The antitumor activity in vivo of examined compounds was assayed as described in the legend to Table I.

Acknowledgment. Financial support of the Institute of Immunology and Expermental Therapy, Polish Academy of Sciences, and Italian Ministero della Publica Istruzione (Fondi 60%) is gratefully acknowledged. Thanks are due to Mrs. M. Bontemps-Gracz for the determination of cytotoxicity and to Dr. J. Paradziej-Lukowicz for evaluation in vivo antileukemic activity.

Antimalarials. 16. Synthesis of 2-Substituted Analogues of 8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline as Candidate Antimalarials

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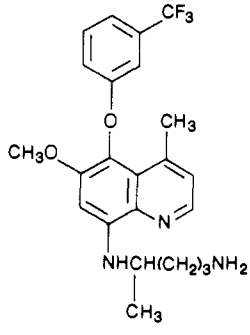
A series of 2-substituted analogues of the exceptional drug 8-[(4-amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline (I) were prepared and evaluated for both suppressive and prophylactic antimalarial activity. The preparation of analogues of compound I was of interest due to the high level of both blood and tissue schizonticidal activity demonstrated by this compound. One analogue, **8a**, was found to be both more active and less toxic than the parent compound I. In addition, three analogues of example **8a** were prepared. Although two of the three analogues showed significant antimalarial activity, both were inferior to compound **8a**.

In a preceding paper in this series,[1] we reported the preparation of a series of 5-(aryloxy)-4-methylprimaquine analogues. Several of these compounds surprisingly were found to be highly active in both the suppressive and radical curative antimalarial screens. Example I, the 5-

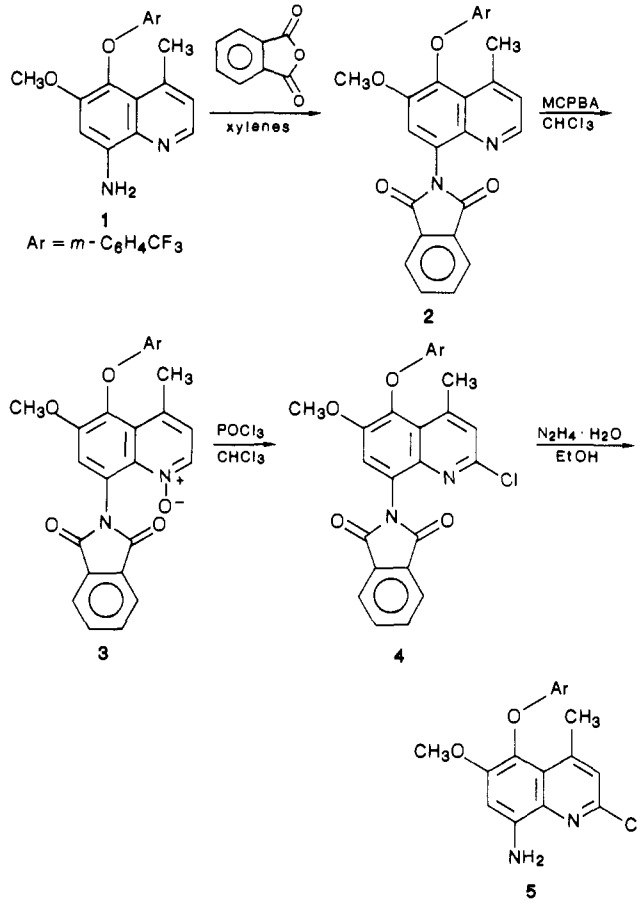


I

[3-(trifluoromethyl)phenoxy] analogue, was selected for preclinical studies which showed that, although the compound was more active than primaquine, it was also more toxic, especially with respect to methemoglobin formation. On the basis of a report[2] that a 2-methoxy substituent in a pamaquine analogue led to a decrease in toxicity, we felt it would be desirable to prepare selected examples of I bearing a 2-alkoxy group.

Chemistry. The key intermediate in the preparations of the four 2-substituted analogues of I (**8a–d**) was the 2-chloroquinoline **5**. Attempts to prepare this intermediate via the procedure used earlier by Talati and co-workers,[3] who prepared a similar analogue, failed. The approach used in the current work is shown in Scheme I. The previously described[1] 8-aminoquinoline **1** was protected as the phthalimide **2** and then converted to the *N*-oxide **3** with *m*-chloroperbenzoic acid in chloroform.[4] Treatment

Scheme I

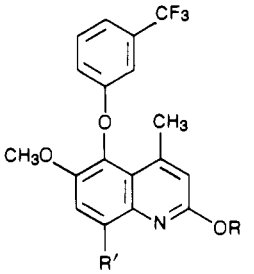


of compound **3** with excess phosphorous oxychloride afforded the 2-chloroquinoline **4**, which was deprotected with excess hydrazine hydrate to afford the requisite quinoline **5**. The intermediate 2-substituted quinolines **6a–c** were prepared by treating **5** with the appropriate nucleophile in dimethylformamide as shown in Scheme II. Side-chain introduction was accomplished by alkylating the 8-aminoquinolines with 4-iodo-1-phthalimidopentane in acetonitrile. Diisopropylamine was utilized as the acid acceptor except in the preparation of intermediate **7c**, where sodium bicarbonate was used. Removal of the

(1) LaMontagne, M. P.; Blumbergs, P.; Strube, R. E. *J. Med. Chem.* **1982**, *25*, 1094.
(2) Mislow, K.; Koepfli, J. B. *J. Am. Chem. Soc.* **1946**, *68*, 1553. Wiselogle, F. Y. *A Survey of Antimalarial Drugs, 1941–1945*; Edwards: Ann Arbor, MI, 1946; Vol. 1.
(3) Talati, S. M.; Latham, M. R.; Moore, E. G.; Hargreaves, G. W.; Blanton, C. D. *J. Pharm. Sci.* **1970**, *59*, 491.
(4) Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721.

0022-2623/89/1832-1728$01.50/0

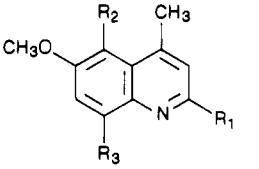
Table I. Data for Compounds 6a–c, 7a–c, and 8a–d



no.	R	R′	mp, °C	recryst solvent	% yield	formula	anal.[a]
6a	CH_3	NH_2	114–117	hexanes	86	$C_{19}H_{17}F_3N_2O_3$	F
6b	4-ClC_6H_4	NH_2	183–186[b]	Et_2O[c]	69	$C_{24}H_{18}ClF_3N_2O_3$·HCl	Cl, F
6c	4-$ClC_6H_4CH_2$	NH_2	93–95	ligroin	67	$C_{25}H_{20}ClF_3N_2O_3$	Cl, F
7a	CH_3	$NHCH(CH_3)(CH_2)_3Pth$[d]	121–124	*i*-PrOH	67	$C_{32}H_{30}F_3N_3O_5$	F
7b	4-ClC_6H_4	$NHCH(CH_3)(CH_2)_3Pth$[d]	185–195[b,e]	EtOAc	81	$C_{37}H_{31}ClF_3N_3O_5$·HCl	Cl, F
7c	4-$ClC_6H_4CH_2$	$NHCH(CH_3)(CH_2)_3Pth$[d]	149–151	*i*-PrOH	77	$C_{38}H_{33}ClF_3N_3O_5$	Cl, F
8a	CH_3	$NHCH(CH_3)(CH_2)_3NH_2$	146–149	CH_3CN	78	$C_{24}H_{28}F_3N_3O_3·C_4H_6O_4$	F
8b	4-ClC_6H_4	$NHCH(CH_3)(CH_2)_3NH_2$	115–119	EtOAc–hex	62	$C_{29}H_{29}ClF_3N_3O_3·C_4H_6O_4$	Cl, F
8c	4-$ClC_6H_4CH_2$	$NHCH(CH_3)(CH_2)_3NH_2$	144–145	CH_3CN–MeOH	76	$C_{30}H_{31}ClF_3N_3O_3·C_4H_6O_4$	Cl, F
8d	H	$NHCH(CH_3)(CH_2)_3NH_2$	228–231	EtOH–Et_2O	66[f]	$C_{23}H_{26}F_3N_3O_3$·HCl	Cl, F

[a] In addition to C, H, N. [b] Hydrochloride salt. [c] Slurried only. [d] Pth = phthalimido. [e] With decomposition. [f] From 8c.

Table II. Data for Compounds 11, 13–20, 22–27, and 29–33



no.	R_1	R_2	R_3	mp, °C	recryst stolvent	% yield	formula	anal.[a]
11	H	H	Pth[b]	292–294	CH_3OH[c]	96	$C_{19}H_{14}N_2O_3$	
13	Cl	H	Pth	295–297	DMF	78	$C_{19}H_{13}ClN_2O_3$	Cl
14	Cl	H	NH_2	146–148	*i*-PrOH	87	$C_{11}H_{11}ClN_2O$	
15	OCH_3	H	NH_2	134–135	*i*-PrOH–CH_3OH	83	$C_{12}H_{14}N_2O_2$	
16	OCH_3	H	$NHCH(CH_3)(CH_2)_3Pth$	119–121	*d*	69	$C_{25}H_{27}N_3O_4$	
17	OCH_3	H	$NHCH(CH_3)(CH_2)_3NH_2$	149–150	EtOH–Et_2O	60	$C_{17}H_{25}N_3O_2·C4H_6O_4$	
18	H	$O(CH_2)_5CH_3$	NO_2	53–54[e]	*d*	54	$C_{17}H_{22}N_2O_4$	
19	H	$O(CH_2)_5CH_3$	NH_2	70–71[f]	petr ether	72	$C_{17}H_{24}N_2O_2$	
20	H	$O(CH_2)_5CH_3$	Pth	184–185	EtOH	94	$C_{25}H_{26}N_2O_4$	
22	Cl	$O(CH_2)_5CH_3$	Pth	178–179	EtOH[c]	91	$C_{25}H_{25}ClN_2O_4$	Cl
23	Cl	$O(CH_2)_5CH_3$	NH_2	74–75	Et_2O–petr ether	70	$C_{17}H_{23}ClN_2O_2$	Cl
24	OCH_3	$O(CH_2)_5CH_3$	NH_2	56–57	EtOH–H_2O	80	$C_{18}H_{26}N_2O_3$	
25	OCH_3	$O(CH_2)_5CH_3$	$NHCH(CH_3)(CH_2)_3Pth$	*g*		53	$C_{31}H_{39}N_3O_5$	
26	OCH_3	$O(CH_2)_5CH_3$	$NHCH(CH_3)(CH_2)_3NH_2$	111–112	*i*-PrOH–Et_2O	75	$C_{23}H_{37}N_3O_3·C_4H_6O_4$	
27	H	*m*-$OCH_2C_6H_4CF_3$	Pth	191–193	CH_3OH[c]	89	$C_{27}H_{19}F_3N_2O_4$	
29	Cl	*m*-$OCH_2C_6H_4CF_3$	Pth	213–215	EtOAc	83	$C_{27}H_{18}ClF_3N_2O_4$	Cl
30	Cl	*m*-$OCH_2C_6H_4CF_3$	NH_2	88–90	hexane[c]	89	$C_{19}H_{16}ClF_3N_2O_2$	
31	OCH_3	*m*-$OCH_2C_6H_4CF_3$	NH_2	98–100	hexane	45	$C_{20}H_{19}F_3N_2O_3$	
32	OCH_3	*m*-$OCH_2C_6H_4CF_3$	$NHCH(CH_3)(CH_2)_3Pth$	145–147	CH_2Cl_2–CH_3OH	35	$C_{33}H_{32}F_3N_3O_5$	
33	OCH_3	*m*-$OCH_2C_6H_4CF_3$	$NHCH(CH_3)(CH_2)_3NH_2$	154–156[h]	CH_3OH–Et_2O	73	$C_{25}H_{30}F_3N_3O_3·0.5C_4H_6O_4$	F

[a] In addition to C, H, N. [b] Pth = phthalimido. [c] Slurried only. [d] Chromatographed. [e] Lit.[5] mp 53–54 °C. [f] Lit.[5] mp 69–71 °C. [g] Oil. [h] Hemisuccinate salt.

phthalimide protection with hydrazine hydrate in refluxing ethanol afforded the desired 8-quinolinediamines with the exception of **8d**, which was prepared via hydrogenolysis of **8c** over palladium catalyst. The high level of activity displayed by the 2-methoxy analogue **8a** prompted the syntheses of three additional examples, the 5-unsubstituted analogue **17**, the 5-(1-hexyloxy) analogue **26**, and the 5-[[3-(trifluoromethyl)benzyl]oxy] analogue **33**. Analogue **26** was selected on the basis of the high level of activity demonstrated by the 2-desmethoxy compound prepared by Chen et al.[5] The unsubstituted analogue **17** was prepared from 8-amino-6-methoxy-4-methylquinoline[6] via the procedure shown in Schemes I and II. Analogues **26** and **33** were prepared from 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline[1] via alkylation with the appropriate alkyl halide in the presence of tetrabutylammonium hydroxide followed by reduction of the 8-nitro group. The remainder of the sequence was as shown in Schemes I and II. Physical constants are presented in Tables I and II.

Biological Activity Data. Compounds **8a-d** were evaluated for suppressive antimalarial activity against *Plasmodium berghei* in mice.[7,8] Compound **8a**, the 2-

(5) Chen, E. H.; Tanabe, K.; Saggiomo, A. J.; Nodiff, E. A. *J. Med. Chem.* **1987**, *30*, 1193.

(6) Campbell, K. N.; Elderfield, R. C.; Gensler, W. J.; Sommers, A. H.; Kremer, C. B.; Kupchan, S. M.; Tinker, J. F.; Dressner, J. A.; Ramanek, B. N.; Campbell, B. K. *J. Am. Chem. Soc.* **1947**, *69*, 1465.

Scheme II

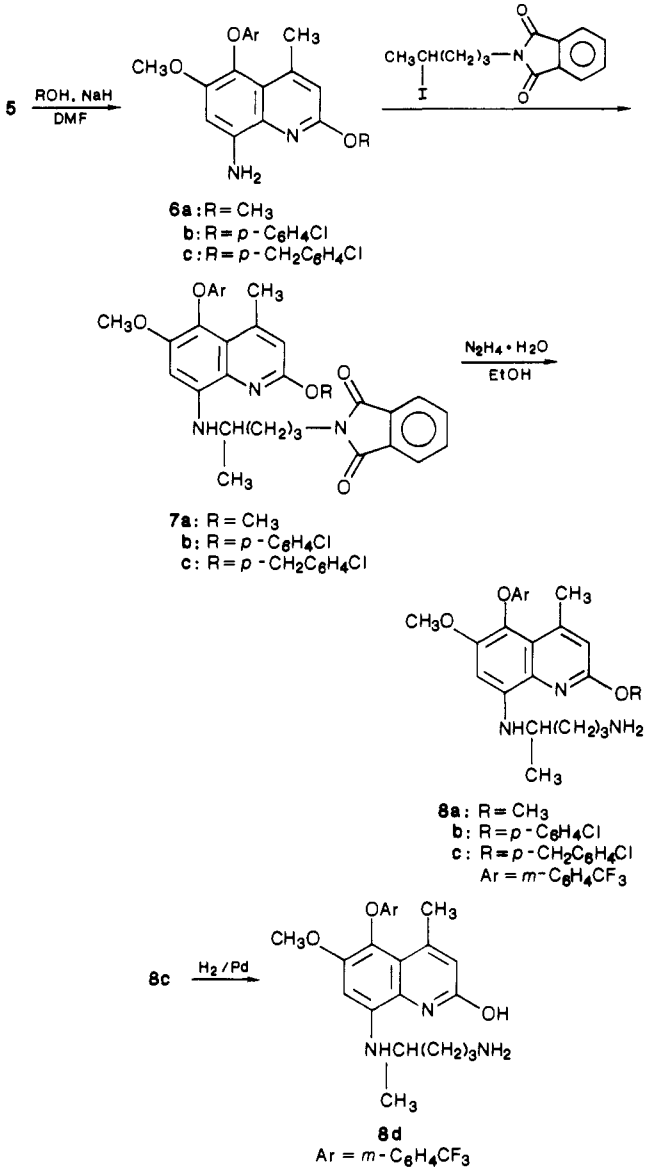


Table III. Suppressive Antimalarial Activity Data[a] for *P. berghei* Infected Rane Mice

	ΔMST, days, at mg/kg, sc[7,8]							
compd	5	10	20	40	80	160	320	640
primaquine				I	I	9 (A)	2T	5T
I	I	I	1C	4C	5C	5C	5C	4C, 1T
8a	I	I	3C	5C	5C	5C	5C	4C, 1T
17	I	I	I	I	7.0 (A)	5T	5T	5T
26	I	I	10.5 (A)	2C	5C	4C	5T	5T
33	I	1C, 8.1 (A)	1C	2C	2C/1T, 4C	1C/4T	3T	

[a] Abbreviations used are I = inactive, C = cure, and T = toxic.

methoxy analogue, was highly active in this screen and was, in fact, slightly more active than compound I. This is in contrast with the early work[2] where a 2-methoxy substituent, while decreasing the toxicity, decreased the antimalarial activity as well. Compounds **8b–d** were inactive and nontoxic. The activity data for **8a** are shown in Table III along with the data for primaquine and compound I. As mentioned earlier, the high level of activity demonstrated by compound **8a** against *P. berghei* in mice prompted the synthesis of three additional examples, the 5-unsubstituted analogue **17**, the 5-(1-hexyloxy) analogue **26**, and the 5-[[3-(trifluoromethyl)benzyl]oxy] analogue **33**. With respect to suppressive antimalarial activity (Table III), example **17** was essentially inactive and quite toxic. Examples **26** and **33** were comparable in activity to compound I. However, both were significantly more toxic. In addition, compounds **8a**, **17**, and **26** were evaluated for radical curative antimalarial activity against *Plasmodium cynomolgi* in the rhesus monkey.[9] The data are shown in Table IV along with those for primaquine and the parent compound I. Compound **8a** was superior to I with 2/4 cures at a dosage of 0.1 mg/kg (×7). Examples **17** and **26** were clearly inferior to **8a**. Example **33** was not tested in this screen, presumably due to the toxicity shown in the suppressive test. Molar primaquine indices were calculated via regression analysis for compounds I, **8a**, and **17**. The index for **8a** was approximately twice that of I and 13 times that of primaquine.

As mentioned in the introduction, the goal of the present work was to prepare a less toxic analogue of compound I. Among the toxic side effects of the 8-aminoquinolines, in general, is their induction of methemoglobin formation, a side effect which may represent a significant limitation in the use of the 8-aminoquinolines. Compound **8a** was evaluated for its methemoglobin-inducing properties in dogs. The detailed data have been published elsewhere

Table IV. Radical Curative Antimalarial Activity Data for *P. cynomolgi* Infected Rhesus Monkeys

	mg/kg (salt) per day (×7), po[9]					molar primaquine index[a]
compd	0.0316	0.10	0.316	1.0	1.3	
primaquine[b]	*d*	0/2C	0/2C	1/2C	6/6C	1.0
I[c]	0/2C	0/2C	2/2C	2/2C	*d*	6.8
8a[c]	0/2C	2/4C	4/4C	2/2C	*d*	12.8
17[c]	*d*	0/2C	2/2C	2/2C	*d*	6.8
26[c]	0/3C	1/4C 0/1C	3/3C	2/2C	*d*	
33	*d*	*d*	*d*	*d*	*d*	

[a] Ratio of the molar ED_{50} of primaquine, I, **8a**, and **17** divided by the ED_{50} of primaquine, determined by regression analysis. [b] Diphosphate salt. [c] Succinate salt. [d] Not tested.

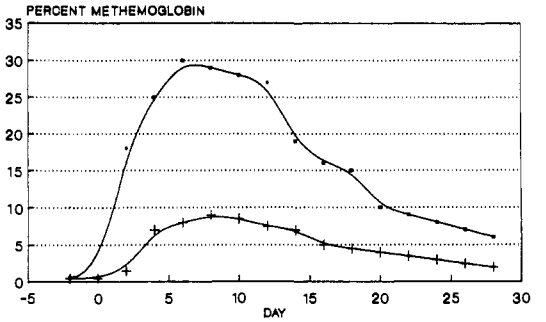


Figure 1. Methemoglobin formation for compounds I (■) and **8a** (+). Compounds I and **8a** were administered at a dosage of 0.0116 mmol/kg per day on days 0–3.

(7) Osdene, T. S.; Russell, P. B.; Rane, L. J. *J. Med. Chem.* **1967**, *10*, 431.

(8) The testing was performed at the Leo Rane Laboratory, University of Miami, FL. In the primary test against *P. berghei*, five mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the drug. Routinely, the drug was administered subcutaneously in sesame or peanut oil. The mean survival time (MST) of infected control mice is 6.2 ± 0.5 days. A 100% extension in survival time of the treated mice is evidence of antimalarial activity. Mice surviving 60 days are considered cured.

(9) Schmidt, L. N.; Rossan, R. N.; Fisher, K. F. *Am. J. Trop. Med. Hyg.* **1963**, *12*, 494.

Table V. Acute Toxicity in the Rat[a,b]

sex	route of admin	compd	LD_{50}, mg/kg (salt)
male	oral[c]	primaquine	177
male	oral	I	259
male	oral	**8a**	429
female	oral[d]	primaquine	244
female	oral	I	401
female	oral	**8a**	416
male	ip[e]	I	86
male	ip	**8a**	102
female	ip[f]	I	54
female	ip	**8a**	71

[a] Chan, P. K.; et al. In *Principles and Methods of Toxicology*; Hayes, A., Ed.; Raven Press: New York, 1984; pp 1–52. [b] Fischer 344 rats used in all tests. [c] 80 rats. [d] 100 rats. [e] 74 rats. [f] 85 rats.

by other workers.[10] However, it can be said that compound **8a** produced approximately one-third the methemoglobin levels as the parent compound I. The comparative data are graphically shown in Figure 1. Also, a comparison of the acute toxicities of compounds I and **8a**, shown in Table V, shows that compound **8a** is significantly less toxic than compound I in the rat either by oral or intraperitoneal administration. The data, therefore, indicate that compound **8a** represents a significantly more active and less toxic analogue of the parent compound I.

Experimental Section

All melting points and boiling points are uncorrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. Ethanol used in this work was specially denatured grade 3A alcohol (90% ethanol, 5% 2-propanol, and 5% methanol by volume).

6-Methoxy-4-methyl-8-phthalimido-5-[3-(trifluoromethyl)phenoxy]quinoline (2). A mixture of 8-aminoquinoline 1[1] (6.96 g, 20 mmol) and phthalic anhydride (3.25 g, 22 mmol) in xylene (100 mL) was refluxed for 24 h with water removal via a Dean–Stark trap. After cooling, filtration gave 9.5 g (100%) of the title compound, mp 228–230 °C. Recrystallization from EtOH raised the melting point to 228-231 °C. Anal. ($C_{26}H_{17}F_3N_2O_4$) C, H, F, N. Similarly prepared were compounds **11**, **20**, and **27** (Table II).

6-Methoxy-4-methyl-8-phthalimido-5-[3-(trifluoromethyl)phenoxy]quinoline 1-Oxide (3). A solution of compound **2** (3.0 g, 6.27 mmol) and 100% MCPBA (2.17 g, 12.6 mmol) in $CHCl_3$ (20 mL) was stirred at room temperature for 41 h and then filtered. The filtrate was washed with 10% $NaHSO_3$ (50 mL) and saturated $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), and concentrated to a yellow solid. Two recrystallizations from EtOH gave 2.14 g (63%) of the title compound as the ethanolate, mp 236–237 °C. Anal. ($C_{26}H_{17}F_3N_2O_5 \cdot C_2H_6O$) C, H, F, N.

The following were similarly prepared: **6-methoxy-4-methyl-8-phthalimidoquinoline 1-oxide** [**12**, 83%, mp 288–290 °C dec ($CHCl_3$/EtOH)], **5-(1-hexyloxy)-6-methoxy-4-methyl-8-phthalimidoquinoline 1-oxide** [**21**, 77%, mp 199–200 °C (EtOH). Anal. ($C_{25}H_{26}N_2O_5$) C, H, N], and **6-methoxy-4-methyl-8-phthalimido-5-[[3-(trifluoromethyl)benzyl]oxy]quinoline 1-oxide** [**28**, 83%, mp 220–222 °C].

2-Chloro-6-methoxy-4-methyl-8-phthalimido-5-[3-(trifluoromethyl)phenoxy]quinoline (4). A solution of ethanolate **3** (32.7 g, 60.5 mmol) in $CHCl_3$ (500 mL) was treated with $POCl_3$ (55 mL, 92 g, 60 mmol) over 15 min. The solution was refluxed for 2 h, cooled, and poured onto ice (1.5 L) and the pH was adjusted to 12 with 20% NaOH (700 g). The separated aqueous layer was extracted with $CHCl_3$ (2 × 200 mL). The combined $CHCl_3$ layers were washed with H_2O (2 × 200 mL), saturated $NaHCO_3$ (200 mL), dried ($MgSO_4$), and evaporated in vacuo to a white solid. Recrystallization from EtOH gave 23.2 g (75%) as the first crop of title compound, mp 227–229 °C. Anal. ($C_{26}H_{16}N_2ClF_3O_4$) C, H, N, Cl, F. Similarly prepared were **13**, **22**, and **29** (Table II).

8-Amino-2-chloro-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline (5). A suspension of phthalimide **4** (23.2 g, 45.2 mmol) in EtOH (900 mL) was treated with excess hydrazine hydrate (75%, 16.75 mL) and the mixture was refluxed with mechanical stirring for 3 h. After cooling, the solids were filtered and washed with CH_2Cl_2. The combined filtrate and washings were evaporated in vacuo to a small volume and diluted with CH_2Cl_2 (500 mL). The CH_2Cl_2 was extracted with 20% KOH (3 × 200 mL) and brine, dried (K_2CO_3), and evaporated in vacuo to an amber gum. Recrystallization from cyclohexane–ligroin (5:2, 500 mL) with charcoal gave 15.4 g (89%) as the first crop of title compound, mp 133–135 °C. Anal. ($C_{18}H_{14}ClF_3N_2O_2$) C, H, Cl, F, N. Similarly prepared were **14**, **23**, and **30** (Table II).

8-Amino-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline (6a). A solution of MeOH (0.824 g, 25.8 mmol) in DMF (anhydrous, 60 mL) under a N_2 atmosphere was treated with NaH (50% oil dispersion, 1.02 g, 21.4 mmol). After H_2 evolution ceased, chloroquinoline **5** (7.5 g, 19.6 mmol) was added and the mixture was heated at 90 °C for 1 h. After cooling, the reaction mixture was poured onto ice (600 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with H_2O (3×), dried (K_2CO_3) and evaporated in vacuo. This material was combined with material obtained from two smaller runs (on 0.5 g and 2.0 g of the chloroquinoline) and chromatographed on silica gel (EM, 500 g) with 1% methanol in CH_2Cl_2. The yellow (product) band was collected and evaporated in vacuo to yield 8.5 g (86%) of the title compound, mp 113–115 °C. Recrystallization from hexanes raised the melting point to 114–117 °C. Similarly prepared were 8-aminoquinolines **6b** and **6c** (Table I) and **15**, **24**, and **31** (Table II).

2,6-Dimethoxy-4-methyl-8-[(4-phthalimido-1-methylbutyl)amino]-5-[3-(trifluoromethyl)phenoxy]quinoline (7a). A mixture of quinoline **6a** (8.0 g, 21.2 mmol), diisopropylamine (2.14 g, 21.2 mmol), and 4-iodo-1-phthalimidopentane (IPP, 7.26 g, 21.2 mmol) in CH_3CN (40 mL) was refluxed for 24 h, after which time additional diisopropylamine (2.14 g, 21.2 mmol) and IPP (7.26 g, 21.2 mmol) were added. After refluxing for 24 h, more diisopropylamine (1.07 g, 10.6 mmol) and IPP (3.63 g, 10.6 mmol) were added and the refluxing was continued for 24 h. The cooled mixture was diluted with H_2O (20 mL) and stirred in the ice bath until crystallization was complete. Filtration and recrystallization from 2-propanol gave 8.4 g (67%) as the first crop of title compound, mp 120–124 °C. Further recrystallization raised the melting point to 121–124 °C.

Similarly prepared were phthalimides **7b** (Table I) and **16**, **25**, and **32** (Table II). Preparation of **7c** (Table I) required substitution of sodium bicarbonate for diisopropylamine.

8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline Succinate (8a). A solution of phthalimide **7a** (7.5 g, 12.6 mmol) in EtOH (500 mL) was treated with excess hydrazine hydrate (75%, 4.5 mL) and refluxed for 10 h. After cooling overnight, the solids were filtered and washed with CH_2Cl_2. The combined filtrate and washings were evaporated in vacuo to a small volume and diluted with CH_2Cl_2 (200 mL). The CH_2Cl_2 solution was washed with 20% KOH (3 × 75 mL) and brine, dried (K_2CO_3), and evaporated in vacuo to an oil. This oil was dissolved in CH_3CN (20 mL) and treated with a solution of succinic acid (1.42 g, 12 mmol) in a mixture of MeOH (5 mL) and CH_3CN (20 mL) to give 6.3 g (86%) of the title compound. Recrystallization from CH_3CN yielded 5.7 g (78%) as the first crop of title compound, mp 146–149 °C.

Similarly prepared were 8-quinolinediamines **8b** and **8c** (Table I) and **17**, **26**, and **33** (Table II).

8-[(4-Amino-1-methylbutyl)amino]-2-hydroxy-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline Hydrochloride (8d). To a solution of the free base of **8c** (9.2 g, 16 mmol) in HOAc (8.9 mL) and 50% aqueous EtOH (160 mL) was added palladium black (1.6 g) and the resulting mixture was hydrogenated at 45 psig for 48 h. The catalyst was filtered; the filtrate was diluted with H_2O and 1 N HCl and extracted with EtOAc to remove colored impurities. The EtOAc was back-washed with 1 N HCl; the combined acid layer was basified with K_2CO_3 and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with H_2O, dried (K_2CO_3), and evaporated to 6.9 g (94%)

(10) Anders, J.; Chung, H.; Theorides, A. *Fundam. Appl. Toxicol.* 1988, *10*, 270.

of solid free base. This material was dissolved in EtOH (75 mL). The solution was treated with 7.5 N HCl in 2-propanol (2 mL, 15 mmol) and then diluted with Et_2O (100 mL). Filtration gave 4.9 g (66%) as the first crop of title compound, mp 225–228 °C. Recrystallization from EtOH–Et_2O raised the melting point to 228–231 °C.

6-Methoxy-4-methyl-8-nitro-5-[[3-(trifluoromethyl)benzyl]oxy]quinoline (9). A 12-L flask was charged with 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline[1] (225 g, 0.961 mol), 3-(trifluoromethyl)benzyl chloride (225 g, 1.16 mol), tetrabutylammonium hydroxide (40% in water, 700 g), and chlorobenzene (5 L). The mixture was stirred at 60–65 °C for 5 days, cooled, and filtered. The filtrate was diluted with methylene chloride (4 L), washed with water (2 × 5 L), dried ($MgSO_4$), and concentrated to a thick syrup, which was chromatographed on an aluminum oxide column and eluted with methylene chloride. The product fraction was collected and concentrated to a thick oil, which was slurried in ether–petroleum ether (1:1) to give the title compound, 171 g (45%), mp 105–107 °C. This material was used without further purification in the next step.

Similarly prepared was **5-(1-hexyloxy)-6-methoxy-4-methyl-8-nitroquinoline** (18) (Table II).

8-Amino-6-methoxy-4-methyl-5-[[3-(trifluoromethyl)benzyl]oxy]quinoline (10). A 2-L Parr bottle was charged with 8-nitroquinoline **9** (50 g, 0.127 mol) in warm (45 °C) THF–ethanol (750 mL:200 mL). Platinum oxide (3.75 g) was added to the solution and the mixture was hydrogenated at 50 psig until 3.1 equiv of H_2 was absorbed (about 5–7 min). The reaction mixture was cooled and filtered (Celite). The filtrate was concentrated to an oil, which was slurried in hexane to yield crude product. The crude products from three runs were combined, dissolved in ether, and treated with charcoal. After filtering (Celite), the filtrate was concentrated and diluted with hexane to yield the title compound, 89 g (64%), mp 80–82 °C. This material was used without further purification.

8-Amino-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (19). This material was prepared via the reduction conditions reported by Campbell et al.[6] A mixture of 8-nitroquinoline **18** (88.3 g, 0.277 mol), water (140 mL), dibutyl ether (140 mL), and acetic acid (140 mL) was heated on a steam bath to give a homogeneous solution. The solution was cooled to 70 °C and iron filings (140 g, 2.5 mol) were added portionwise over a 20-min period. The mixture exothermed to 95 °C and was allowed to cool for 60 min. The mixture was then heated at 95 °C for 18 h, cooled, and filtered. The solid was slurried with ether (3 × 1800 mL) and the slurry was filtered. The combined ether extracts were concentrated to 500 mL, washed with 2% aqueous NaOH, dried ($MgSO_4$), treated with Norit A, and filtered (Celite). The filtrate from the original reaction mixture was extracted with ether (2 × 500 mL). The combined ether extract was washed with 2% NaOH and dried ($MgSO_4$). The ether layers were combined and concentrated to a green semisolid (140 g). This material was recrystallized from petroleum ether to give 58 g (72.5%) of pure product, mp 70–71 °C.

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Synthesis and Antiviral Activity of 3′-*C*-Cyano-3′-deoxynucleosides

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A series of 3′-*C*-cyano-3′-deoxynucleosides have been synthesized and evaluated as antiviral agents. Reaction of 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranos-3′-ulosyl derivatives of uracil, 4-*N*-acetylcytosine, and adenine with sodium cyanide gave a mixture of epimeric cyanohydrins, which after 3′-deoxygenation yielded the corresponding 3′-*C*-cyano-3′-deoxy-β-D-*xylo*-pentofuranosyl derivatives **10**. These compounds were epimerized to the corresponding β-D-*ribo*-pentofuranosyl derivatives **11**. Desilylation of **10** and **11** gave the deprotected 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- and -*ribo*-pentofuranosyl nucleosides. These derivatives of uridine, cytidine, and adenine, as well as the 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- and -*ribo*-pentofuranosyl, 3′-*C*-cyano-2′,3′-dideoxy-β-D-*threo*- and -*erythro*-pentofuranosyl, and 3′-*C*-cyano-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl derivatives of thymine, were evaluated for their antiviral activity. None of the compounds proved active against the replication of retroviruses (human immunodeficiency virus, murine sarcoma virus) at concentrations that were not toxic to the host cells. However, the 3′-*C*-cyano-3′-deoxy-β-D-*xylo*- (**12e**) and -*ribo*-pentofuranosyl (**13e**) derivatives of adenine showed activity against some DNA (i.e., vaccinia) and RNA (i.e., Sindbis, Semliki forest) viruses at concentrations well below the cytotoxicity threshold.

A number of sugar-modified nucleosides show antiviral activity.[1] These compounds may interfere with viral encoded enzymes which catalyze reactions that only occur in the virus-infected cell.[2] This is the case for the potent and selective anti-human immunodeficiency virus (HIV) agents 2′,3′-dideoxynucleosides **1–4**, which in their 5′-triphosphate form interfere with the HIV reverse transcriptase,[3,4] an enzyme specific for retroviruses. Other sugar-modified nucleosides, such as various arabinofuranosyl,[5,6]

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