46, 98106-18-4; **46**·HCl, 98106-04-8; **47**, 98106-19-5; **17**·HCl, 98106-05-9; **48**, 98106-20-8; **48**·HCl, 98106-06-0; **49**, 98106-21-9; **49**·HCl, 98106-07-1; **50**, 98106-22-0; **50**·HCl, 98106-08-2; **51**, 98106-23-1; **51**·HCl, 98106-09-3; **52**, 98106-24-2; **52**·HCl, 98106-10-6; **53**, 98106-25-3; **53**·HCl, 98106-11-7; **54**, 98106-26-4; **54**·HCl, 98106-12-8; **55**, 98106-46-8; **55**·HCl, 98106-27-5; **56**, 98106-47-9; **56**·HCl, 98106-28-6; **57**, 98106-29-7; **58**, 98106-30-0; **59**, 98106-31-1; **60**, 98106-32-2; **61**, 98106-33-3; **61**·HCl, 98106-48-0; **62**, 98106-34-4; **63**, 98106-35-5; **64**, 98106-49-1; **64**·HCl, 98106-39-9; **65**, 98106-50-4; **65**·HCl, 98106-40-2; **66**, 98106-41-3; **67**, 98106-42-4; **68**, 98106-43-5; **69**, 98106-44-6; **70**, 98106-45-7; **71**, 98106-36-6; **72**, 98106-37-7; **73**, 98106-38-8; carboethoxypiperazine, 120-43-4; 1-(*p*-fluorophenyl)-6-fluoro-7-(4-carboethoxypiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hexahydro-1,4-diazepine, 505-66-8; thiomorpholine, 123-90-0; 4-piperidinol, 5382-16-1; *N*,*N*-dimethyl-4-piperidinamine, 50533-97-6; 3-pyrrolidinol, 40499-83-0; *N*-(3-pyrrolidinyl)acetamide, 79286-74-1; 1-propionylpiperazine, 76816-54-1; piperazinone, 5625-67-2; 1-methylpiperazinone, 59702-07-7; isopropylmethylamine, 4747-21-1; *N*-methyl-*N*-(3-pyrrolidinyl)acetamide, 79286-87-6; aniline, 62-53-3; 2-fluoroaniline, 348-54-9; 3-fluoroaniline, 372-19-0; 4-fluoroaniline, 371-40-4; 4-bromoaniline, 106-40-1; 4-chloroaniline, 106-47-8; 4-hydroxyaniline, 123-30-8; 4-methoxyaniline, 104-94-9; 4-methylaniline, 106-49-0; 6-aminobenzodioxole, 14268-66-7; 2,4-difluoroaniline, 367-25-9; 2-methylaniline, 95-53-4; 2,6-dimethylaniline, 87-62-7.

4-Substituted 5-[*m*-(Trifluoromethyl)phenoxy]primaquine Analogues as Potential Antimalarial Agents

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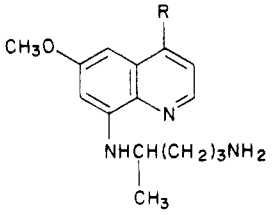
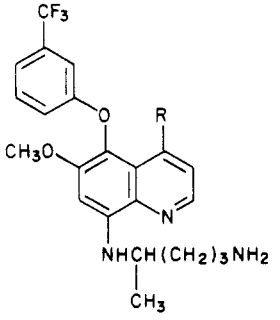
Five 4-substituted 5-[*m*-(trifluoromethyl)phenoxy]primaquine analogues were synthesized and tested for radical curative activity against *Plasmodium cynomolgi* in Rhesus monkeys and for blood schizonticidal antimalarial activity against *Plasmodium berghei* in mice. In addition, they were evaluated for causal prophylactic antimalarial activity against *Plasmodium berghei yoelii* in mice. One compound, 4-ethyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (**2b**), showed radical curative activity equivalent to 4-methyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (**2a**). A second compound showed radical curative activity slightly less than **2a** and **2b**; the remaining three compounds were not active against *P. cynomolgi*. All five compounds showed much higher blood schizonticidal activity and less toxicity than primaquine; however, none of the compounds were as active as **2a**. Three of four compounds tested showed high activity against *P. berghei yoelii*.

For many years primaquine (**1a**), which is a radical curative drug,[3] has been the drug of choice for the treatment of relapsing *Plasmodium vivax* and *Plasmodium malariae*. Primaquine (**1a**) is effective in clearing the tissues of parasites but is ineffective as a blood schizonticide. Moreover, its toxicity precludes administration of a single curative dose. Recently, LaMontagne and co-workers[1,2] reported that 4-methyl-5-[*m*-(trifluoromethyl)phenoxy]-primaquine (**2a**) was a highly effective antimalarial agent that possessed both tissue and blood schizonticidal activity. In addition, **2a** had a significantly better therapeutic index than primaquine (**1a**).



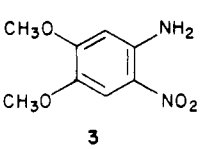
1a, R = H
b, R = C_2H_5
c, R = CH_2=CH



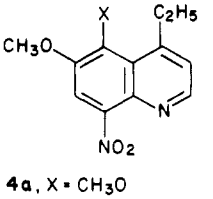
2a, R = CH_3
b, R = C_2H_5
c, R = CH_2=CH
d, R = CH_2OH
e, R = CH_3OCH_2
f, R = $(CH_3O)_2CH$

In an earlier study we reported that 4-ethyl- and 4-vinylprimaquine (**1b** and **1c**, respectively) showed radical curative activity similar to primaquine but were less toxic.[3] Thus, the synthesis of 4-ethyl- and 4-vinyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (**2b** and **2c**) is a logical extension of our earlier work. In order to gain information concerning the optimal substituent pattern for this class of compounds, we were also interested in the synthesis of the 4-hydroxymethyl, 4-methoxymethyl, and 4-dimethoxymethyl analogues **2d–f**. In this paper we present the synthesis and antimalarial evaluation of **2b–f**.

Chemistry. Compound **2b** was prepared by a procedure analogous to that used by LaMontagne to prepare **2a**.[1,2] Thus, 4-amino-5-nitroveratrole (**3**) was subjected to a modified Skraup reaction using chloro-3-pentanone to give the 4-ethylquinoline analogue (**4a**). Mild hydrolysis of **4a** followed by treatment with phosphorus oxychloride yielded the 5-chloroquinoline **4b**. Treatment of **4b** with the potassium salt of *m*-(trifluoromethyl)phenol afforded **4c**. Stannous chloride reduction of **4c** followed by standard attachment of the primaquine side chain gave **2b**.



3



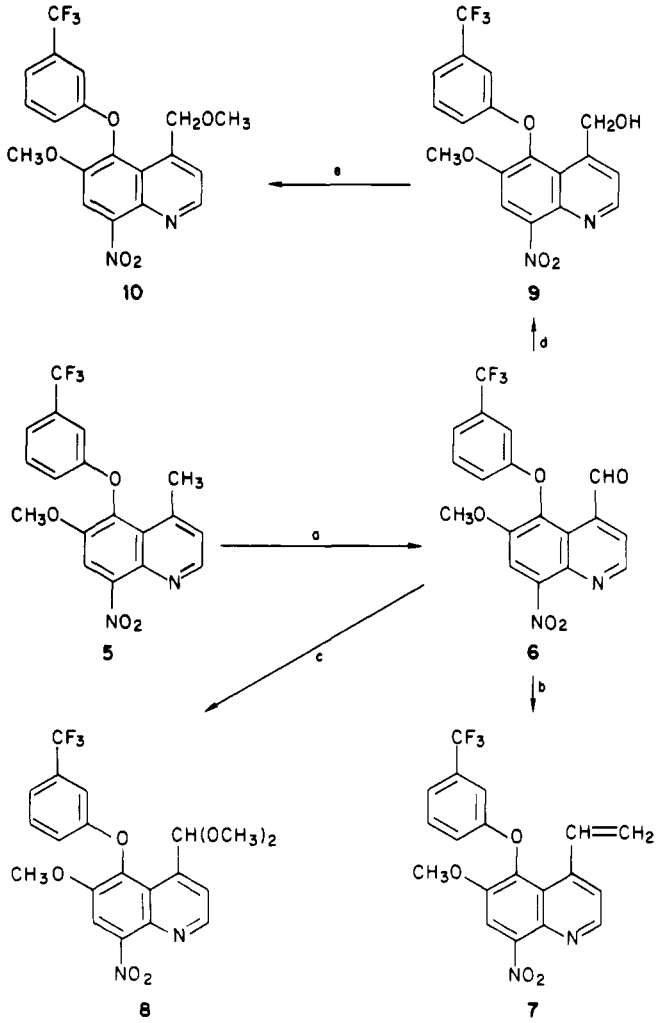
4a, X = CH_3O
b, X = Cl
c, X = *m*-$CF_3C_6H_4O$

In order to prepare compounds **2c–f**, the nitroquinolines **7–10** were required. These intermediates were prepared from 4-methyl-6-methoxy-5-[*m*-(trifluoromethyl)phenoxy]-8-nitroquinoline[1,2] as shown in Chart I. Selenium dioxide oxidation of **5** gave the 4-carboxaldehyde **6**, which

(1) LaMontagne, M. P.; Blumbergs, P.; Strube, R. E. *J. Med. Chem.* **1982**, *25*, 1094.
(2) Strube, R. E.; LaMontagne, M. P. U.S. Patent 4 431 807, 1984.
(3) Carroll, F. I.; Berrang, B. D.; Linn, C. P. *J. Med. Chem.* **1979**, *22*, 1363.

0022-2623/85/1828-1564$01.50/0

Chart I[a]



[a] (a) SeO_2, (b) $(C_6H_5)_3P=CH_2$, (c) CH_3OH, H^+, (d) $NaBH_4$, EtOH, −50 °C, (e) CH_3I.

was used to prepare the intermediate nitroquinolines **7–10**. Subjection of **6** to the Wittig reaction using methylenetriphenylphosphorane and inverse addition gave the 4-vinylnitroquinoline **7**. Treatment of **6** with methanol under *p*-toluenesulfonic acid catalysis gave the dimethyl acetal **8**. Sodium borohydride reduction of **6** in ethanol at −50 °C gave the 4-hydroxymethyl analogue **9**. Methylation of **9** under phase-transfer conditions gave the 4-(methoxymethyl)-8-nitroquinoline (**10**). The intermediate nitroquinolines were converted to the 8-aminoquinoline analogues **2b–f** by using procedures previously reported for other 8-nitroquinolines.[3] This involved stannous chloride reduction, followed by alkylation with 4-iodo-1-phthalimidopentane and removal of the phthaloyl protecting group with hydrazine. In the case of **2c** attempts to remove the protecting group with hydrazine were unsuccessful. However, the use of a hydroxylamine sodium methoxide mixture in methanol affected a clean removal of the phthaloyl protecting group to give the desired **2c**.

Biological Testing. Compounds **2b–f** were tested for radical curative activity against *Plasmodium cynomolgi* in Rhesus monkeys[4,5] and for suppressive antimalarial activity against *Plasmodium berghei* in mice.[6] The data

Table I. Antimalarial Activities against *P. cynomolgi* in Rhesus Monkeys[a,b]

compd	dose,[c] mg/kg	cures[d]	relapses[e]
1[f]	0.1	0/2	
	0.316	0/2	
	1.0	1/2	
2a[f]	0.1	0/1	
	0.316	2/2	
	1.0	2/2	
2b	0.1	0/2	20, 34
	0.316	2/2	
	1.0	2/2	
2c	1.0	0/2	12, 19
2d	1.0	0/1	
2e	0.1	0/2	8, 8
	0.316	1/2	28
	1.0	2/2	
2f	1.0	0/2	24, 44

[a] Data were supplied by H. A. Musallam and B. T. Poon, Walter Reed Army Institute of Research. [b] Tests were carried out by SEATO Medical Research Laboratory, Bangkok.[4,5] [c] Dose administered via stomach tube once daily for 7 days with 5 mg of base/kg of chloroquine. [d] Monkeys that did not relapse are considered cured (see ref 4). [e] The number given is the days between the end of treatment and relapse. [f] Taken from ref 1.

along with a comparison of the data for primaquine and **2a** are shown in Tables I and II, respectively. Compound **2b**, which shows 2/2 cures at both 0.316 and 1.0 mg/kg in the *P. cynomolgi* screen, has radical curative activity identical with **2a**. Compound **2e**, which shows 1/2 cures at 0.316 mg/kg and 2/2 cures at 1.0 mg/kg, respectively, was slightly less active than **2a** and **2b**. All three compounds are more active than primaquine in the *P. cynomolgi* screen. Compounds **2c**, **2d**, and **2f** were inactive in this screen at 1.0 mg/kg. Compounds **2b** and **2d–f** all showed much higher activity than primaquine in the *P. berghei* test, with **2b** (three cures at 20 mg/kg) having the greatest activity. All five compounds were less toxic than primaquine. None of the compounds were as active as **2a** against *P. berghei*, which showed one cure and three cures, respectively, at 5 and 10 mg/kg.

Compounds **2b** and **2d–f** were also tested for causal prophylactic activity against sporozoite induced *P. berghei yoelii* in rodents (Table III).[7,8] Compounds **2d–f** were active at 10, 40, and 160 mg/kg when administered subcutaneously. Compounds **2d–f** given orally were active at 40 mg/kg. Compound **2e** was also active at 10 mg/kg when administered orally.

The data in Tables I and II show that high radical curative activity as well as high blood schizonticidal activity combined with low toxicity is retained when the 4-methyl group of **2a** is replaced by an ethyl (**2b**) or methoxymethyl (**2e**) group. Replacement of the methyl of **2a** with a vinyl group (**2c**), a hydroxymethyl group (**2d**), or a dimethoxymethyl moiety (**2f**) results in loss of radical curative activity. However, compound **2f** gives moderate blood schizonticidal activity with a slight increase in toxicity whereas compounds **2c** and **2d** have much lower blood schizonticidal activity than **2a**.

The high activity of **2d**, **2e**, and **2f** against *P. berghei yoelii* (Table III) gives presumptive evidence for the causal prophylactic activity of these three compounds.

Experimental Section

Melting points were determined on a Kofler hot stage micro-

(4) Schmidt, L. N.; Rossan, R. N.; Fradkin, R.; Woods, J. *Bull. WHO* **1966**, *34*, 783.
(5) The test procedure is described in World Health Organization (1972b); WHO/MAL/72.763 (cyclostyled report), World Health Organization: Geneva.
(6) Osdene, T. S.; Russel, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.
(7) Mort, H.; Montouri, W. *Am. J. Trop. Med. Hyg.* **1975**, *24*, 179.
(8) Kinnamon, K. E.; Rane, D. S. *Am. J. Trop. Med. Hyg.* **1979**, *28*, 937.

Table II. Antimalarial Activity against *P. berghei* in Rodents[a]

compd	ΔMST, C or T:[b] dose, mg/kg							
	5	10	20	40	80	160	320	640
$1 \cdot 2H_3PO_4$					9.0	2T	5T	5T
2a[c]	1C	3C	5C	5C	5C	5C	5C	1C, 4T
2b	1.7	5.3	3C	4C	4C	5C	5C	1C, 3T
2c				−0.1		3.7		8.1
2d	0.6	1.4	3.6	3.8	1C	14.8	13.1	4T
2e	2.8	6.6	1C	5C	5C	4C	4C	2C
2f	1.9	2.5	5.5	8.5	1C	3C	2C	5T

[a] Tests were carried out by the Rane Laborabory, University of Miami, Miami, FL, using blood-induced *P. berghei* infected mice (five animals per group) by the method described by Osdene et al.[6] Test data were supplied by Dr. E. A. Steck of Walter Reed Army Institute of Research. [b] ΔMST, mean survival time over controls (6.2 ± 0.5 days). A compound is considered active if MST of the treated group is more than twice that of the control group: C, number of cures (mice surviving 60 days); T, number of toxic deaths occurring on days 2–5 after infection. [c] Taken from ref 1.

Table III. Antimalarial Activity against *P. berghei yoelii* in Rodents[a]

compd	dose, mg/kg	cures sc	cures po	toxic
2b	10	6/25		
	40	5/25		
	160	2/25		
2d	2.5	0/10	3/10	7
	10	10/15	3/10	
	40	14/15	10/10	
	160	3/5		2T (sc)
2e	2.5	1/5	0/5	
	10	8/10	5/5	
	40	9/10	4/5	
	160	5/5		
2f	2.5	0/5	0/5	
	10	9/15	0/5	
	40	12/15	4/5	
	160	10/10		

[a] These tests were carried out by the Rane Laboratory, University of Miami, Miami, FL, using sporozoite-induced *P. Berghei yoelii* infected mice.[7,8] The test compound was dissolved or suspended in 0.5% hydroxyethylcellulose–0.1% Tween 80 and administered either orally (po) or subcutaneously (sc) at several dose levels to groups of five mice on the day of challenge. Prophylactic activity is evidenced by survival of drug-treated mice to 30 days. Survival of 40% or more of the mice in the treated group may be considered as an indication of activity.

scope using a calibrated thermometer. IR spectra were measured with a Perkin-Elmer Model 267 or 467 grating infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. MS were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, IL, or Integral Microanalytical Laboratories, Inc., Raleigh, NC.

5,6-Dimethoxy-4-ethyl-8-nitroquinoline (4a). A solution of 9 g (0.045 mol) of 4-amino-5-nitroveratrole (**3**)[1] in 150 mL of concentrated phosphoric acid was cooled to 10 °C while 6.5 g (0.054 mol) of 1-chloropentan-3-one was added with stirring. The temperature of the mixture was gradually raised to 85 °C. The exothermic reaction was kept at 85–90 °C over a 1-h period. An additional 3 g of 1-chloropentan-3-one was added carefully, and the temperature was controlled so that it did not exceed 93 °C. After 1.5 h, the brown reaction mixture was cooled and diluted with 600 mL of ice water. A small amount of insoluble material was removed by filtration. The filtrate was basified with ammonia and extracted with chloroform. This gave 6.5 g of brown syrup, which was chromatographed on silica gel with methylene chloride–ethyl acetate as eluent. Concentration of the product fractions gave 2.1 g (18%) of **4a** as red-brown crystals. The sample recrystallized from a methylene chloride and methanol mixture had the following: mp 72–73 °C; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, CH_3CH_2), 3.26 (q, CH_3CH_2), 3.95 (s, 2 OCH_3), 7.08 (d, H_3), 7.7 (s, H_7), 8.6 (d, H_2). Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

4-Ethyl-6-methoxy-8-nitro-5-[*m*-(trifluoromethyl)phenoxy]quinoline (4c). The dimethoxyquinoline **4a** (2 g, 7.6 mmol) was refluxed with 2 mL of concentrated hydrochloric acid in 100 mL of ethanol–water (1:1). Upon cooling, 1.4 g of red-brown crystalls of 4-ethyl-5-hydroxy-6-methoxy-8-nitroquinoline separated: mp >250 °C dec; NMR (Me_2SO-d_6) δ 1.2 (t, CH_3CH_2), 3.5 (q, CH_3CH_2), 3.8 (s, OCH_3), 7.25 (d, H_3), 7.65 (s, H_7), 8.53 (d, H_2). The crude compound without further purification was heated with 20 mL of phosphorus oxychloride at 75–80 °C for 2 h. After concentration in vacuo, the residue was partitioned between chloroform and aqueous ammonia. The organic phase after removal of the solvent gave 1.2 g (59%) of **4b**: NMR ($CDCl_3$) δ 1.3 (t, CH_3CH_2), 3.5 (q, CH_3CH_2), 4.03 (s, OCH_3), 7.2 (d, H_3), 7.6 (s, H_7), 8.64 (d, H_2). A solution of 1.2 g (0.0074 mol) of *m*-(trifluoromethyl)phenol in 10 mL of water that contained 0.5 g (0.0089 mol) of potassium hydroxide was evaporated to dryness under vacuum. The resulting salt was heated and stirred in an oil bath at 135 °C under argon while 1.2 g (0.045 mol) of the 5-chloroquinoline **4b** was introduced in small portions over a period of 2 min. After 20 min, the mixture was cooled and extracted with methylene chloride. The organic solution was extracted with sodium bicarbonate solution and evaporated to dryness. The product **4c** was purified by chromatography on silica gel with methylene chloride as eluent. This gave 1.1 g (63%) of pure **4c** as a yellow viscous material: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, CH_3CH_2), 3.1 (q, CH_3CH_2), 3.83 (s, OCH_3), 7.2 (m, phenoxy, H_2), 7.78 (s, H_7), 8.76 (d, H_2). Anal. ($C_{19}H_{15}F_3N_2O_4$) C, H.

6-Methoxy-8-nitro-5-[*m*-(trifluoromethyl)phenoxy]quinoline-4-carboxaldehyde (6). The quinoline **5**[1] (5.0 g, 0.013 mol) was dissolved in 120 mL of dioxane. To the clear solution were added 45 mL of acetic acid and 45 mL of acetic anhydride (the addition of acetic anhydride was essential; without it yields were noticeably lower). Freshly sublimed selenium dioxide (1.8 g, 0.013 mol) was added with stirring and the suspension refluxed for 5 h. After the mixture cooled to room temperature, the precipitated selenium metal was separated by filtration and the filtrate evaporated to a dark syrup, which crystallized in part. The crude product was heated with 100 mL of THF and 10 mL of 3 N hydrochloric acid on the steam bath for 15 min. The neutralized solution was concentrated in vacuo and extracted with methylene chloride. The extract was concentrated to 60 mL, filtered, and diluted with an equal volume of 2-propanol. Upon cooling, yellow crystals of **6** separated. The filtrate was concentrated and chromatographed on silica gel with a methylene chloride–ethyl acetate mixture as eluent. The combined yield of **6** was 4.2 g (81%). A sample recrystallized from acetone–2-propanol had the following: mp 204–205 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, OCH_3), 7.15 (m, phenoxy), 7.66 (d, H_3), 7.91 (s, H_7), 9.02 (d, H_2), 10.74 (s, CHO). Anal. ($C_{18}H_{11}F_3N_2O_5$) C, H, N.

6-Methoxy-8-nitro-5-[*m*-(trifluoromethyl)phenoxy]-4-vinylquinoline (7). The quinoline-4-carboxaldehyde **6** (5.5 g, 0.014 mol) was dissolved in 250 mL of hot THF. While the solution was carefully cooled to −70 °C, a suspension of 5 g (0.014 mol) of methyltriphenylphosphonium bromide in 40 mL of ice-cold ether was slowly treated with 0.012 mol of butyllithium in hexane. After 20 min a small amount of the phosphonium bromide remained undissolved. The cooled (−30 °C) supernatant solution was carefully, under N_2 with stirring, added to the cold aldehyde mixture, which required about 45 min. Toward the end of the addition the mixture began to turn brown. It was allowed to gradually warm to room temperature while stirring under N_2 was continued for 2 h. A small amount of 2-propanol and 0.5 mL of acetic acid was added to the product, and subsequently the

Table IV. 4-Substituted 8-[4-Amino-1-(methylbutyl)amino]-6-methoxy-5-[(trifluoromethyl)phenoxy]quinolines (2)

compd	salt	mp, °C (recrystn solvent)	yield,[a] %	formula	anal.
2b	HBr[b]	165–168 (*i*-PrOH–Et_2O)	43	$C_{24}H_{30}Br_2F_3N_3O_2$	C, H, Br, N
2c	fumarate	160–162 (*i*-PrOH–MeCN)	15	$C_{28}H_{30}F_3N_3O_6$[c]	C, H, N
2d	citrate	190–192 (EtOH)	49	$C_{29}H_{36}F_3N_3O_{10}$[d]	C, H, N
2e	H_3PO_4	92–94 (EtOH)	37	$C_{24}H_{31}F_3N_3O_7P$	C, H, N
2f	fumarate	145–147 (EtOH)	71	$C_{29}H_{34}F_3N_3O_8$[e]	C, H, N

[a] Calculated from 8-nitroquinoline. [b] Solutions of **2b**·HBr gradually decomposed when stored at 25 °C over a period of a few days. [c] This salt was hydrated with 0.75 mol of water. [d] This salt was hydrated with 0.50 mol of water. [e] This salt was a monohydrate.

mixture was concentrated to a dark brown syrup. This was extracted with a mixture of 2-propanol and carbon tetrachloride. Tan crystals separated from the solution, which after filtration and washing with ice-cold 2-propanol had mp 169–170 °C and weighed 3 g. The syrup that remained after evaporation of the filtrate was purified by silica gel column chromatography (methylene chloride–2% ethyl acetate eluent), which yielded an additional 0.6 g of the same product as above: total yield 3.6 g (72%); ^{1}H NMR ($CDCl_3$) δ 3.8 (s, OCH_3), 5.26 (m, CH=CH_2), 7.75 (s, H_7), 8.76 (d, H_2). Anal. ($C_{18}H_{11}F_3N_2O_5$) C, H, N.

4-(Dimethoxymethyl)-6-methoxy-8-nitro-5-[*m*-(trifluoromethyl)phenoxy]quinoline (8). A solution of 6 g (0.015 mol) of **6** in a 1:1 mixture of tetrahydrofuran–methanol (200 mL) was refluxed with a catalytic amount (0.3 %) of *p*-toluenesulfonic acid for 1 h. The solution was cooled and concentrated in vacuo at low temperature to a small volume (~40 mL). The dimethyl acetal crystallized spontaneously and was immediately collected by filtration and washed with 2-propanol. The dried tan product (5.5 g, 82%) had the following: mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 3.18 (s, 2 OCH_3), 3.8 (s, OCH_3), 6.04 [s, C*H*(OCH_3)$_2$], 7.81 (s, H_7), 7.85 (d, H_3), 8.9 (d, H_2). Anal. ($C_{20}H_{17}F_3N_2O_6$) C, H, N.

4-(Hydroxymethyl)-6-methoxy-8-nitro-5-[*m*-(trifluoromethyl)phenoxy]quinoline (9). A solution of 8 g (0.020 mol) of **6** in 100 mL of THF and 30 mL of ethanol was cooled to −50 °C while 1 g (0.027 mol) of solid sodium borohydride was introduced in small portions with stirring over a period of 1 h. After an additional hour, the solution was concentrated under diminished pressure at room temperature and diluted with water. The resulting suspension was allowed to stand for 1 h at 0 °C. The precipitate was collected by filtration, washed with large amounts of water, and immediately dried in vacuo to give 7.2 g (88%) of **9**. A sample recrystallized from methylene chloride–hexane had the following: mp 196–198 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.8 (s, OCH_3), 5.1 (s, CH_2OH), 7.7 (d, H_3), 7.79 (s, H_7), 8.8 (d, H_2). Anal. ($C_{18}H_{13}F_3N_2O_5$) C, H, N.

6-Methoxy-4-(methoxymethyl)-8-nitro-5-[*m*-(trifluoromethyl)phenoxy]quinoline (10). To an equilibrated mixture of 100 mL of THF, 0.1 g (0.3 mmol) of ethyltributylammonium iodide, 1.5 g (0.012 mol) of dimethyl sulfate, and 0.7 g (0.012 mol) of potassium hydroxide in 0.5 mL of water was added 4.3 g (0.011 mol) of **9**. The suspension was vigorously stirred for 20 h. An additional 0.6 g (0.005 mol) of dimethyl sulfate and 0.3 g (0.005 mol) of potassium hydroxide dissolved in 0.2 mL of water was added to the mixture and stirring continued for 3 h. The resulting suspension was filtered and concentrated to a small volume. The remainder was partitioned with methylene chloride and water. The organic phase was isolated and evaporated to dryness and the residue dried in vacuo. Extraction of the product with carbon tetrachloride–2-propanol gave 3.1 g (70%) of **10** as tan colored crystals: mp 176–177 °C; ^{1}H NMR δ ($CDCl_3$) 3.41 (s, CH_3OCH_2), 3.78 (s, OCH_3), 4.87 (s, CH_3OCH_2), 7.63 (d, H_3), 7.75 (s, H_7), 8.77 (d, H_2). Anal. ($C_{19}H_{15}F_3N_2O_5$) C, H, N.

8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-(methoxymethyl)-5-[*m*-(trifluoromethyl)phenoxy]quinoline (2e) Phosphate. The following procedure is typical of that used to prepare target compounds **2b** and **2d–f** (Table IV). A solution of 3.1 g (0.0076 mol) of **10** in 100 mL of THF was cooled to 5 °C and diluted with 50 mL of ethanol and 20 mL of 2 N hydrochloric acid. After the mixture was cooled to −10 °C, 7.2 g (0.032 mol) of stannous chloride and 200 mg of tin powder was added and the resulting suspension stirred at 5–10 °C for 1 h. An excess of 20% sodium hydroxide solution was added, which led to the separation of an organic phase. This was isolated and evaporated to dryness. The residue was dissolved in chloroform and extracted with water. Evaporation of the organic layer gave 2.3 g of 8-amino-6-methoxy-4-(methoxymethyl)-5-[*m*-(trifluoromethyl)-phenoxy]quinoline: ^{1}H NMR ($CDCl_3$) δ 3.33 (s, CH_3OCH_2), 3.71 (s, OCH_3), 4.84 (s, CH_3OCH_2), 6.61 (s, H_7), 7.45 (d, H_3), 8.43 (d, H_2). The material was used in the subsequent alkylation without further purification. With efficient stirring a solution of 7 g (0.02 mol) of 4-iodo-1-phthalimidopentane in 2 g (0.02 mol) of triethylamine was added over a period of 8 h to a solution of 2.3 g (0.006 mol) of the above 8-aminoquinoline in 0.5 mL of DMF kept at 90 °C under nitrogen. The cooled product was dissolved in methylene chloride and extracted with water. The residue that was left after evaporation of the organic phase was chromatographed on silica gel with methylene chloride as eluent to give 2.2 g (73%) of alkylated product: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, CH_3CH), 3.31 (s, CH_3OCH_2), 3.78 (s, OCH_3), 4.80 (s, CH_3OCH_2), 6.34 (s, H_7), 7.43 (d, H_3), 7.65 (m, phthaloyl), 8.40 (d, H_2).

The combined product from two alkylations (4.3 g, 0.0073 mol) was dissolved in 200 mL of ethanol that contained 0.45 g (0.014 mol) of hydrazine. After heating of the solution at 60 °C for 4 h, the resulting precipitate was separated by filtration and the filtrate evaporated to a sticky solid. The solid was extracted with ether and the insoluble removed by filtration. Removal of the solvent in vacuo gave 3.1 g (93%) of a yellow-brown syrup, which was dissolved in 50 mL of ethanol and treated with a solution of 1 g (0.01 mol) of phosphoric acid in 10 mL of ethanol. This provided a clear yellow-brown solution from which the monophosphate crystallized slowly upon standing overnight. To complete the crystallization the mixture was cooled for 1 day at 5 °C. Filtration gave 3.2 g (82%) of the title compound: mp 92–94 °C dec; ^{1}H NMR (Me_2SO-d_2) δ 1.32 (d, CH_3CH), 3.35 (CH_3OCH_2), 3.84 (s, CH_3O), 4.78 (s, CH_3OCH_2), 6.60 (s, H_7), 8.45 (d, H_2). Anal. $C_{24}H_{28}F_3N_3O_3$·H_3PO_4 C, H, N.

8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-5-[*m*-(trifluoromethyl)phenoxy]-4-vinylquinoline (2c) Fumarate. The 8-nitro-4-vinylquinoline **7** was converted to 6-methoxy-8-[(4-phthalimido-1-methylbutyl)amino]-5-[*m*-(trifluoromethyl)phenoxy]-4-vinylquinoline by a procedure similar to that described for **10**.

The alkylated product (4.5 g, 0.11 mol) was dissolved in 6 mL of ethanol and 7 mL of THF. A cold mixture of 1.1 g (0.02 mol) of sodium methoxide and 0.7 g (0.01 mol) of hydroxylamine hydrochloride in methanol (35 mL) was added with stirring. After 15 h a solution of 1 g (0.015 mol) of hydroxylamine hydrochloride and 1.5 g (0.03 mol) of sodium methoxide in 30 mL of methanol was introduced into the mixture and stirring continued for 5 h. TLC indicated that the reaction was practically complete at this time. After addition of 20 mL of water, the mixture was concentrated to a small volume and extracted with chloroform. Evaporation of the extract gave 3.6 g of an orange syrup. An ethanolic solution of the syrup (3.5 g, 0.008 mol) was treated with 1 g (0.0085 mol) of fumaric acid in 20 mL of ethanol. The solution was concentrated to a small volume and cooled at −15 °C for several days. The crystalline yellow fumarate (3.3 g, 73%) was collected, washed with 2-propanol–acetonitrile, and vacuum dried: mp 160–162 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.22 (d, CH_3CH), 3.74 (s, OCH_3), 5.22 (m, CH=CH_2), 6.32 (s, fumarate), 6.56 (s, H_7), 8.42 (d, H_2). Anal. ($C_{28}H_{30}F_3N_3O_6$·$^3/_4H_2O$) C, H, N.

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