

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

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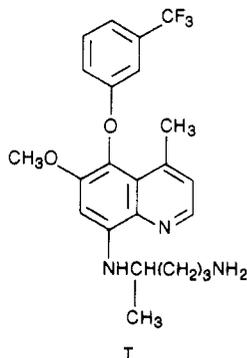
Antimalarials. 16. Synthesis of 2-Substituted Analogues of 8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline as Candidate Antimalarials

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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**.

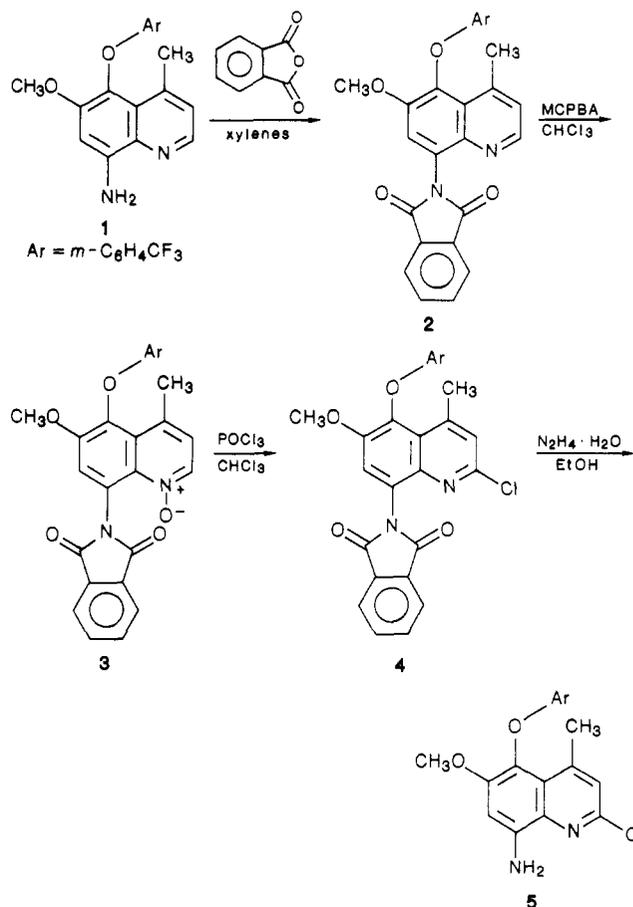
In a preceding paper in this series,¹ we reported the preparation of a series of 5-(aryloxy)-4-methylprimaquine analogues. Several of these compounds surprisingly were found to be highly active in both the suppressive and radical curative antimalarial screens. Example I, the 5-



[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 report² 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 described¹ 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

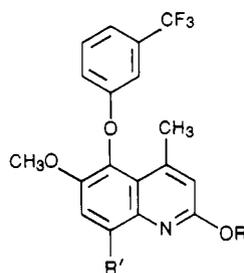
Scheme I



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

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- Talati, S. M.; Latham, M. R.; Moore, E. G.; Hargreaves, G. W.; Blanton, C. D. *J. Pharm. Sci.* **1970**, *59*, 491.
- Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721.

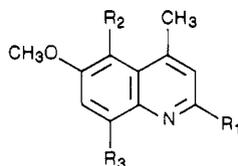
Table I. Data for Compounds 6a-c, 7a-c, and 8a-d



| 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 ₃ N ₂ O ₃ | F |
| 6b | 4-ClC ₆ H ₄ | NH ₂ | 183-186 ^b | Et ₂ O ^c | 69 | C ₂₄ H ₁₈ ClF ₃ N ₂ O ₃ ·HCl | Cl, F |
| 6c | 4-ClC ₆ H ₄ CH ₂ | NH ₂ | 93-95 | ligroin | 67 | C ₂₅ H ₂₀ ClF ₃ N ₂ O ₃ | Cl, F |
| 7a | CH ₃ | NHCH(CH ₃)(CH ₂) ₃ Pth ^d | 121-124 | <i>i</i> -PrOH | 67 | C ₃₂ H ₃₀ F ₃ N ₃ O ₅ | F |
| 7b | 4-ClC ₆ H ₄ | NHCH(CH ₃)(CH ₂) ₃ Pth ^d | 185-195 ^{b,e} | EtOAc | 81 | C ₃₇ H ₃₁ ClF ₃ N ₃ O ₅ ·HCl | Cl, F |
| 7c | 4-ClC ₆ H ₄ CH ₂ | NHCH(CH ₃)(CH ₂) ₃ Pth ^d | 149-151 | <i>i</i> -PrOH | 77 | C ₃₈ H ₃₃ ClF ₃ N ₃ O ₅ | Cl, F |
| 8a | CH ₃ | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 146-149 | CH ₃ CN | 78 | C ₂₄ H ₂₈ F ₃ N ₃ O ₃ ·C ₄ H ₈ O ₄ | F |
| 8b | 4-ClC ₆ H ₄ | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 115-119 | EtOAc-hex | 62 | C ₂₉ H ₂₉ ClF ₃ N ₃ O ₃ ·C ₄ H ₈ O ₄ | Cl, F |
| 8c | 4-ClC ₆ H ₄ CH ₂ | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 144-145 | CH ₃ CN-MeOH | 76 | C ₃₀ H ₃₁ ClF ₃ N ₃ O ₃ ·C ₄ H ₈ O ₄ | Cl, F |
| 8d | H | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 228-231 | EtOH-Et ₂ O | 66 ^f | C ₂₅ H ₂₆ F ₃ N ₃ O 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 solvent | % yield | formula | anal. ^a |
|-----|------------------|--|---|----------------------|---|---------|---|--------------------|
| 11 | H | H | Pth ^b | 292-294 | CH ₃ OH ^c | 96 | C ₁₉ H ₁₄ N ₂ O ₃ | |
| 13 | Cl | H | Pth | 295-297 | DMF | 78 | C ₁₉ H ₁₃ ClN ₂ O ₃ | Cl |
| 14 | Cl | H | NH ₂ | 146-148 | <i>i</i> -PrOH | 87 | C ₁₁ H ₁₁ ClN ₂ O | |
| 15 | OCH ₃ | H | NH ₂ | 134-135 | <i>i</i> -PrOH-CH ₃ OH | 83 | C ₁₂ H ₁₄ N ₂ O ₂ | |
| 16 | OCH ₃ | H | NHCH(CH ₃)(CH ₂) ₃ Pth | 119-121 | <i>d</i> | 69 | C ₂₅ H ₂₇ N ₃ O ₄ | |
| 17 | OCH ₃ | H | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 149-150 | EtOH-Et ₂ O | 60 | C ₁₇ H ₂₅ N ₃ O ₂ ·C ₄ H ₈ O ₄ | |
| 18 | H | O(CH ₂) ₅ CH ₃ | NO ₂ | 53-54 ^e | <i>d</i> | 54 | C ₁₇ H ₂₂ N ₂ O ₄ | |
| 19 | H | O(CH ₂) ₅ CH ₃ | NH ₂ | 70-71 ^f | petr ether | 72 | C ₁₇ H ₂₄ N ₂ O ₂ | |
| 20 | H | O(CH ₂) ₅ CH ₃ | Pth | 184-185 | EtOH | 94 | C ₂₅ H ₂₆ N ₂ O ₄ | |
| 22 | Cl | O(CH ₂) ₅ CH ₃ | Pth | 178-179 | EtOH ^c | 91 | C ₂₅ H ₂₅ ClN ₂ O ₄ | Cl |
| 23 | Cl | O(CH ₂) ₅ CH ₃ | NH ₂ | 74-75 | Et ₂ O-petr ether | 70 | C ₁₇ H ₂₃ ClN ₂ O ₂ | Cl |
| 24 | OCH ₃ | O(CH ₂) ₅ CH ₃ | NH ₂ | 56-57 | EtOH-H ₂ O | 80 | C ₁₈ H ₂₆ N ₂ O ₃ | |
| 25 | OCH ₃ | O(CH ₂) ₅ CH ₃ | NHCH(CH ₃)(CH ₂) ₃ Pth | <i>g</i> | | 53 | C ₃₁ H ₃₈ N ₃ O ₅ | |
| 26 | OCH ₃ | O(CH ₂) ₅ CH ₃ | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 111-112 | <i>i</i> -PrOH-Et ₂ O | 75 | C ₂₃ H ₂₇ N ₃ O ₃ ·C ₄ H ₈ O ₄ | |
| 27 | H | <i>m</i> -OCH ₂ C ₆ H ₄ CF ₃ | Pth | 191-193 | CH ₃ OH ^c | 89 | C ₂₇ H ₁₉ F ₃ N ₂ O ₄ | |
| 29 | Cl | <i>m</i> -OCH ₂ C ₆ H ₄ CF ₃ | Pth | 213-215 | EtOAc | 83 | C ₂₇ H ₁₈ ClF ₃ N ₂ O ₄ | Cl |
| 30 | Cl | <i>m</i> -OCH ₂ C ₆ H ₄ CF ₃ | NH ₂ | 88-90 | hexane ^c | 89 | C ₁₉ H ₁₆ ClF ₃ N ₂ O ₂ | |
| 31 | OCH ₃ | <i>m</i> -OCH ₂ C ₆ H ₄ CF ₃ | NH ₂ | 98-100 | hexane | 45 | C ₂₀ H ₁₉ F ₃ N ₂ O ₃ | |
| 32 | OCH ₃ | <i>m</i> -OCH ₂ C ₆ H ₄ CF ₃ | NHCH(CH ₃)(CH ₂) ₃ Pth | 145-147 | CH ₂ Cl ₂ -CH ₃ OH | 35 | C ₃₃ H ₃₂ F ₃ N ₃ O ₅ | |
| 33 | OCH ₃ | <i>m</i> -OCH ₂ C ₆ H ₄ CF ₃ | NHCH(CH ₃)(CH ₂) ₃ NH ₂ | 154-156 ^h | CH ₃ OH-Et ₂ O | 73 | C ₂₅ H ₃₀ F ₃ N ₃ O ₃ ·0.5C ₄ H ₈ O 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-methylquinoline⁶ via the

procedure shown in Schemes I and II. Analogues 26 and 33 were prepared from 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline¹ 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

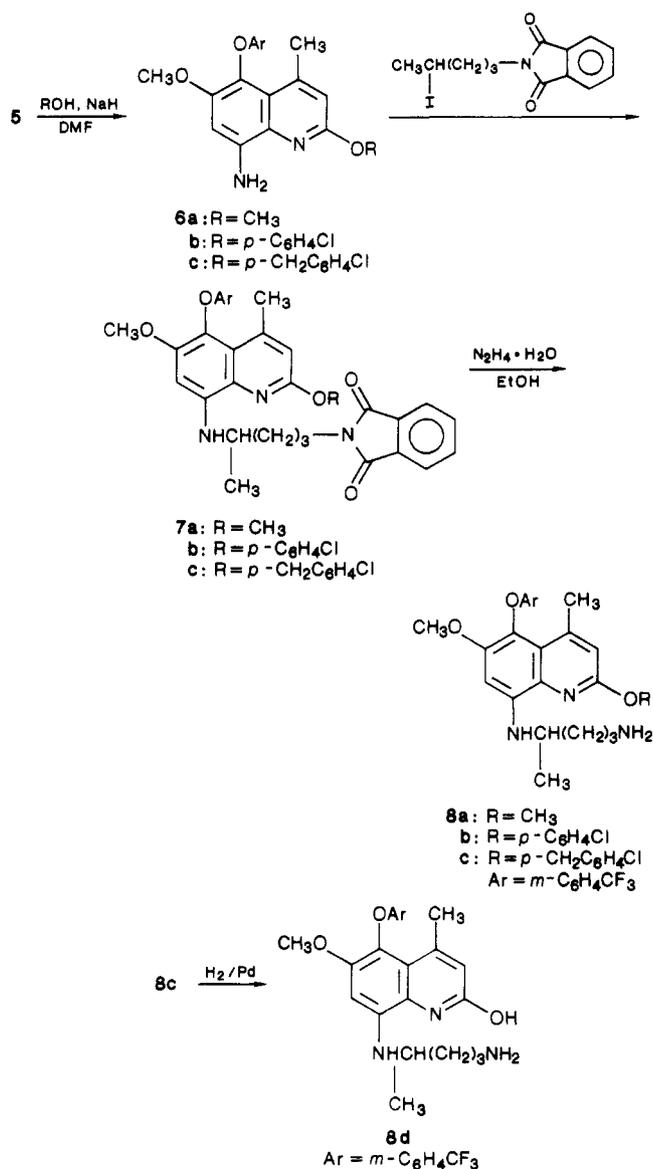


Table III. Suppressive Antimalarial Activity Data^a for *P. berghei* Infected Rane Mice

| compd | ΔMST, days, at mg/kg, sc ^{7,8} | | | | | | |
|-----------------|---|---------|----------|----|---------|-------|-----------|
| | 5 | 10 | 20 | 40 | 80 | 160 | 320 640 |
| prima- quine | | | | 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, | 1C | 2C | 2C/1T, | 1C/4T | 3T |
| | | 8.1 (A) | | | 4C | | |

^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

(7) Osden, 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.

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

| compd | mg/kg (salt) per day (×7), po ⁹ | | | | | molar primaquine index ^a |
|-------------------------|--|------|-------|------|------|---|
| | 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 | 3/3C | 2/2C | d | |
| | | | 0/1C | | | |
| 33 | d | d | d | d | d | |

^a Ratio of the molar ED₅₀ of primaquine, I, 8a, and 17 divided by the ED₅₀ of primaquine, determined by regression analysis. ^b Diphosphate salt. ^c Succinate salt. ^d Not tested.

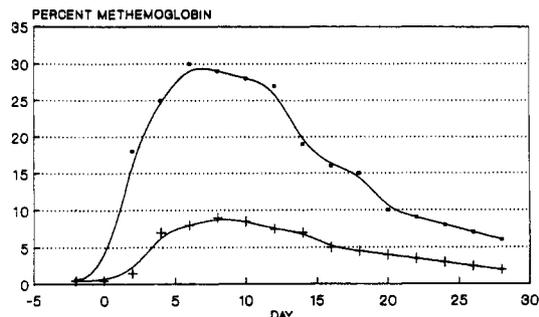


Figure 1. Methemoglobin formation for compounds I (■) and 8a (+). Compounds I and 8a were administered at a dosage of 0.0116 mmol/kg per day on days 0–3.

contrast with the early work² 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

(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 |

^aChan, P. K.; et al. In *Principles and Methods of Toxicology*; Hayes, A., Ed.; Raven Press: New York, 1984; pp 1-52. ^bFischer 344 rats used in all tests. ^c80 rats. ^d100 rats. ^e74 rats. ^f85 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 1¹ (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. (C₂₆H₁₇F₃N₂O₄) 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 CHCl₃ (20 mL) was stirred at room temperature for 41 h and then filtered. The filtrate was washed with 10% NaHSO₃ (50 mL) and saturated NaHCO₃ (2 × 50 mL), dried (MgSO₄), 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. (C₂₆H₁₇F₃N₂O₅·C₂H₆O) C, H, F, N.

The following were similarly prepared: **6-methoxy-4-methyl-8-phthalimidoquinoline 1-oxide** [12, 83%, mp 288–290 °C dec (CHCl₃/EtOH)], **5-(1-hexyloxy)-6-methoxy-4-methyl-8-phthalimidoquinoline 1-oxide** [21, 77%, mp 199–200 °C (EtOH). Anal. (C₂₅H₂₆N₂O₅) 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 CHCl₃ (500 mL) was treated with POCl₃ (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 CHCl₃ (2 × 200 mL). The combined CHCl₃ layers were washed with H₂O (2 × 200 mL), saturated NaHCO₃ (200 mL), dried (MgSO₄), 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. (C₂₆H₁₆N₂ClF₃O₄) 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 CH₂Cl₂. The combined filtrate and washings were evaporated in vacuo to a small volume and diluted with CH₂Cl₂ (500 mL). The CH₂Cl₂ was extracted with 20% KOH (3 × 200 mL) and brine, dried (K₂CO₃), 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. (C₁₈H₁₄ClF₃N₂O₂) 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 N₂ atmosphere was treated with NaH (50% oil dispersion, 1.02 g, 21.4 mmol). After H₂ 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 CH₂Cl₂. The CH₂Cl₂ was washed with H₂O (3×), dried (K₂CO₃) 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 CH₂Cl₂. 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 CH₃CN (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 H₂O (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 CH₂Cl₂. The combined filtrate and washings were evaporated in vacuo to a small volume and diluted with CH₂Cl₂ (200 mL). The CH₂Cl₂ solution was washed with 20% KOH (3 × 75 mL) and brine, dried (K₂CO₃), and evaporated in vacuo to an oil. This oil was dissolved in CH₃CN (20 mL) and treated with a solution of succinic acid (1.42 g, 12 mmol) in a mixture of MeOH (5 mL) and CH₃CN (20 mL) to give 6.3 g (86%) of the title compound. Recrystallization from CH₃CN 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 H₂O 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 K₂CO₃ and extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts were washed with H₂O, dried (K₂CO₃), 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 Et₂O (100 mL). Filtration gave 4.9 g (66%) as the first crop of title compound, mp 225–228 °C. Recrystallization from EtOH–Et₂O 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-nitroquinoline¹ (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 (MgSO₄), 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 H₂ 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 (MgSO₄), 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 (MgSO₄). 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-pentofuranosyl 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 transcrip-

tase,^{3,4} an enzyme specific for retroviruses. Other sugar-modified nucleosides, such as various arabinofuranosyl,^{5,6}

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