Inhibition of Rat Passive Cutaneous Anaphylaxis by 3-(Tetrazol-5-yl)quinolines[1]

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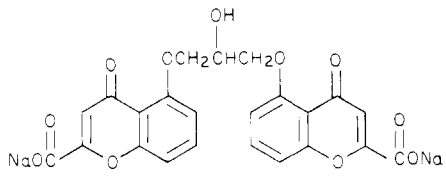
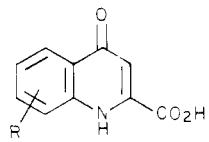
Quinoline-3-carboxylic acid (3) was found to have weak oral activity in the rat passive cutaneous (PCA) assay. In an effort to increase activity, the synthesis of structurally related compounds was initiated. This led to substituted 3-(tetrazol-5-yl)quinolines, some of which are equal in potency, when given orally, to doxantrazole. Further work resulted in the synthesis of 4-oxoquinolines, one of which, 8-chloro-1,4-dihydro-4-oxo-3-(tetrazol-5-yl)quinoline (**132**), is 33-fold more active than disodium cromoglycate (ip) and 32-fold more active than doxantrazole (po).

In the 10 years since the introduction of disodium cromoglycate (DSCG, **1**) for the therapy of asthma and



1 (DSCG)



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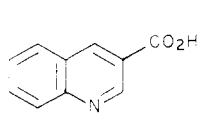
allergic diseases[2] there have been intensive efforts in numerous laboratories to find additional DSCG-like antiallergic agents.[3] Of particular interest to us is the discovery of agents which, unlike DSCG, have oral activity. To find DSCG-like agents we have relied on the IgE-mediated passive cutaneous anaphylaxis (PCA) assay in rats.[4] This assay is felt to be, at least on a biochemical basis, an excellent model for human immediate hypersensitivity reactions. However, a great many agents, e.g., antiserotonins, are active in the PCA assay, and further tests are necessary to define the type of pharmacological activity being observed. Thus, in our search for DSCG-like agents we have relied on initial screening in the rat PCA assay followed by further testing in other pharmacological assays to find compounds whose biological activity profile matches that of DSCG.

Previously,[5] we described our work on a series of quinoline-2-carboxylic acids (**2**) which are effective inhibitors of the PCA reaction in rats but have no oral activity. During this work, we tested several related compounds which were available from other work in our laboratories. Among these was quinoline-3-carboxylic acid (**3**) which was found to be orally active in the rat PCA assay. In this paper, we describe how, beginning from this initial lead, we developed a series of 4-oxo-3-(tetrazol-5-yl)quinolines (**4**), some of which are a 1000-fold more



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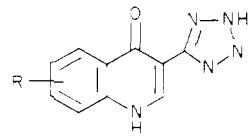

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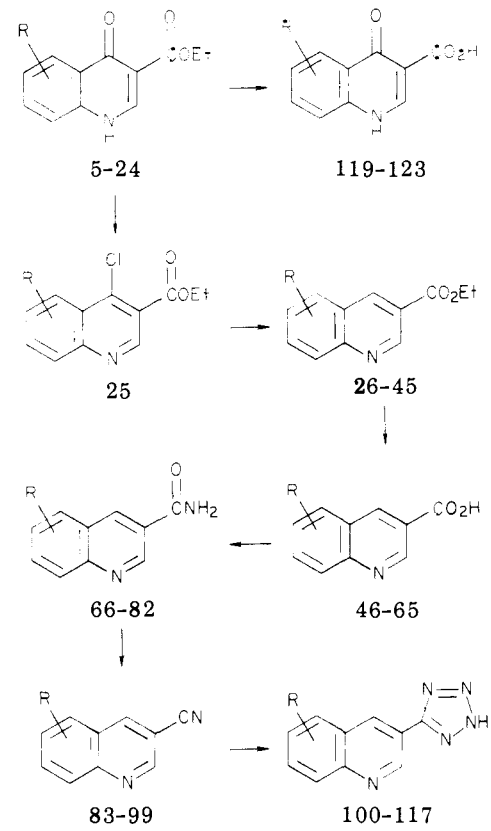
potent in the rat PCA assay than **3**.

Prior to the preparation of this paper there have been several reports describing antiallergic and/or PCA inhibitory activity of 3-substituted quinolines and structurally related compounds.[6] There is a Japanese patent[7] which claims 1,4-dihydro-4-oxo-3-(tetrazol-5-yl)quinoline along with fused bis derivatives. Hall et al.[8] have previously reported the PCA inhibitory activity of 1,4-dihydro-4-oxoquinoline-3-carboxylic acids. Their results are similar to those we report in Table IV and are included for comparison purposes. Antiallergic activity has also been reported for a series of 4-oxo-*N*-(tetrazol-5-yl)quinoline-3-carboxamides.[9] Other related compounds reported to have antiallergic activity include 3-nitro-2,4-dihydroxyquinolines,[10] 4-oxocinnoline-3-carboxylic acids,[11] 4-oxocinnoline-3-propionic acids,[12] and 3-(tetrazol-5-yl)-chromones.[13]

Scheme I



Chemistry. Two approaches have been used by previous workers for the synthesis of quinoline-3-carboxylic acids. One approach is from 3-bromoquinolines by conversion to the nitriles with cuprous cyanide followed by alkaline hydrolysis to give the acid.[14,15] Except for the synthesis of **3**, our attempts to use this general route were not successful. Therefore, we used, with some modifications, the second approach,[16] which is illustrated in

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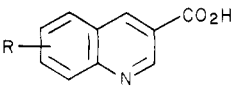
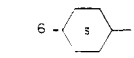
Table I. Quinoline-3-carboxylic Acids[a]



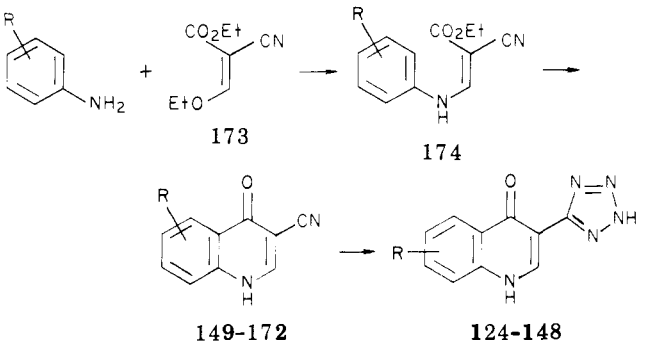
no.	R	MED, mg/kg[b] ip	MED, mg/kg[b] po	formula[c]	mp, °C	recrystn solv	yield, %
3	H	50	150	*d*	275-280	*d*	*d*
46	6-F		>50	$C_{10}H_6FNO_2 \cdot HCl$	>250	*e*	90
47	6-CF_3	>25	>50	$C_{11}H_6F_3NO_2$	198	*e*	60
48	6-CH_3O	>5		$C_{11}H_9NO_3$	>260	MeOEtOH-H_2O	66
49		>25		$C_{16}H_{17}NO_3$	259-261	*e*	90
50	6-butyl			$C_{14}H_{15}NO_2$	203-207	EtOH	68
51	6-cyclohexyl	>25		$C_{16}H_{17}NO_2$	227-228	*e*	57
52	7-CF_3	>25	>25	$C_{11}H_6F_3NO_2$	208-210	*e*	65
53	7-CH_3O	>25		$C_{11}H_9NO_3 \cdot HCl$	240 dec	MeOEtOH	74
54	8-F	>25	150	$C_{10}H_6FNO_2 \cdot 0.5H_2O$	240 dec	*e*	51
55	8-Cl	25	150	$C_{10}H_6ClNO_2$	>260	*e*	56
56	8-CF_3	50	75	*f*	206-208	*e*	59
57	8-CH_3	>50	>25	$C_{11}H_9NO_2$	>250	*e*	27
58	8-CH_3CH_2	>50	75	$C_{12}H_{11}NO_2$	193-197	acetone	16
59	8-CH_3O	25	150	$C_{11}H_9NO_3$	>250	*e*	52
60	8-CH_3CH_2O	>25	>50	$C_{12}H_{11}NO_3$	>250	*e*	84
61	5,8-$(MeO)_2$	>25	>50	$C_{12}H_{11}NO_4$	>260	*e*	70
62	6,8-F_2	25		$C_{10}H_5F_2NO_2$	257-258	EtOH	86
63	7,8-Me_2	25	50	$C_{12}H_{11}NO_2$	216 dec	*e*	72
64	7,8-$(CH_2)_4$	25	50	$C_{14}H_{13}NO_2$	240-243	EtOH	79
65	7,8-benzo	25	50	$C_{14}H_9NO_2$[g]	250	*e*	87

[a] Except for 3, these compounds were prepared by method E. See Experimental Section. [b] Minimum effective dose. See text for discussion. [c] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. [d] See ref 14 for method of preparation. [e] Not recrystallized; washed with H_2O. [f] Lit. mp[16] 208-209. [g] Carbon analysis was within 0.5%.

Scheme I. The ethyl 4-oxoquinoline-3-carboxylates **5–24** utilized as starting materials are readily available from substituted anilines and diethyl ethoxymethylenemalonate.[17] With meta-substituted anilines it is possible to obtain mixtures of the 5- and 7-substituted quinolines. However, in each case only single products were isolated, which were assigned as the 7-substituted derivatives from their ^1H NMR spectra. These were converted to the 4-chloro derivatives **25** either with thionyl chloride or, preferably, phosphorus oxychloride. In most cases, the intermediate 4-chloro derivatives were not characterized and were utilized without purification. The dehalogenations of **25** to the esters **26–45** (Table V) were initially done with palladium on carbon in acetic acid, but we later found that palladium on carbon with triethylamine in ethanol was superior with respect to speed and reproducibility. However, on a large scale (1 mol) we found it difficult to prevent partial further reduction to 1,4-dihydroquinolines. Normally, the esters were isolated as low-melting solids or oils; however, as indicated in Table V it was sometimes convenient to isolate them as a hydrochloride or other salt. However, drying the salts at 95 °C in vacuo is sufficient to cause loss of the hydrogen chloride and reversion to the free base. The esters were hydrolyzed under basic conditions to give the desired acids **46–65** (Table I), some of which, upon acidification of the hydrolysis reaction, were isolated as the hydrochloride salts.

3-(Tetrazol-5-yl)quinoline, **100**, was prepared as previously described.[18] Substituted derivatives **101–117** (Table II) were prepared from the respective quinoline-3-carboxylic acid derivatives (Scheme I). The acids were initially converted to the amides **66–82** (Table VI) either via the acid chloride or the mixed anhydride. The amides were then dehydrated to the nitriles **83–99** (Table VII) with thionyl chloride–dimethylformamide at room temperature. Attempts to prepare the nitriles by dehalogenation of

Scheme II



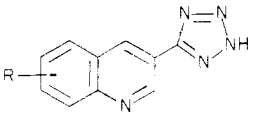
4-chloro-3-cyanoquinolines using the conditions described above for the esters **25** gave mixtures of products and were not further pursued.

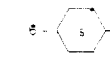
The tetrazoles **101–117** (Table II) were prepared from the nitriles in the usual manner with sodium azide and ammonium chloride in dimethylformamide. To obtain a nitro-substituted derivative, which was not possible using Scheme I, 7,8-dimethyl-3-(tetrazol-5-yl)quinoline was nitrated in sulfuric acid to give **118** (Table II). Nitration was assumed to occur at the 5 position by analogy to literature examples.[19]

The 4-oxoquinoline-3-carboxylic acids **119–123** (Table I) were obtained from the intermediate esters by basic hydrolysis.

The 4-oxo-3-(tetrazol-5-yl)quinolines **124–148** (Table III; Scheme II) were prepared from the 3-cyano-4-oxoquinolines **149–172** (Table VIII) under the same conditions used for the 4-unsubstituted tetrazoles. The requisite nitriles were prepared from ethyl ethoxymethylenecyanoacetate (**173**) and the appropriate aniline either by combining **173** and the aniline directly in phenyl ether or Dowtherm A and slowly heating to reflux or, alternatively,

Table II. 3-(Tetrazol-5-yl)quinolines[a]



no.	R	MED, mg/kg[b] ip	MED, mg/kg[b] po	formula[c]	mp, °C	recrystn solv	yield, %
100	H	10	25	*d*	247-250	*n*-PrOH	63
101	6-F	<25	50	$C_{10}H_6FN_5$	250	*e*	78
102	6-CH_3O	10	>25	$C_{11}H_9N_5O \cdot 0.5H_2O$	260	MeOEtOH	53
103		5	10	$C_{16}H_{17}N_5O \cdot HCl$[f]	243 dec	*e*	10
104	6-butyl	5	>25	$C_{14}H_{15}N_5$	180-182	EtOH	24
105	6-cyclohexyl	5	>25	$C_{16}H_{17}N_5 \cdot HCl$	220 dec	EtOH	24
106	7-CF_3	<10	25	$C_{11}H_6F_3N_5$	260	acetone-H_2O	80
107	7-CH_3O	5	>25	$C_{11}H_9N_5O \cdot 0.5HCl$[g]	246 dec	MeOEtOH	29
108	8-F	>10		$C_{10}H_6FN_5$	260	MeOEtOH-H_2O	90
109	8-CF_3	<25	25	$C_{11}H_6F_3N_5$	192-193		83
110	8-CH_3	<25	25	$C_{11}H_9N_5$	189-200 dec	acetone-benzene	65
111	8-CH_3CH_2	2.5	5	$C_{12}H_{11}N_5$	173	H_2O	39
112	8-CH_3O	2.5	>25	$C_{11}H_9N_5O$	260	MeOEtOH	57
113	5,8-$(MeO)_2$	5	>50	$C_{12}H_{11}N_5O_2$	250	*e*	61
114	6,8-F_2	10	>50	$C_{10}H_5F_2N_5$	260	*e*	53
115	7,8-Me_2	1	25	$C_{12}H_{11}N_5$	238-242	EtOAc	42
116	7,8-$(CH_2)_4$	5	5	$C_{14}H_{13}N_5$	259-261	EtOH	28
117	7,8-benzo	5	10	$C_{14}H_9N_5$	240-245	EtOH	54
118	7,8-Me_2-5-NO_2	2.5	25	$C_{12}H_{10}N_6O_2$	180	EtOH	19[h]

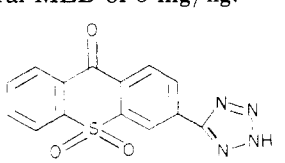
[a] Prepared by method K (see Experimental Section), except where otherwise noted. [b] Minimum effective dose. See text for discussion. [c] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. [d] Lit.[18] mp 249-251. [e] Not recrystallized; washed with H_2O. [f] Chlorine analysis within 0.4%. [g] N: calcd, 28.5; found, 27.9. [h] Prepared by method L (see Experimental Section). Nitrogen analysis was within 0.5%.

by initial formation of the intermediate enamine **174** and then adding **174** to the refluxing solvent.[20] As was the case with the 4-oxoquinoline-3-carboxylates, only the 7-substituted quinolines were isolated from the meta-substituted anilines.

The final tetrazoles **124–148** were extremely insoluble compounds, which made recrystallization difficult. Most were purified by dissolving in aqueous base followed by acidification to give a gel-like precipitate which was difficult to filter and dry.

All but two of the anilines required for the above syntheses were commercially available. 4-Cyclohexylaniline was prepared from 4-cyclohexylphenol by the method of Scherrer,[21] and 4-cyclohexyloxyaniline was prepared from *p*-fluoronitrobenzene and cyclohexanol.

Pharmacology. Compounds were evaluated for their ability to inhibit the PCA reaction in Sprague–Dawley rats by the method previously described.[5] Compounds were tested either intraperitoneally (ip) or orally (po) over a range of progressively lower doses, e.g., 10, 5, 2.5 mg/kg, etc., until the lowest dose giving greater than 50% inhibition ($p \leq 0.05$, Student's t test) was found, and this result is reported in Tables I–IV as the minimum effective dose (MED). In most cases, the MED is the result of a single series of experiments in which groups of six animals were used at all dose levels and in positive and negative controls. In our assay, the ED_{50} (95% confidence limits, number of animals) of DSCG when given intraperitoneally is 2.6 mg/kg (1.9–3.3, 264 animals), while doxantrazole (**175**)[22] has an oral MED of 5 mg/kg.



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For testing, the compounds were usually prepared as suspensions in acacia. However, certain compounds (see below) were prepared for testing by ball-milling the acacia suspensions. Thus, in Table III results of oral dosing are reported with and without ball-milling of the acacia suspension.

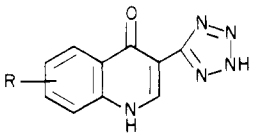
Discussion

Following the finding that **3** had significant oral activity in the PCA assay at a dose of 150 mg/kg, we began to prepare a series of derivatives substituted in the benzo portion of the quinoline ring (Table I) and found that activity could be enhanced, e.g., **64**. However, the finding that 3-(tetrazol-5-yl)quinoline (**100**; Table II) was substantially more active than **3** led us to concentrate on the tetrazole derivatives.

For the tetrazoles listed in Table II, alkyl groups in the 8 or 7,8 positions gave the highest oral activity, particularly **111** and **116**, which have activities in the same range as doxantrazole. However, increased oral activity did not necessarily follow increased intraperitoneal activity, as shown by the results with **104**, **105**, **107**, and **112–114**. It is interesting to note that, while the 6-methoxy and 6-cyclohexyl derivatives **102** and **105**, respectively, had no significant oral activity at the screening dose, the 6-cyclohexyloxy derivative **103** showed increased oral activity, while all three had similar activity when dosed by the intraperitoneal route. We conclude from this that absorption and distribution are sensitive to substituent effects, but attempts to correlate these results with physical properties using regression-analysis techniques were not successful. This failure is not surprising given the limited number and range of substituents.

Although the compounds in Table II had good oral activity, the finding that the 4-oxo derivatives in Table III had even greater activity led us to further concentrate our efforts on this series. These compounds were initially

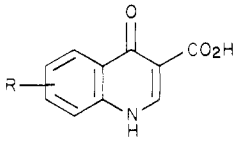
Table III. 1,4-Dihydro-4-oxo-3-(tetrazol-5-yl)quinolines[a]



no.	R	MED, mg/kg[b] ip	MED, mg/kg[b] po	formula[c]	recrystn solv	yield, %
124	H	1.25	>20	$C_{10}H_7N_5O \cdot 0.75H_2O$	*d*	19
125	6-F	1.25	>20	$C_{10}H_6FN_5O \cdot 0.5H_2O$[e]	*d*	63
126	6-Cl	>10	>25	$C_{10}H_6ClN_5O$	*d*	93
127	6-CH_3	1.25	>25	$C_{11}H_9N_5O \cdot 0.5H_2O$[f]	*d*	64
128	6-CH_3CH_2	<5	0.625 (0.156)[g]	$C_{12}H_{11}N_5O \cdot 0.75H_2O$	*d*	38
129	7-CH_3CH_2	<5	>10	$C_{12}H_{11}N_5O \cdot 0.5H_2O$[h]	*d*	27
130	7-MeO	10		$C_{11}H_9N_5O_2$	Me_2SO	68
131	8-F	0.625	10 (2.5)[g]	$C_{10}H_6FN_5O$	*d*	70
132	8-Cl	0.078 (0.156)[g]		$C_{10}H_6ClN_5O$	DMF	90
133	8-Br	>5	>10	$C_{10}H_6BrN_5O$	*d*	88
134	8-CF_3	0.156	>25	$C_{11}H_6F_3N_5O$	*d*	82
135	8-CH_3	>5	>10	$C_{11}H_9N_5O$	DMF	12
136	8-CH_3CH_2	0.312	>25	$C_{12}H_{11}N_5O$	*d*	80
137	8-$CH(CH_3)_2$	1.25	10	$C_{13}H_{13}N_5O$	*d*	83
138	8-CH_3O	0.15	0.312	$C_{11}H_9N_5O_2 \cdot 0.9H_2O$	*d*	59
139	8-$(CH_3)_2CHO$	0.078	1.25	$C_{13}H_{13}N_5O_2$	DMF	48
140	8-CH_3S	10	25	$C_{11}H_9N_5OS$	*d*	96
141	8-CH_3SO_2	10	>25	$C_{11}H_9N_5O_3S$[i]	*d*	92[i]
142	5,8-F_2	>0.156	10	$C_{10}H_5F_2N_5O$[j]	DMF-MeOH	22
143	5,8-Cl_2	>0.156	0.312	$C_{10}H_5Cl_2N_5O$	DMF-MeOH	19
144	6,8-Cl_2	>0.156	>10	$C_{10}H_5Cl_2N_5O \cdot 0.5H_2O$[k]	DMF	27
145	7,8-Cl_2	>0.156	>10	$C_{10}H_5Cl_2N_5O$	DMF	29
146	5,8-$(MeO)_2$	1.25	>10	$C_{13}H_{13}N_5O_2$	DMF	24
147	8-F-6-CH_3	2.5	>10	$C_{11}H_9FN_5O \cdot 0.5H_2O$[l]	*d*	72
148	7,8-$(CH_2)_4$		>25	$C_{14}H_{13}N_5O \cdot 0.1H_2O$	*d*	87

[a] Prepared by method K (see Experimental Section). [b] Minimum effective dose. See text for discussion. [c] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. Melting points of all these compounds were greater than 275 °C. [d] Not recrystallized but reprecipitated with acid and washed with H_2O and/or methanol. [e] Nitrogen analysis was within 0.5%. [f] Carbon and nitrogen analyses were within 0.5%. [g] Activity in parentheses is of ball-milled suspension (see text). [h] Carbon analysis was within 0.5%. [i] Prepared by method N (see Experimental Section). [j] Hydrogen analysis was within 0.5%. [k] Karl Fischer water determination: calcd, 3.2; found 3.1. [l] Karl Fischer water determination: calcd, 3.1; found, 2.3.

Table IV. 1,4-Dihydro-4-oxoquinoline-3-carboxylic Acids



no.	R	MED, mg/kg[a] ip	MED, mg/kg[a] po
119	6-OMe[b]	>50	>100
120	7-OMe[c]	>50	>100
121	8-OMe[d]	10	>100
122	8-F[e]		>100
123	8-Cl[c]		>100

[a] Minimum effective dose. See text for discussion. [b] See ref 28. [c] See ref 7. [d] See ref 31. [e] Prepared by method E (see Experimental Section), mp 275–280 dec. Anal ($C_{10}H_6NO_3F$) C, H, N.

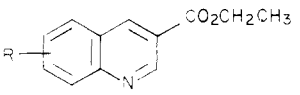
prepared as the result of our exploring alternative routes to the 4-unsubstituted tetrazoles for which we prepared the intermediate 4-oxoquinolinecarbonitriles. The activity of the 4-oxo-3-tetrazoles (Table III) is strikingly greater than that of the 4-oxo-3-carboxylates (Table IV), and the latter compounds lack oral activity at the doses tested.

The initial 4-oxo-3-(tetrazol-5-yl)quinoline tested was the 8-fluoro derivative **131** which although more potent intraperitoneally showed only moderate oral activity. However, with the 8-chloro derivative **132**, we found extremely potent activity by both routes. Further evaluation of **132** showed the activity was dependent on particle size and that ball-milling the acacia suspension increased the oral activity. A similar effect was observed with **131**. Economic constraints prevented us from evaluating all the compounds in Table III in this manner, but it was felt that, since we were observing increases of from two- to fivefold significantly active compounds would be found at our screening doses of 10 and 25 mg/kg.

In the structure–activity relationships in Table III, we quickly found that moving the chloro or fluoro moiety from the 8 position to the 6 position resulted in a dramatic loss in oral activity. Exactly the opposite effect was found with the ethyl group. Replacing the chloro group at position 8 by alkoxy groups resulted in retention of activity; replacement by trifluoromethyl or alkyl groups gave a loss in oral but not systemic activity; and, finally, replacement by bromo, methylthio, or methylsulfonyl resulted in a loss of activity by both routes. Adding a second substituent, as in compounds **142**–**148**, did not increase activity and, in most cases, was detrimental to oral activity.

In summary, we were able, starting from quinoline-3-carboxylic acid with an oral MED of 150 mg/kg in the PCA assay, to increase activity through a series of structural modifications to obtain **132** with an MED of 0.156 mg/kg. The key modification was the replacement of the carboxyl group with tetrazole. The reasons for the

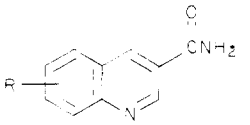
Table V. Ethyl Quinoline-3-carboxylates



no.	R	formula[a]	methods	mp, °C	recrystn solv	yield, %
26	6-F	$C_{12}H_{10}FNO_2$	A, C	105-107	cyclohexane	10
27	6-CF_3	$C_{13}H_{10}F_3NO_2$	B, C	138-140	cyclohexane	43
28	6-OMe	*b*	B, C	83-85	cyclohexane	35
29	6-oxocyclohexyl	$C_{18}H_{21}NO_3 \cdot HCl$[c]	B, C	203 dec	*d*	74
30	6-*n*-butyl	$C_{16}H_{19}NO_2 \cdot HNO_3$	A, C	124-127	H_2O	62
31	6-cyclohexyl	$C_{18}H_{21}NO_2 \cdot HCl$[c]	B, C	174-176	EtOH-Et_2O	71
32	7-CF_3	$C_{13}H_{10}F_3NO_2$	A, C	74-76	EtOH	31
33	7-OMe	*e*	B, C	*e*	*d*	84
34	8-F	$C_{12}H_{10}FNO_2$	B, D	51-53	*f*	75
35	8-Cl	$C_{12}H_{10}ClNO_2$	B, C	88-90	cyclohexane	68
36	8-CF_3	*g*	A, C	86-88	benzene-hexane	78
37	8-Me	$C_{13}H_{13}NO_2$	A, C	82-86	*f*	15
38	8-Et	*e*	B, C	*e*	oil	52
39	8-OMe	$C_{13}H_{13}NO_3$	B, C	61-63	EtOH-hexane	38
40	8-OEt	$C_{14}H_{15}NO_3$	B, C	70-72	cyclohexane	52
41	5,8-$(OMe)_2$	$C_{14}H_{15}NO_4$	B, C	134-135	cyclohexane	14
42	6,8-F_2	$C_{12}H_9F_2NO_2$	A, C	109-110	cyclohexane	50
43	7,8-Me_2	$C_{14}H_{15}NO_2 \cdot HCl$	B, C	159-162	EtOH-EtOAc	25
44	7,8-tetramethylene	$C_{16}H_{17}NO_2$	B, C	60-70	hexane	24
45	7,8-benzo	$C_{16}H_{13}NO_2$	A, C	175-182	DMF	33

[a] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. [b] Lit.[37] mp 81-83. [c] Chlorine analysis was within 0.4%. [d] Washed with ethyl ether. [e] Not characterized. [f] Purified by dissolving in base and reprecipitating with acid. [g] Lit.[16] mp 88-89.5.

Table VI. Quinoline-3-carboxamides



no.	R	formula[a]	method	mp, °C	recrystn solv	yield, %
66	6-F	$C_{10}H_7FN_2O$	F	214-218	EtOH	48
67	6-OMe	$C_{11}H_{10}N_2O_2$	F	220	H_2O	36
68	6-oxocyclohexyl	$C_{16}H_{18}N_2O_2$	F	199-201	EtOAc	48
69	6-*n*-butyl	*b*	F	200-204	MeOEtOH	33
70	6-cyclohexyl	*b*	F	212-217	EtOH	40
71	7-CF_3	*b*	G	214	MeOEtOH-H_2O	66
72	7-OMe	$C_{11}H_{10}N_2O_2$	F	228-229	*d*	21
73	8-Me	*e*	F	*e*	*d*	83
74	8-Et	$C_{12}H_{12}N_2O$[c]	G	196	*d*	70
75	8-F	*e*	H	209	H_2O	15
76	8-CF_3	$C_{11}H_7F_3N_2O$	F	227-228	*i*-PrOH	48
77	8-OMe	$C_{11}H_{10}N_2O_2$[c,f]	F	233	*d*	61
78	5,8-$(OMeO)_2$	$C_{12}H_{12}N_2O_3$	F	>260	*d*	39
79	6,8-F_2	$C_{10}H_6F_2N_2O$	F	256-258	*d*	63
80	7,8-Me_2	$C_{12}H_{12}N_2O$	F	180-182	EtOH	59
81	7,8-$(CH_2)_4$	$C_{14}H_{14}N_2O$	F	269-272	MeOEtOH	13
82	7,8-benzo	$C_{14}H_{10}N_2O$	F	272-275	MeOEtOH	77

[a] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. [b] Did not analyze; low nitrogen. [c] Within 0.5% for C. [d] Washed with dilute NH_4OH. [e] Not characterized. [f] Lit.[36] mp 250-251.

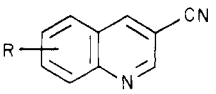
greatly increased activity of the tetrazole derivatives is unknown. Although our study of substituent effects is limited, it is clear from the data discussed above that both the 4-oxo moiety and substituents in the benzo ring have a pronounced effect on activity. In future publications we will discuss the effects on PCA activity of substituting on the tetrazolo and pyrido moieties of **132**.

As stated in the introduction, PCA testing is only the initial screen in our search for orally active DSCG-like agents and, therefore, certain of these compounds were evaluated in a range of pharmacological models.[23] (These models include evaluation for antihistamine and antiserotinin activity, bronchoprovocation tests in dogs, and evaluation for cardiovascular and central nervous system activities.) From these studies it was concluded that these compounds are DSCG-like and one of them, **132**, was selected for further development. However, during animal toxicity studies, **132** was found to produce crystalluria, which is not surprising given its low solubility, and was dropped from further study. Evaluation of other compounds in this series as alternatives to **132** is under investigation.

Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp block or Uni-melt oil bath and are uncorrected. The IR spectra were measured as Nujol mulls on a Perkin-Elmer infrared spectrometer. The ^1H NMR spectra were measured in $CDCl_3$, Me_2SO-d_6, or CF_3CO_2D solution on a Varian A-60 or a T-60 spectrometer. The IR and ^1H NMR spectra were consistent with the assigned structure in all cases. Elemental analyses were

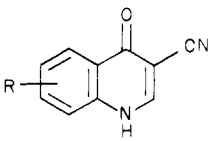
Table VII. Quinoline-3-carbonitriles[a]



no.	R	formula[b]	mp, °C	recrystn solv	yield, %
83	6-F	oil			75
84	6-OMe	$C_{11}H_8N_2O$[c]	95	MeOH-H_2O	95
85	6-oxocyclohexyl	*d*	*d*	*e*	88
86	6-*n*-butyl	$C_{14}H_{14}N_2$	51-53	hexane	38
87	6-cyclohexyl	oil	*d*		62
88	7-CF_3	$C_{11}H_5F_3N_2$	152	EtOH	33
89	7-OMe	oil	*d*		69
90	8-Me	*d*	*d*	*e*	52
91	8-Et	$C_{12}H_{10}N_2$	96	EtOH	76
92	8-F	$C_{10}H_5FN_2$	175	*e*	76
93	8-CF_3	$C_{11}H_5F_3N_2$	134-135	cyclohexane	84
94	8-OMe	$C_{11}H_8N_2O$[f]	175	*e*	91
95	5,8-$(OMe)_2$	*d*	140-150	*e*	69
96	6,8-F_2	$C_{10}H_4F_2N_2$	202-204	*i*-PrOH	61
97	7,8-Me_2	$C_{12}H_{10}N_2$	162-164	hexane-benzene	97
98	7,8-$(CH_2)_4$	$C_{14}H_{12}N_2$[g]	131-132	*e*	79
99	7,8-benzo	*d*	173-175	EtOH	88

[a] Compounds prepared by method I (see Experimental Section). [b] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. [c] Lit.[15] mp 132-133. [d] Not characterized. [e] Not recrystallized, washed with 10% NH_4OH. [f] Carbon analysis within 0.5%. [g] Carbon analysis within 0.6%.

Table VIII. 1,4-Dihydro-4-oxoquinoline-3-carbonitriles[a]



no.	R	formula[b]	recrystn solv	yield, %
149	H	*c*	*d*	14
150	6-F	*e*	*d*	4
151	6-Cl	*e*	MeOEtOH-H_2O	58
152	6-CH_3	$C_{11}H_8N_2O$	*d*	68
153	6-CH_2CH_3	$C_{12}H_{10}N_2O$	*d*	60
154	7-CH_2CH_3	$C_{12}H_{10}N_2O$	*d*	60
155	7-OCH_3	$C_{11}H_8N_2O_2$	DMF	29
156	8-F	*e*	MeOEtOH	15
157	8-Cl	$C_{10}H_5ClN_2O$	*d*	87
158	8-Br	$C_{10}H_5BrN_2O$	*d*	65
159	8-CF_3	$C_{11}H_5F_3N_2O$	*d*	47
160	8-CH_3	$C_{11}H_8N_2O$	*d*	77
161	8-CH_2CH_3	$C_{12}H_{10}N_2O$	*d*	20
162	8-$CH(CH_3)_2$	*e*	PrOH	26
163	8-OCH_3	$C_{11}H_8N_2O_2$[f]	MeOEtOH-H_2O	7
164	8-$OCH(CH_3)_2$	$C_{13}H_{12}N_2O_2$	*d*	64
165	8-SCH_3	$C_{11}H_8N_2OS$[g]	MeOEtOH	44
166	5,8-F_2	$C_{10}H_4F_2N_2O$	*d*	100
167	5,8-Cl_2	$C_{10}H_4Cl_2N_2O$[h]	*d*	50
168	6,8-Cl_2	$C_{10}H_4Cl_2N_2O$	*d*	89
169	7,8-Cl_2	$C_{10}H_4Cl_2N_2O$	*d*	71
170	5,8-$(MeO)_2$	$C_{12}H_{10}N_2O_3$	*d*	55
171	8-F-6-CH_3	$C_{11}H_7FN_2O$	*d*	77
172	7,8-$(CH_2)_4$	$C_{14}H_{12}N_2O$	DMF	49

[a] Compounds prepared by method M (see Experimental Section). [b] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. Melting points of all these compounds were greater than 275 °C. [c] Lit.[38] mp 301. [d] Not recrystallized; washed with ethyl ether. [e] Not characterized. [f] Lit.[39] mp 295 °C. [g] Carbon analysis was within 0.5%. [h] Known compound; see ref 20a.

determined at the 3M Central Research Laboratory. Where analyses are indicated only by symbols of elements, they are within ±0.4% of the theoretical values.

The general procedures listed in the tables and the preparation of the requisite starting materials are described by the following examples.

Anilines. The requisite anilines, except for the 4-cyclohexyl and 4-(cyclohexyloxy) derivatives, were commercially available.

4-(Cyclohexyloxy)-1-nitrobenzene (176). To a stirred suspension, under nitrogen, of sodium hydride (21.1 g, 57% in mineral oil, 0.5 mol) in 500 mL of dimethylformamide was added dropwise 50 g (0.5 mol) of cyclohexanol at a rate such that the temperature did not exceed 46 °C. After the addition was complete, the reaction mixture was stirred for an additional 2 h at ambient temperature and then 70.5 g (0.5 mol) of 4-fluoro-1-nitrobenzene was added dropwise while the temperature was kept between 35 and 40 °C with the aid of an ice bath. After the addition was complete, the reaction was stirred for 1 h at ambient temperature and then for an additional hour at 50 °C. On cooling, the reaction mixture was cautiously diluted with H_2O (2000 mL)

and extracted with 2 × 500 mL of methylene chloride. (An emulsion formed which slowly separated on standing.) The combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), stirred with Darco, filtered, and concentrated to a dark oil, which was distilled to give 75 g (0.34 mol, 67%) of **176**, bp 151–155 °C (0.4 mmHg) [lit.[24] bp 189–191 °C (12 mm)].

4-(Cyclohexyloxy)aniline (177). To a refluxing mixture of 75 g (0.34 mol) of **176** and 1 g of 10% Pd/C in 400 mL of ethanol was added 60 mL of 85% hydrazine hydrate at a sufficient rate to maintain reflux without external heating. After the addition was complete, refluxing was continued for 2 h, and then the solution was filtered (Celite) and concentrated to an oil, which was distilled to give 59 g (0.31 mol, 91%) of **177**, bp 131–135 °C (0.8 mmHg) [lit.[24] bp 128 °C (0.2 mm)].

4-(4-Cyclohexylphenoxy)-2-phenylquinazoline (178). 4-Cyclohexylphenol (88 g, 0.5 mol) was added in small portions over 20 min to a suspension of sodium hydride (24.9 g, 53% in mineral oil, 0.55 mol) in 400 mL of diglyme; during the addition, the temperature rose to 40 °C. The reaction mixture was stirred an additional 30 min at ambient temperature; then 120 g (0.5 mol) of 4-chloro-2-phenylquinazoline (Am-ex-OL, Aldrich Chemical Co.) was added and the temperature rose to 60 °C. The mixture was heated to 105 °C for 1 h. After cooling, the reaction mixture was poured onto ice–H_2O, and the resulting precipitate was collected on a filter, washed with H_2O, and dried at 100 °C in vacuo to give 180 g (0.47 mol, 95%) of **178** suitable for further transformations. Recrystallization from cyclohexane gave analytical material, mp 141–142 °C. Anal. ($C_{26}H_{24}N_2O$) C, H, N.

3-(4-Cyclohexylphenoxy)-2-phenylquinazoline (179). A solution of 180 g (0.47 mol) of **176** in Nujol (total volume 400 mL) was mechanically stirred for 2 h at 325–365 °C. The reaction mixture was cooled to room temperature, diluted with 1500 mL of petroleum ether, and vigorously stirred for 1 h. The precipitate was collected on a filter and air-dried to give 147 g (0.39 mol, 82%), mp 210–220 °C. Recrystallization from benzene gave material suitable for analysis, mp 220–221 °C. Anal. ($C_{26}H_{24}N_2O$) C, H, N.

4-Cyclohexylaniline (180). Compound **179** (29 g, 0.076 mol) was refluxed overnight in 300 mL of ethanol and 60 mL of 50% NaOH. After cooling to room temperature, the reaction mixture was acidified with 37% HCl and warmed at 50 °C for 20 min. The solution was then made alkaline with 10% NaOH and extracted with ethyl ether. The extract was washed with saturated NaCl and concentrated to 13 g of brown oil.

This oil was combined with the oil obtained by the same procedure from an additional 118 g of **179**. Distillation of the combined oils gave 43 g (0.25 mol, 50%) of **180**, bp 110–114 °C (0.3 mmHg), which solidified on cooling, mp 48–52 °C [lit.[25] mp 50.8–52.4 °C].

Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylates were prepared by the method of Price and Roberts[17] and had physical constants in agreement with literature values or satisfactory elemental analyses: **5** (6-fluoro[26]), **6** [6-(trifluoromethyl)[27]], **7** (6-methoxy[28]), and **8** [6-(cyclohexyloxy)] mp 260 °C [Anal. ($C_{18}H_{21}NO_4$) C, H, N]; **9** (6-*n*-butyl[29]) and **10** (6-cyclohexyl) mp >260 °C [Anal. ($C_{18}H_{21}NO_3$) C, H, N]; **11** [7-(trifluoromethyl)[26]], **12** (7-methoxy[30]) and **13** (8-fluoro) mp 210–212 °C [Anal. ($C_{12}H_{10}FNO_3$) C, H, N; **14** (8-chloro[31]), **15** [8-(trifluoromethyl)[27]], **16** (8-methyl[32]) and **17** (8-ethyl) mp 233–240 °C [Anal. ($C_{14}H_{15}NO_3$) C, H, N]; **18** (8-methoxy[31]), **19** (8-ethoxy[33]), **20** (5-8-dimethoxy[34]) and **21** (6,8-difluoro) mp 268–269 °C [Anal. ($C_{12}H_9F_2NO_3$) C, H, N]; **22** (7,8-dimethyl) mp >260 [Anal. ($C_{14}H_{15}NO_3$) C, H, N]; **23** (7,8-tetramethylene[35]) and **24** (7,8-benzo[32]).

Method A. Ethyl 4-Chloro-8-(trifluoromethyl)quinoline-3-carboxylate (25, R = 8-CF_3). A mixture of 180 g (0.63 mol) of **15** in 210 mL of thionyl chloride was refluxed for 3 h, during which the reaction mixture became homogeneous. The hot solution was cautiously added to concentrated NH_4OH (excess) and ice. The resulting mixture was extracted twice with chloroform. The combined extracts were washed twice with H_2O, dried ($MgSO_4$), and evaporated to 170 g (0.63 mol, 100%) of yellow oil, which was used directly in method C.

Method B. Ethyl 4-Chloro-8-methoxyquinoline (25, R = 8-MeO). A mixture of 31 g (0.125 mol) of **16** and 23 mL (~0.25 mol) of phosphorus oxychloride was refluxed for 2 h, during which the reaction became homogeneous. The hot reaction solution was "cautiously added dropwise" to 100 mL of concentrated NH_4OH and 300 g of ice. (The phosphorus oxychloride should react vigorously with the aqueous solution, if not there is danger of a delayed, violent reaction.) The resulting mixture was extracted with an equal volume of methylene chloride, and the organic extract was washed with 10% NH_4OH, then dried ($MgSO_4$), and concentrated to a brown oil, which solidified to 29 g (0.11 mol, 88%) of the desired 4-chloro derivative suitable for further transformation.

Method C. Ethyl 8-(Trifluoromethyl)quinoline-3-carboxylate (36). A mixture of 170 g (0.63 mol) of ethyl 4-chloro-8-(trifluoromethyl)quinoline-3-carboxylate, 12 g of 10% Pd/C, and 800 mL of acetic acid was shaken overnight in a Parr hydrogenator. (Observed hydrogen absorption was 93% of theory.) The resulting slurry was warmed, filtered to remove catalyst, and allowed to stand at 15 °C overnight. The precipitated solid was filtered and washed with petroleum ether to give 86 g of **33**, mp 83–85 °C (lit.[16] mp 88–89.5 °C). Dilution of the filtrate with petroleum ether gave an additional 40 g: mp 83–85 °C; combined yield 126 g (0.44 mol), 70%.

Method D. Ethyl 8-Fluoroquinoline-3-carboxylate (34). A mixture of 48 g (0.19 mol) of ethyl 4-chloro-8-fluoroquinoline-3-carboxylate (obtained as an oil from the requisite 4-oxoquinoline by method A), 55 mL (~0.38 mol) of triethylamine, 2 g of 5% Pd/C (50% water-wet), and 300 mL of ethanol was shaken in a Parr hydrogenator until the theoretical amount of hydrogen was absorbed (~2 h). The reaction mixture was filtered (Celite), concentrated to an oil, diluted with 10% NH_4OH, and extracted with methylene chloride. The organic extract was washed with 10% NH_4OH, dried ($MgSO_4$), and concentrated to give **31** as a yellow solid (40 g, 0.18 mol, 95%), mp 51–53 °C. Anal. ($C_{12}H_{10}FNO_2$) C, H, N.

Method E. 8-(Trifluoromethyl)quinolinecarboxylic Acid (56). Compound **36** (86 g, 0.32 mol) was refluxed in 500 mL of 10% NaOH for 1 h and then acidified with 37% HCl. The resulting precipitate was collected on a filter and dried overnight at 110 °C in vacuo to give 47.4 g (61%), mp 206–208 °C (lit.[16] mp 208–209 °C).

Method F. 8-(Trifluoromethyl)quinoline-3-carboxamide (76). A mixture of 47 g (0.2 mol) of **56** and 100 mL of thionyl chloride was refluxed for 2 h, and then the $SOCl_2$ was removed in vacuo. The resulting solid was dissolved in 800 mL of chloroform, and then ammonia gas was bubbled thru the resulting solution until it turned to a consistent paste (~2 h). The white solid was collected on a filter and washed with chloroform, followed by warm H_2O. Recrystallization from methoxyethanol–2-propanol (1:12) gave 36 g (75%) of **76**, mp 227–228 °C. Anal. ($C_{11}H_7F_3N_2O$) C, H, N.

Method G. 8-Methoxyquinoline-3-carboxamide (77). To a stirred mixture of 73 g (0.36 mol) of **59**, 38 g (0.38 mol) of triethylamine, and 400 mL of dioxane cooled to 10 °C with an ice bath was added dropwise 38 g (0.35 mol) of ethyl chloroformate, maintaining the temperature at 10 °C. The resulting mixture was stirred for 1 h after the addition was completed and then ammonia gas was bubbled through the solution for 5 min. The solution was allowed to stir for 1 h and diluted with H_2O, and the resulting solid was collected on a filter and dried to give 44 g of **77**, mp 233 °C (lit.[36] mp 250–251 °C).

Method H. Identical to method G, except following the addition of ammonia gas the resulting solution was concentrated to remove most of the dioxane, the residue was diluted with 5% NaOH, and the resulting precipitate was collected on a filter.

Method I. 8-(Trifluoromethyl)quinoline-3-carbonitrile (93). To a solution of 36 g (0.15 mol) of **76** in 250 mL of dimethylformamide cooled to 5 °C was slowly added 26.7 g (0.22 mol) of thionyl chloride. The resulting solution was stirred at ambient temperature for 48 h and then diluted to 1000 mL with H_2O. The resulting beige precipitate was collected on a filter, washed with H_2O, air-dried, and recrystallized from methylene chloride–cyclohexane to yield 31 g (94%) of **93**, mp 134–135 °C. Anal. ($C_{11}H_5F_3N_2$) C, H, N.

Method K. 3-(1*H*-Tetrazol-5-yl)-8-(trifluoromethyl)-quinoline (109). A mixture of 31.1 g (0.14 mol) of **93**, 11.6 g (0.18 mol) of NaN_3, 9.5 g (0.18 mol) of NH_4Cl, and 300 mL of dimethylformamide was sitrred overnight at 120 °C. This mixture was filtered and diluted to 1300 mL with 10% HCl. The resulting

beige precipitate was collected on a filter, washed with H_2O, and dried overnight at 110 °C in vacuo: yield 25.1 g (68%) of **109**; mp 192–193 °C. Anal. ($C_{11}H_6F_3N_5$) C, H, N.

Method L. 7,8-Dimethyl-5-nitro-3-(1*H*-tetrazol-5-yl)quinoline (118). A mixture of 2.25 g (0.01 mol) of **115** (Table II), 10 mL of 96% H_2SO_4, and 1 mL of HNO_3 was heated for 1 h on a steam bath. The reaction mixture was poured onto ice and the precipitate collected on a filter. Three recrystallizations from ethanol gave 0.5 g (19%) of **118**, mp 175–185 °C. Anal. ($C_{12}H_{10}N_6O_2$) C, H; N; calcd, 31.1; found, 31.6.

Method M. 8-Bromo-1,4-dihydro-4-oxoquinoline-3-carbonitrile (158). A solution of 2-bromoaniline (17.2 g, 0.1 mol) and ethyl ethoxymethylenecyanoacetate (16.9 g, 0.1 mol) in 800 mL of phenyl ether was refluxed (internal temperature 255 °C) in a Morton flask with mechanical stirring for 8 h. During the first hour a stream of nitrogen was passed over the solution. The precipitate which formed on cooling was collected on a filter, washed thoroughly with ether, and dried to give 22.5 g (0.09 mol, 90%) of **158**, mp >260 °C. Anal. ($C_{10}H_5BrN_2O$) C, H, N.

Method N. 1,4-Dihydro-8-(methylsulfonyl)-4-oxo-3-(tetrazol-5-yl)quinoline (141). To 10.8 g (0.042 mol) of **140** in 100 mL of refluxing acetic acid was added dropwise 8.5 mL of 30% H_2O_2. The resulting mixture was refluxed overnight (~18 h), cooled, and diluted with H_2O. The product was collected on a filter and washed first with H_2O and then with methanol. Drying overnight in vacuo gave **141**: yield 11.2 g (0.038 mol, 92%); mp >260 °C. Anal. ($C_{11}H_9N_5O_3S$) C, H, N.

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