-Ethyl-6-carbazolyl	255–257	60–70	EtOH–H_2O	$C_{26}H_{24}N_4O$
80	CH_3		C_2H_5O		4-$CH_3OC_6H_4$	282	90	EtOH	$C_{20}H_{21}N_3O_2{\cdot}2H_2O$
81	CH_3		C_2H_5O		$C(CH_3)CH_2COC_6H_5$[b]	230	90	EtOH	$C_{22}H_{23}N_3O_2$
82	CH_3		C_2H_5O		2,4,5-$(CH_3O)_3C_6H_2$	216	90	EtOH	$C_{22}H_{25}N_3O_4{\cdot}H_2O$
83	CH_3		C_2H_5O		9-Anthracenyl	290	80	EtOH	$C_{27}H_{23}N_3O{\cdot}2H_2O$
84	CH_3		C_2H_5O		9-Ethyl-6-carbazolyl	255	70	EtOH	$C_{27}H_{26}N_4O{\cdot}H_2O$

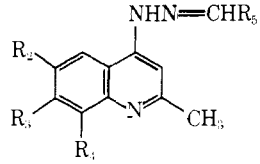
[a] See footnote *a*, Table I. [b] In this case NHN=CHR is NHN=$C(CH_3)CH_2$....

combined triplet was administered subcutaneously (sc) at a dose of 25 mg/kg of compound in Tween 80 to a group of ten mice infected with LD_{90-95} of virus. (The triplets were first tested for overt toxicity in uninfected mice.) Mice were treated twice daily for either 3 (Herpes simplex or Coxsackie B1) or 4 days (Influenza A_2). On the first day, doses were given 3 hr before and immediately after infection. Subsequent daily doses were administered at 6-hr intervals. If 40% or more of the animals survived the test period (14 days for Influenza A_2, 12 days for Herpes simplex, 10 days for Coxsackie B1), the three compounds in the mixture were then tested individually, again at a dose of 25 mg/kg sc in the above regimen. A survival rate of 40% or more indicated statistically significant activity. Individually active compounds were also tested orally at 25 mg/kg. If a triplet mixture was inactive, the individual compounds were considered inactive. The control, 1-aminoadamantane, provided 90% survival rate against Influenza A_2 in treated animals.

Results and Discussion

The 4-quinolinehydrazones active against Influenza A_2 and/or Coxsackie B1 are tablulated in Table I. All compounds active sc were inactive when administered orally

Table III. Free-Wilson Matrix



		R_2		R_3		R_4		R_5				
	Compd	CH_3O	H	C_2H_5O	H	CH_3O	H	2-CH_3O-C_6H_4	3-CH_3O-C_6H_4	4-CH_3O-C_6H_4	2,5-$(CH_3O)_2$-C_6H_3	2,3-$(CH_3O)_2$-C_6H_3
1	1[a]		1		1		1	1				
2	2		1	1			1				1	
3	3		1		1		1			1		
4	4	1			1		1	1				
5	5	1			1		1		1			
6	6	1			1		1			1		
7	8	1			1		1					
8	9		1		1		1					
9	10	1			1		1					
10	11		1		1		1					
11	12		1		1		1					
12	13	1			1		1					
13	14		1		1	1						
14	23		1	1			1	1				
15	27		1		1	1			1			
16	30	1			1		1					1
17	31		1		1	1						
18	32		1	1			1		1			
19	34		1	1			1					1
20	35		1	1			1					
21	36		1	1			1					
22	38		1		1	1				1		
23	39	1			1		1					
24	57		1		1		1					
25	62		1		1		1					
26	64		1		1		1		1			
27	65		1		1		1					1
28	66		1		1		1					
29	67		1		1		1				1	
30	68		1		1	1		1				
31	69		1		1		1					
32	70	1			1		1					
33	71	1			1		1				1	
34	72		1		1	1						1
35	73		1		1	1						
36	74		1		1	1					1	
37	75		1		1	1						
38	77		1		1	1						
39	78		1		1	1						
40	79		1		1	1						
41	80		1	1			1			1		
42	82		1	1			1					
43	83		1	1			1					
44	84		1	1			1					

[a] Numbers in this column refer to Tables I and II.

at 25 mg/kg. Table II lists the inactive derivatives. All 84 compounds were ineffective against Herpes simplex.

Interestingly, survivors of the test generally manifested inflammation or ulceration at the site of compound injection; however, limited studies failed to confirm any relationship between this observation and antiviral activity.

Structure–Activity Correlations. Forty-four of the 84 quinolinehydrazones tested (23 active, 21 inactive against Influenza A_2) are described in the Free–Wilson (FW) matrix shown in Table III. All compounds in the matrix have $R_1 = CH_3$. In order to simplify the matrix and enhance the reliability of the analysis, 22 compounds with substituents occurring two or less times were excluded as were 18 compounds with substituents occurring only in the inactive group of compounds. (It is worth noting that the substituents R_1 = H, R_2 = Cl, and $R_4 = CF_3$ were borne by 13 compounds exclusively in the inactive group and may therefore be an undesirable combination for antiviral activity.) A logit transformation (logit = $\ln P/(100 - P)$, where P is the per cent survivors) was taken as the index of activity, where inactive compounds were assigned a "P" value of 30%.† The logit function was employed to provide

R_5									
3,4-$(CH_3O)_2$-C_6H_3	2,4-$(CH_3O)_2$-C_6H_3	3,4,5-$(CH_3O)_3$-C_6H_2	2,4,5-$(CH_3O)_3$-C_6H_2	4-Methoxy-naphthyl	9-Anthracenyl	9-Ethyl-6-carbazolyl	% survivors, Influenza A_2	Logit (% survivors)	Logit predicted by the FW analysis
							50	0	0.034
							80	1.386	−0.110
							80	1.386	1.761
							80	1.386	1.837
							100	6.907	2.668
							100	6.907	3.563
		1					90	2.197	3.005
				1			85	1.734	−0.159
				1			60	0.405	1.643
					1		60	0.405	−1.073
						1	90	2.197	−0.736
					1		40	−0.405	0.729
			1				80	1.386	−0.400
							90	2.197	0.863
							60	0.405	0.833
							60	0.405	0.830
1							90	2.197	0.659
							40	−0.405	1.696
							50	0	−0.144
	1						70	0.847	0.313
		1					100	6.907	2.031
							90	2.197	1.729
	1						80	1.386	1.287
		1					30	−0.847	1.203
1							30	−0.847	0.691
							30	−0.847	0.865
							30	−0.847	−0.972
	1						30	−0.847	−0.515
							30	−0.847	−0.938
							30	−0.847	0.002
			1				30	−0.847	−0.368
						1	30	−0.847	1.067
							30	−0.847	0.864
							30	−0.847	−1.004
	1						30	−0.847	−0.547
							30	−0.847	−0.970
		1					30	−0.847	1.171
				1			30	−0.847	−0.191
					1		30	−0.847	−1.105
						1	30	−0.847	−0.768
							30	−0.847	2.589
			1				30	−0.847	0.460
					1		30	−0.847	−0.245
						1	30	−0.847	0.093
								Av = 0.55	

better discrimination among the more active compounds (logit 99.9% = 6.9,‡ 90% = 2.2, 80% = 1.38, etc.). The matrix was solved in the usual manner.[6]

Assembling the FW matrix is *per se* helpful in observing certain structure–activity relationships. However, when the numbers of compounds and substituents are large, it is difficult to appreciate which combinations of substituent groups are important to activity by simple inspection.

†Within the range of the survival rates of untreated animals.
‡99.9% used since logit 100% is meaningless.

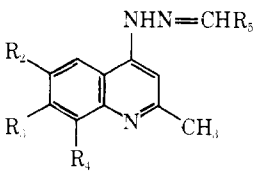
An FW analysis, designed to correlate chemical structure with biological activity, is ideally based on a matrix consisting primarily of active compounds; in this analysis, a relatively large number of inactive compounds (48%) were included to embrace less well-represented substituent groups. This apparent abuse of the FW approach was consciously pursued to determine, in a qualitative sense only, which substituents contributed to the higher survival rates. Optimal substitution patterns were deduced by comparing the relative values of the FW substituent constants at each position (Table IV). The validity of the so-

Table IV. Free-Wilson Substituent Constants

Substituent	No. of occurrences	Computed FW substituent constants
$R_2 = CH_3O$	10	1.39
$R_2 = H$	34	−0.41
$R_3 = C_2H_5O$	10	0.64
$R_3 = H$	34	−0.19
$R_4 = CH_3O$	12	−0.02
$R_4 = H$	32	−0.009
$R_5 = 2\text{-}CH_3OC_6H_4$	4	−0.07
$R_5 = 3\text{-}CH_3OC_6H_4$	4	0.90
$R_5 = 4\text{-}CH_3OC_6H_4$	4	1.80
$R_5 = 2,5\text{-}(CH_3O)_2C_6H_3$	4	−0.90
$R_5 = 2,3\text{-}(CH_3O)_2C_6H_3$	4	−0.93
$R_5 = 3,4\text{-}(CH_3O)_2C_6H_3$	2	0.73
$R_5 = 2,4\text{-}(CH_3O)_2C_6H_3$	4	−0.48
$R_5 = 3,4,5\text{-}(CH_3O)_3C_6H_2$	4	1.24
$R_5 = 2,4,5\text{-}(CH_3O)_3C_6H_2$	3	−0.33
$R_5 = 4\text{-Methoxynaphthyl}$	3	−0.12
$R_5 = 9\text{-Anthracenyl}$	4	−1.03
$R_5 = 9\text{-Ethyl-6-carbazolyl}$	4	−0.70

lution is supported by the consistency of the findings and not by statistical criteria such as the F ratio, since including a number of inactive compounds with the same index of activity distorts the measure of residual variation in the study.

Using this method of analysis it can be concluded that in quinolinehydrazones of the type



(i) $R_2 = CH_3O$ is more favorable for activity than $R_2 = H$; (ii) $R_3 = C_2H_5O$ is more favorable for activity than $R_3 = H$; (iii) in the R_4 position H and CH_3O groups are comparable; (iv) of the R_5 groups studied, the preferred substituents are $R_5 = 3\text{-}CH_3OC_6H_4$, $4\text{-}CH_3OC_6H_4$, $3,4\text{-}(CH_3O)_2C_6H_3$, or $3,4,5\text{-}(CH_3O)_3C_6H_2$.

From the structures of three compounds (Table III, no. 5, 6, 21) that provided total protection at the doses used, we are again persuaded to conclude that CH_3O at R_2, C_2H_5O at R_3, and 3-, 4-, or 3,4,5-methoxylation of the phenyl ring at R_5 are activity-enhancing substituent groups. The two other compounds tested that allowed 100% survival (Table I, no. 17, 37) were excluded from the matrix because the R_5 substituents (C_6H_5 and $3\text{-}FC_6H_4$) were poorly represented. Nevertheless, they again support the conclusion that in this series R_3 is optimally C_2H_5O. The data also suggest that the substitution pattern $R_1 = CH_3$, $R_2 = CH_3O$, $R_3 = C_2H_5O$, and $R_5 = 3\text{-}CH_3OC_6H_4$, $4\text{-}CH_3OC_6H_4$, $3,4\text{-}(CH_3O)_2C_6H_3$, or $3,4,5\text{-}(CH_3O)_3C_6H_2$ would result in more potent compounds on a dosage basis.

We conclude that in the study described the Free-Wilson approach has been of significant value in displaying the data and accommodating both active and inactive compounds to allow potentially useful qualitative conclusions to be drawn.

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Preparation and Anticoagulant Activity of Trimethylsilyl Heparin in Carbowax

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Trimethylsilyl heparin, when administered intraduodenally or intragastrically to rats, did not increase intestinal absorption and, consequently, the clotting times were not influenced. However, suspension of sodium heparin in Carbowax 200 prolonged the whole blood clotting time at a dose of 50 mg/kg when given intraduodenally or intragastrically to rats.

Heparin is a mucopolysaccharide of high molecular weight (17,000–20,000) normally isolated from mammalian tissue. It is used as an anticoagulant for blood as well as in many clinical situations such as in thrombophlebitis, phlebothrombosis, arterial occlusions, and as prophylaxis against thrombosis after trauma to blood vessels, etc.[1] It is usually administered by subcutaneous, intramuscular, or intravenous injection since it is inactive or only slightly active (at very high doses) when given orally. An orally active heparin would have many applications particularly for prophylactic use.

A number of attempts have been made in the past to make a suitable heparin derivative which can be absorbed through the intestinal walls but these approaches have met with only limited success. Koh and Bharucha have claimed preparations of a number of stable, orally active heparinoid