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THE SYNTHESIS OF POTENTIAL ANTIPARASITIC DRUGS

FINAL REPORT

MAY 1990

E. A. Nodiff, S. Chatterjee and K. Tanabe

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) During the period from 1 April 1988 - 31 March 1990, we submitted to WRAIR 23 Target compounds (Table I) and 26 intermediates (Table II). In earlier work, we prepared a series of primaquines with a methyl group at position 4 and a phenylalkoxy group at position 5. These compounds combined low toxicity with a unique dual efficacy against the blood and tissue forms at the malarial parasite. During the past two years, we have attempted to enhance this series by attaching various substituents to the phenyl portion of the 5-phenylalkoxy group (Tables III - V). We have also prepared several compounds in which the terminal phenyl has been replaced by heterocycles (Table VI). At the request of USAMRDC, we have prepared a third group of primaquines which are trisubstituted; these compounds combine a 5-phenoxy or 5-alkoxy group with two additional substituents on the pyridine ring of the quinoline nucleus. (Tables VII - X.) Radical curative screening data for the new compounds are too sparse for SAR correlation but some blood schizontocidal comparisons are presented.			
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FOREWORD

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In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

E A Moody 17 May 1996
PI - Signature DATE

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INTRODUCTION

P. falciparum and *P. vivax* cause 95% of human malaria. *P. falciparum* has no persistent liver forms and thus no potential for relapse; it can be radically cured with a blood schizontocide. *P. vivax* does have persistent liver forms which can cause relapse by intermittent re-invasion of cleared blood. Radical cure of vivax malaria therefore requires a blood and a tissue schizontocide. Unfortunately, the antimalarial chemotherapeutic picture is bleak. Many clinical blood schizontocides are available but they are obsolescent because of the facility with which *P. falciparum* generates resistant strains. For example, mefloquine, the best of the new blood schizontocides, has already encountered resistance, in Thailand and Tanzania, while still in field trials. In stark contrast to the abundance of blood schizontocides, there is only a single drug, primaquine, in general use as a tissue schizontocide (antirelapse drug). Primaquine is also a gametocytocide and a sporontocide and is relatively slow to select resistant strains. However, primaquine is far from the ideal drug; it is a poor blood schizontocide and it has a therapeutic index low enough to make its use hazardous.

In an earlier attempt to improve primaquine we prepared a series of primaquines with an alkoxy group at position 5 and a methyl group at position 4. These compounds were extremely active as blood and tissue schizontocides but were toxic at the upper half of the dosage range (80-640 mg/kg). We were subsequently able to dramatically attenuate the toxicity of these compounds, with minimal activity loss, by attaching a phenyl group to the terminal carbon of the 5-alkoxy group.

During the past two years, we have attempted to further enhance this series by attaching various substituents to the terminal phenyl group (Tables III - V). We have also prepared several compounds in which the terminal phenyl has been replaced by heterocycles (Table VI). At the request of USAMRDC, we have prepared a third group of primaquines which are trisubstituted (Tables VII - X); these compounds combine a 5-phenoxy or 5-alkoxy group with two additional substituents on the pyridine ring of the

quinoline nucleus. Radical curative screening data for the new compounds are too sparse for SAR correlation but some blood schizontocidal comparisons are presented.

TABLE I
TARGET COMPOUNDS SUBMITTED TO WRAIR
(1 April 1988 - 30 March 1990)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
$\text{CH}_3\text{CH}(\text{CH}_2)_3\text{NH}_2$. Fumarate	2.2	KT-1756	BL 54350
$\text{CH}_3\text{CH}(\text{CH}_2)_3\text{NH}_2$. Fumarate	2.57	III-SAN-1	BL 56925

TABLE I (CONTINUED)

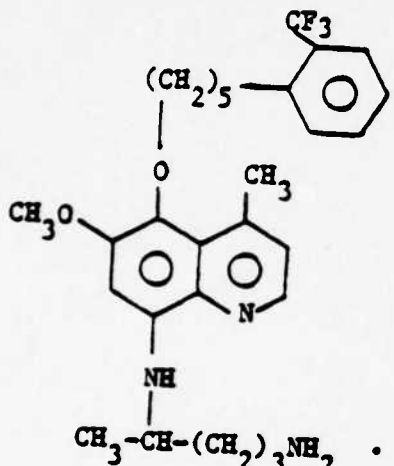
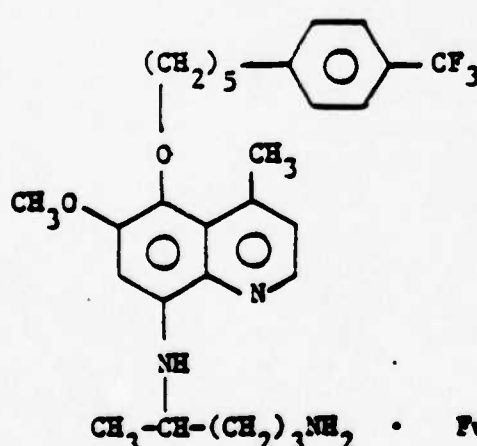
<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
 2.1 II-SAN-36 BL 54967	2.1	II-SAN-36	BL 54967
 2.8 II-SAN-47 BL 55384	2.8	II-SAN-47	BL 55384

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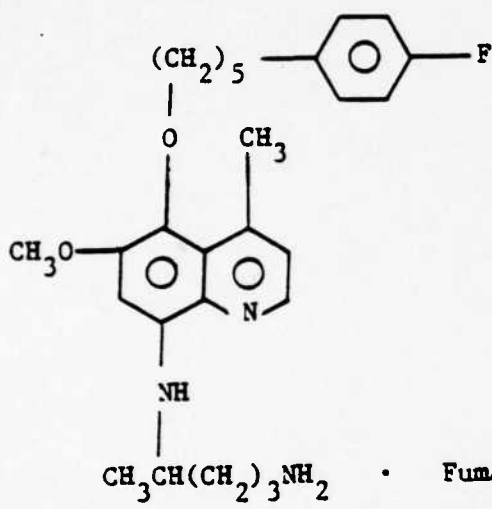
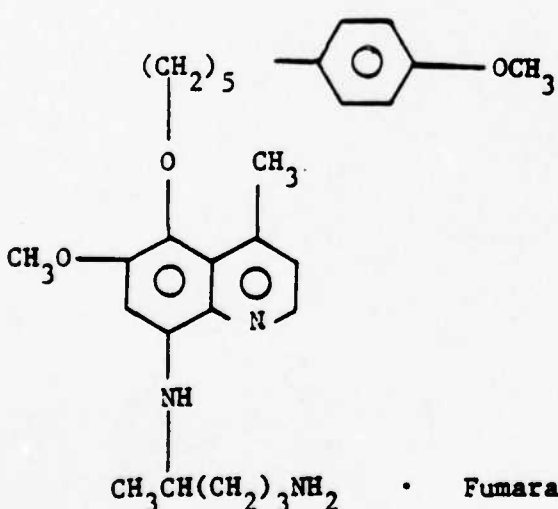
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 2.57 SAN-76 BL 52785			
 2.4 SAN-93 BL 53522			

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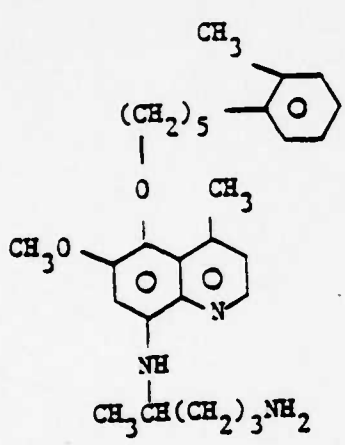
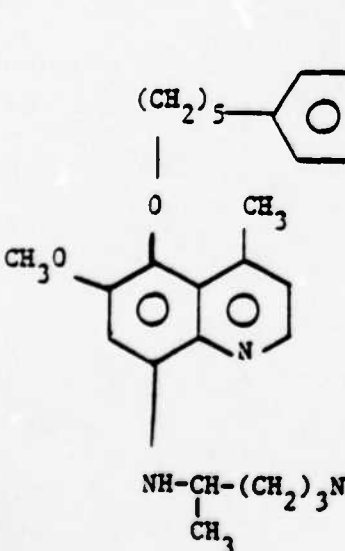
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 3.0 KT 1855 BM 03214 .Fumarate			
 7.3 KT-1860 BM 03705 .Fumarate			

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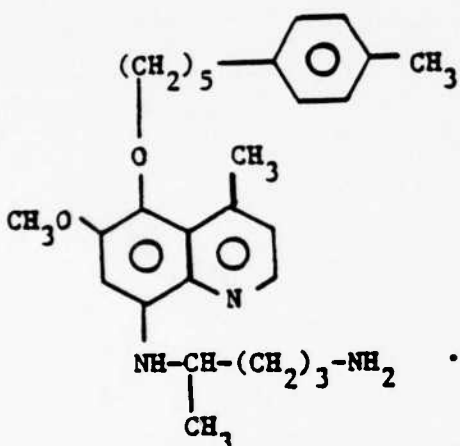
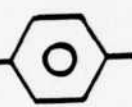
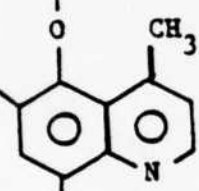
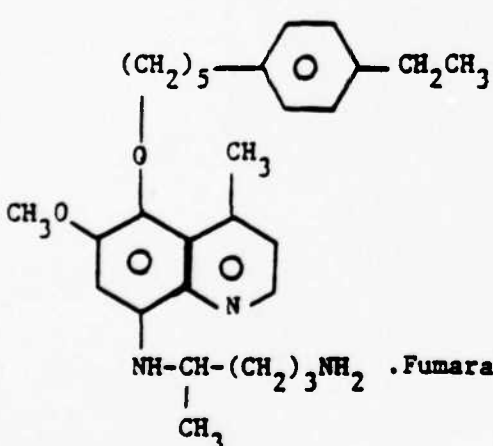
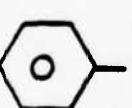
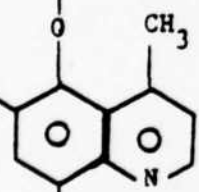
<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
 $(\text{CH}_2)_5$——CH_3 CH_3O——CH_3 $\text{NH}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_3-\text{NH}_2$ • Fumarate	5.5	II-SAN-59	BL 55820
 $(\text{CH}_2)_5$——CH_2CH_3 CH_3O——CH_3 $\text{NH}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_3-\text{NH}_2$ • Fumarate	2.43	IV-SAN-56	BM 03205

TABLE I (CONTINUED)

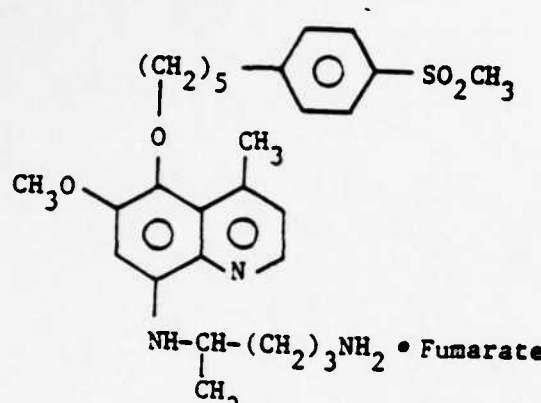
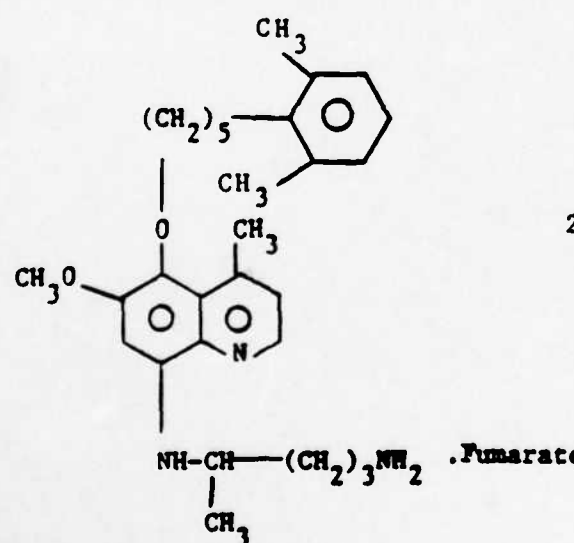
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 2.60 IV-SAN-68 BM 03590			

TABLE I (CONTINUED)

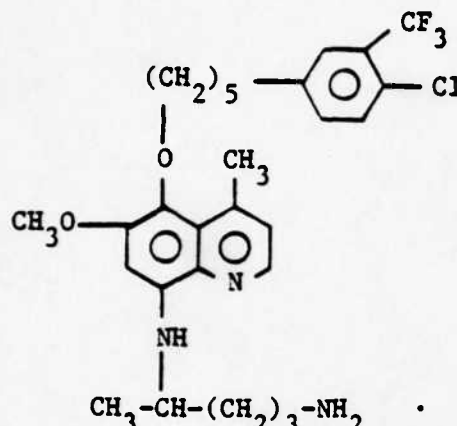
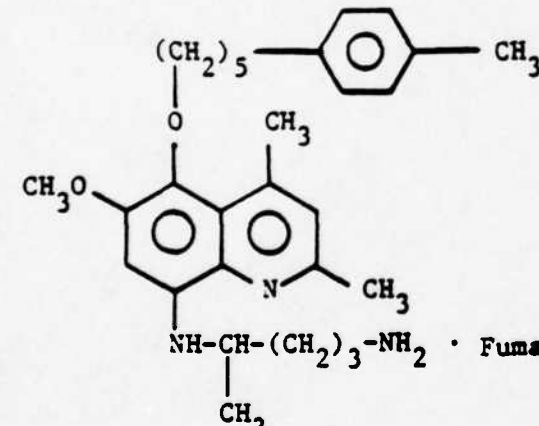
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 1.8 II-SAN-22 BL 54627			
 2.0 IV-SAN-6 BM 01229			

TABLE I (CONTINUED)

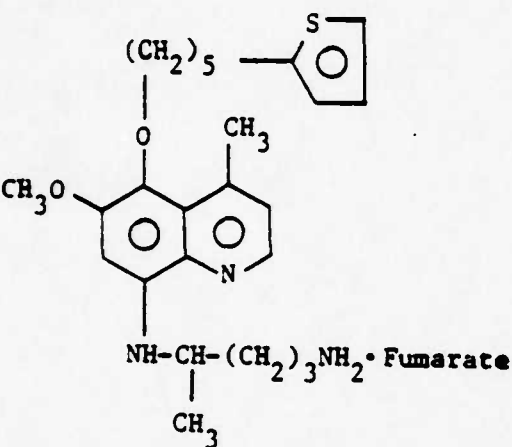
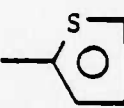
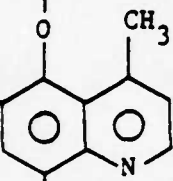
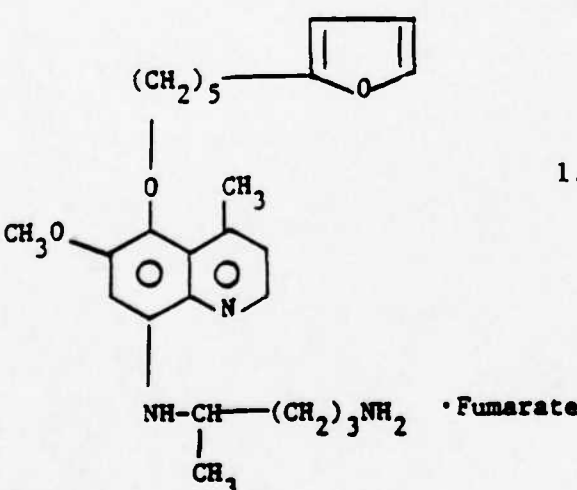
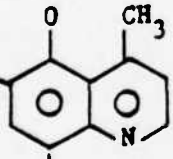
<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
 $(\text{CH}_2)_5$ —  CH_3O —  $\text{NH}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_3\text{NH}_2 \cdot \text{Fumarate}$	3.17	IV-SAN-15	BM 01667
 $(\text{CH}_2)_5$ —  CH_3O —  $\text{NH}-\text{CH}(\text{CH}_3)-(\text{CH}_2)_3\text{NH}_2 \cdot \text{Fumarate}$	1.92	IV-SAN-49	BM 02762

TABLE I (CONTINUED)

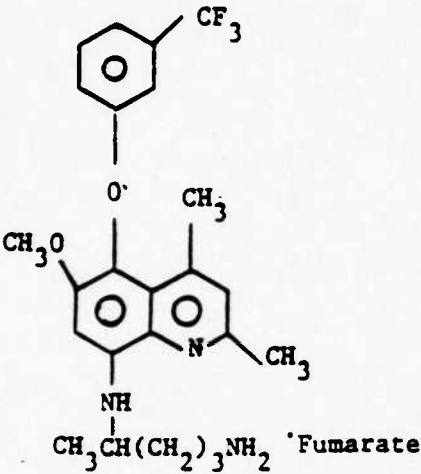
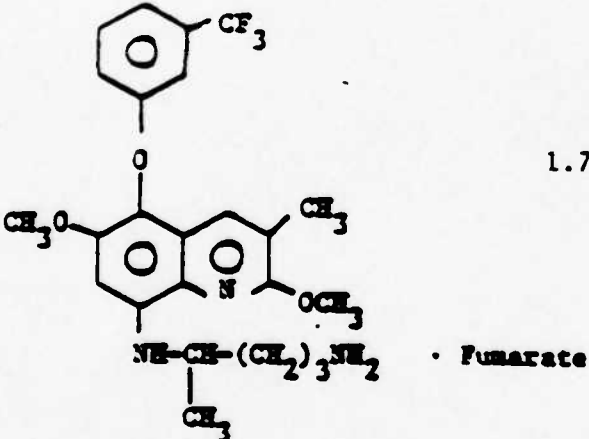
<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	2.1	KT-1848	BM 02744
	1.75	III-SAN-44	BL 58867

TABLE I (CONTINUED)

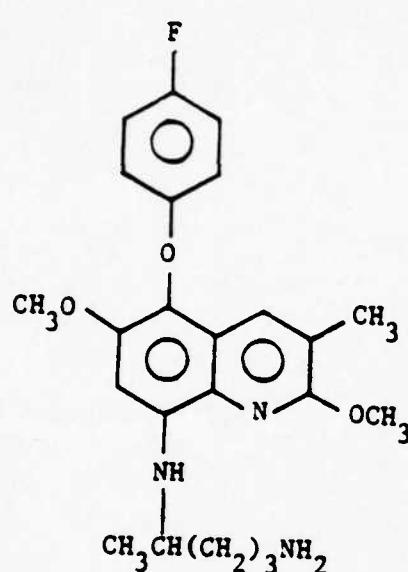
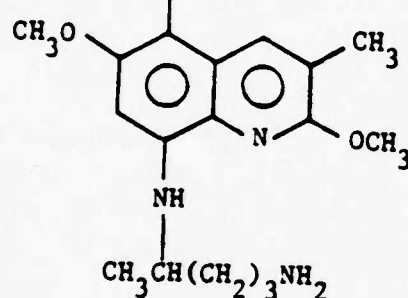
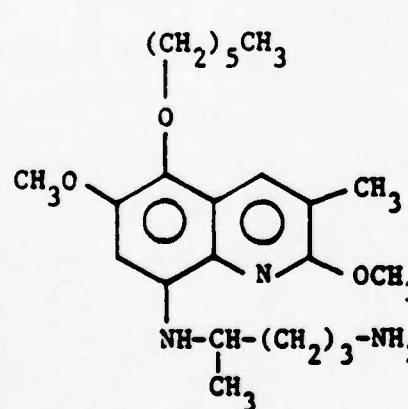
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	1.2	KT-1814	BM 00473
	1.3	KT-1836	BM 02422
	3.1	III-SAN-68	BM 00393

TABLE I (CONTINUED)

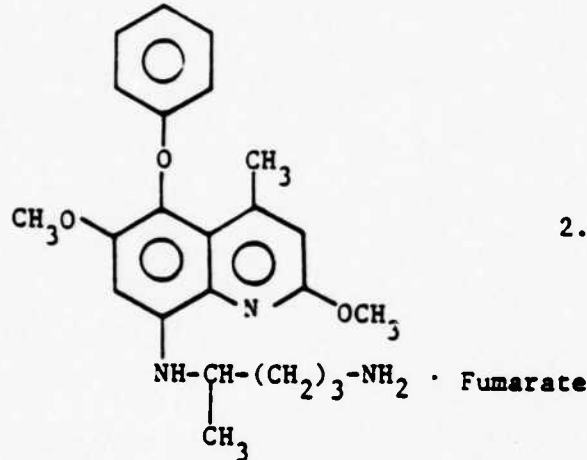
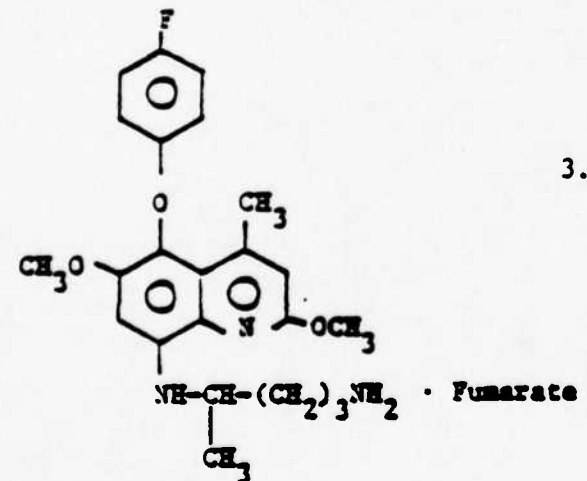
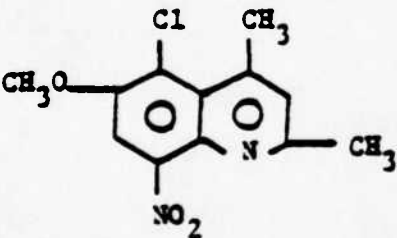
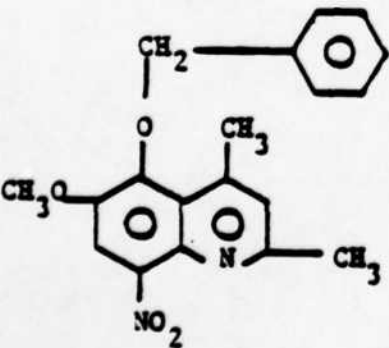
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 2.44 III-SAN-79 BM 00722			
 3.0 III-SAN-33 BL 57888			

TABLE I (CONTINUED)

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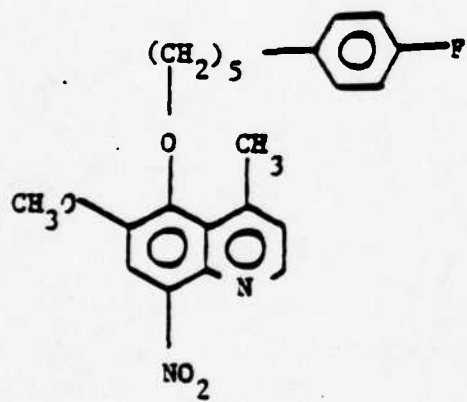
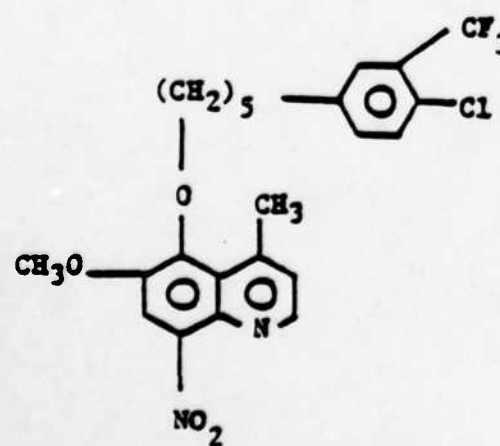
Contract No. DAMD17-88-C-8106

TABLE II
INTERMEDIATES SUBMITTED TO WRAIR
(1 April 1988 - 30 March 1990)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
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	0.5	KT-1759	BL 54529

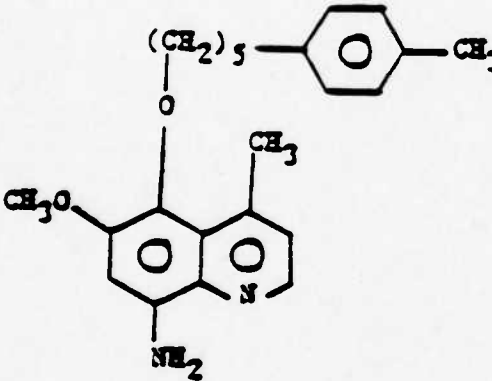
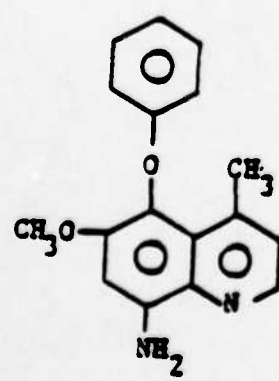
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TABLE II (CONTINUED)

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	0.5	II-SAN-7	BL 54305

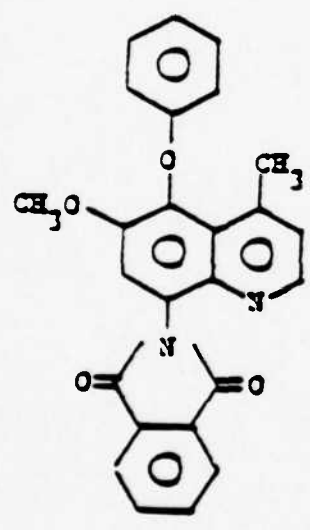
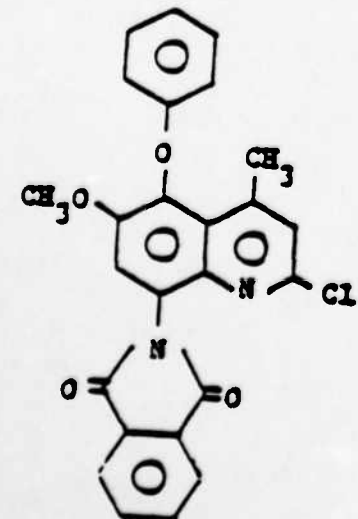
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TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	0.5	II-SAN-55	BL 55900
	0.5	KT-1769	BL 55393

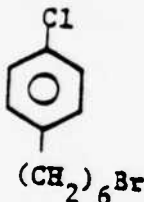
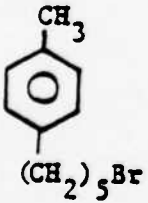
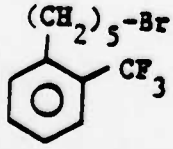
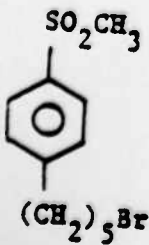
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
 <chem>COc1cc(OC2=CC=CC=C2)c3cc(C)c4c3c5c6ccccc6c7c5c(=O)n8c7ccccc8n4</chem>	0.5	KT-1772	BL 55553
 <chem>COc1cc(OC2=CC=CC=C2)c3cc(C)c(Cl)c4c3c5c6ccccc6c7c5c(=O)n8c7ccccc8n4</chem>	0.5	KT-1775	BL 55946

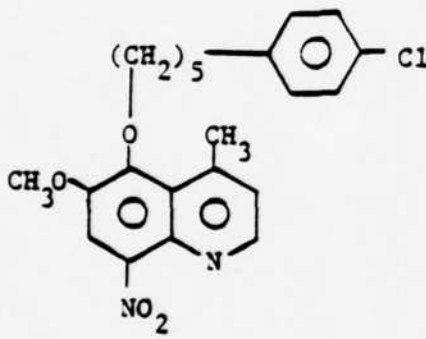
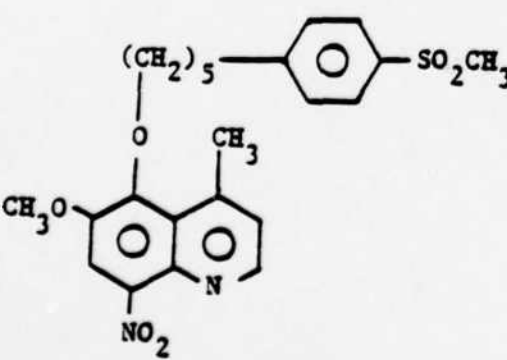
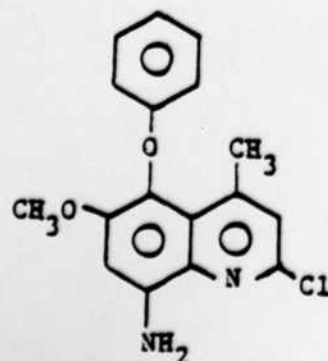
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
 <chem>Clc1ccc(cc1)CCCCCBr</chem>	0.5	KT-1749	BL 53291
 <chem>Cc1ccc(cc1)CCCCBr</chem>	0.5	II-SAN-49D	BL 55937
 <chem>BrCCCCCc1ccccc1C(F)(F)F</chem>	0.5	II-SAN-28C	BL 54798
 <chem>CS(=O)(=O)c1ccc(cc1)CCCCBr</chem>	0.5	II-SAN-79	BL 56201

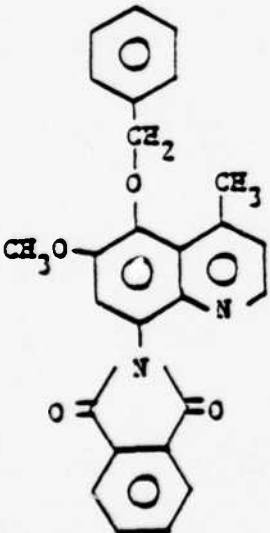
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	0.5	III-SAN-9	BL 57057
	0.5	III-SAN-8	BL 57048
	0.5	KT-1781	BL 56416

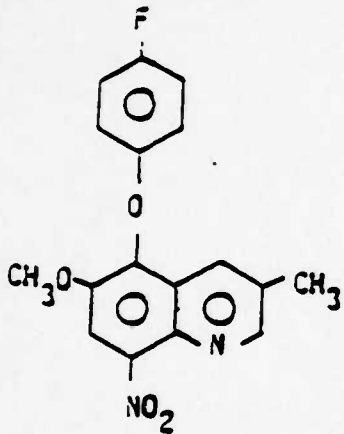
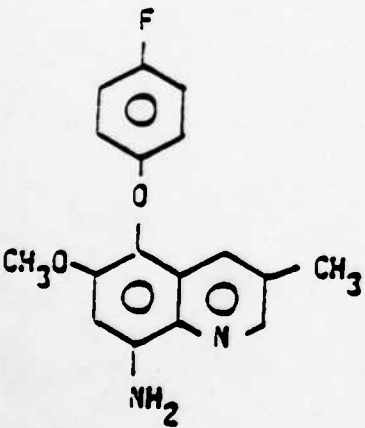
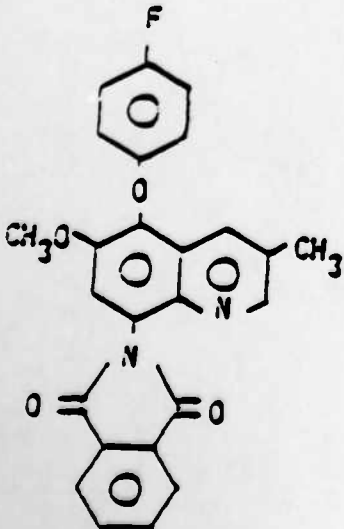
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	0.5	KT-1795	BL 57735

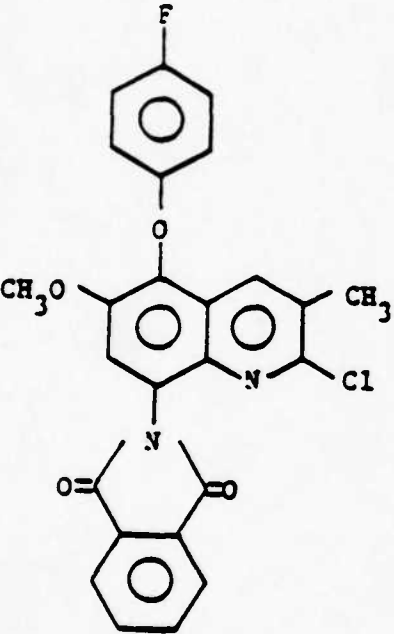
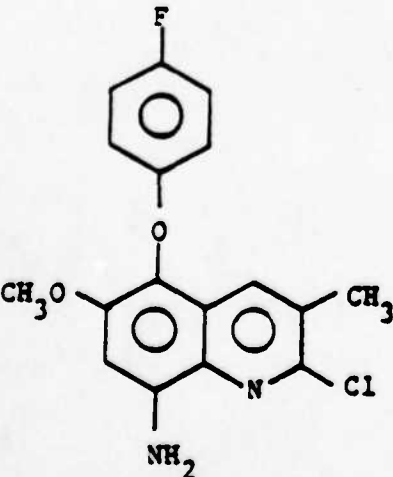
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
 <chem>Cc1cnc2cc(OC)c(OC3=CC=C(F)C=C3)cc2[N+](=O)[O-]</chem>	0.5	KT-1806	BL 59622
 <chem>Cc1cnc2cc(OC)c(OC3=CC=C(F)C=C3)cc2N</chem>	0.5	KT-1807	BL 59631
 <chem>Cc1cnc2cc(OC)c(OC3=CC=C(F)C=C3)cc2N4C(=O)c5ccccc5C4=O</chem>	0.5	KT-1808	BL 59640

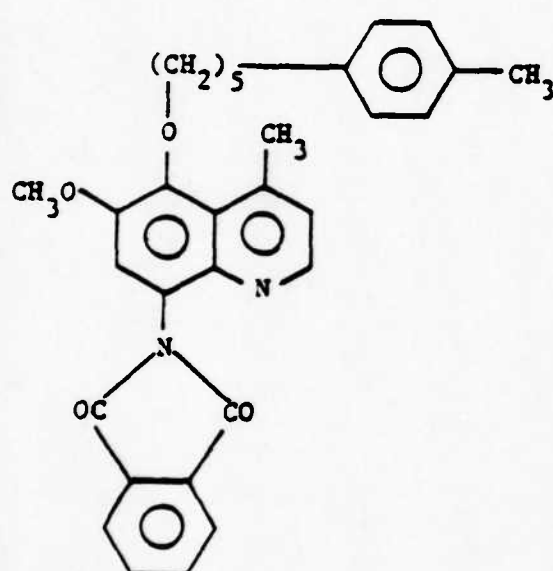
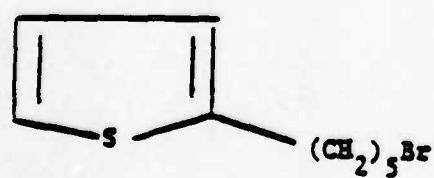
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	0.5	KT-1810	BL 59926
	0.5	KT-1811	BL 59935

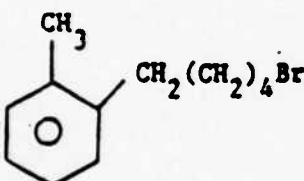
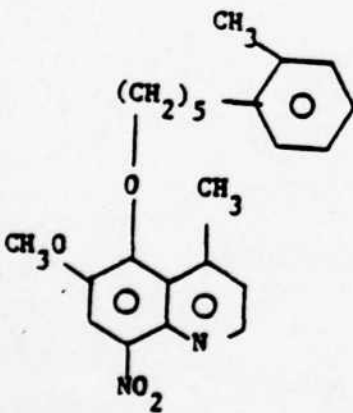
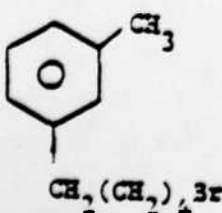
Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	0.5	III-SAN-86	BM 00937
	0.5	IV-SAN-8C	BM 02753

Contract No. DAMD17-88-C-8106

TABLE II (CONTINUED)

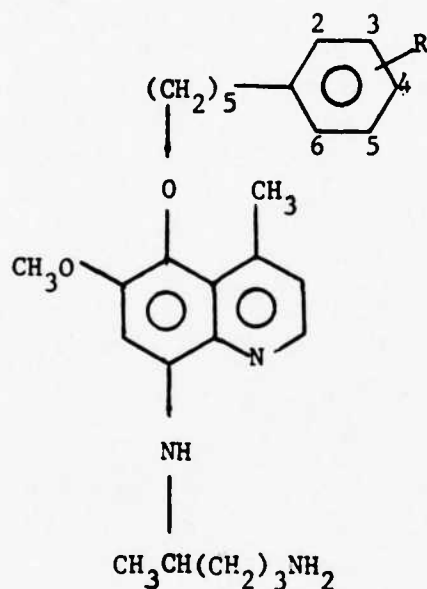
<u>Structure</u>	<u>Quantity, g</u>	<u>FRC Code</u>	<u>WR Number</u>
	0.5	KT 1851	BM 03152
	0.5	KT 1852	BM 03161
	0.5	KT-1856	BM 03661

BIOLOGY

Sufficient blood schizontocidal screening data have been obtained to permit the following structure-activity correlations:

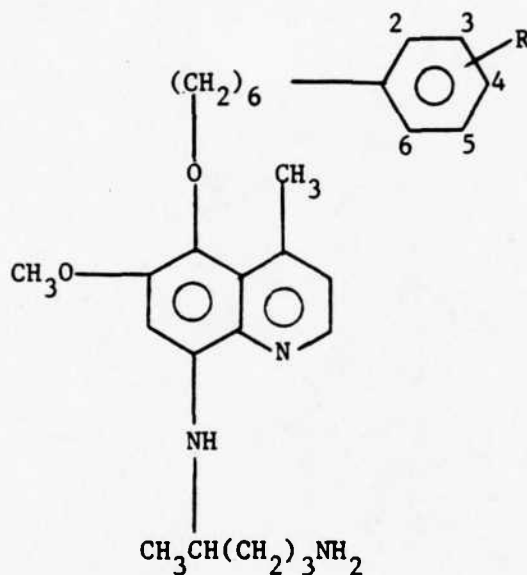
1. Among the 5-[5-(phenyl)pentoxy]primaquines (Table III), introduction of a 2-CF₃ group (BL 54967) or a 4-CH₃ group (BL 55820) produced an increase in therapeutic index over the parent compound (BL 09293). The 4-CF₃ derivative (BL 55384), with 5/5C at 20 mg/kg, should be tested at lower doses. It is of interest that the only derivative with a hydrophilic substituent (BM 01925) was highly toxic.
2. Among the 5-[6-(phenyl)hexoxy]primaquines, addition of a 3-Cl (BL 30841), 3-CF₃ (BL 40448) or 2,3-benzo (BL 45137) group (Tables IV and V) provided a small increase in blood schizontocidal activity and a slight decrease in radical curative activity.
3. The only 5-[5-(heterocycle)pentoxy]primaquine screened to date (BM 01667; Table VI) was 100% curative at 20 mg/kg and should be evaluated at lower doses. The only other compound in this series (BM 02762) has not yet been tested.
4. Table VII includes preliminary blood schizontocidal data for a series of trisubstituted primaquines. These compounds combine a 5-alkoxy or 5-phenoxy group with two additional substituents on the pyridine ring of the quinoline nucleus. In each case one of the two pyridine substituents is at position 2. Tables VIII - X compare these compounds with their 2-unsubstituted prototypes.
5. Among the 5-alkoxyprimaquines (Table VIII), addition of the 2-CH₃O group increased the activity and decreased the toxicity of the 3-methyl derivative (BJ 83486 vs BM 00393) but decreased both the activity and the toxicity of its 4-methyl isomer (BH 89438 vs a).
6. Addition of a 2-CH₃O to 4-methyl-5-phenoxyprimaquine produced a marginal diminution of activity and toxicity (Table IX; BJ 44836 vs BM 00722).
7. Table X suggests that 2-CH₃O,4-CH₃,5-(4-fluorophenoxy)primaquine (BL 57888) is equally toxic but less effective than its 2-desmethoxy analogue. The 3-CH₃ isomer (BM 00473) has less activity and toxicity than the 4-CH₃ isomer (BL 57888).

TABLE III
INFLUENCE OF SUBSTITUENTS ON THE PHENYL GROUP OF
5-[5-(PHENYL)PENTOXY]PRIMAQUINES
BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P.berghei, Mouse)



No.	R	Cures (C), Toxic Deaths (T) or Δ MST							
		Dose, mg/kg							
		5	10	20	40	80	160	320	640
BL 09293	H		3C	4C	5C	5C	5C	3C	1C
BL 50076	3-Cl		4C	5C	5C	5C	3C	1C	3C
BL 56925	4-Cl								
BL 54967	2-CF ₃	1C	3C	3C	5C	5C	5C	5C	5C
BL 49439	3-CF ₃	6.4	2C	5C	5C	5C	5C	3C	
BL 55384	4-CF ₃			5C	5C	5C	5C	3C	4C
BL 52785	4-F	1C	3C	4C	5C	5C	3C	2C	2T
BL 53522	4-OCH ₃	8.1	5C	5C	5C		4C		3.0
BM 03214	2-CH ₃								
BM 03705	3-CH ₃								
BL 55820	4-CH ₃	3C	2C	3C	5C	5C	5C	5C	5C
BM 03205	4-C ₂ H ₅								
BM 01925	4-SO ₂ CH ₃				1T		3T		5T
BM 03590	2,6-(CH ₃) ₂								
BL 50236	3,5-(CF ₃) ₂	4.7	9.1	4C	5C	5C	5C	5C	5C
BL 54627	4-Cl, 3-CF ₃	7.6	1C	4C	5C		5C		4C, 1T

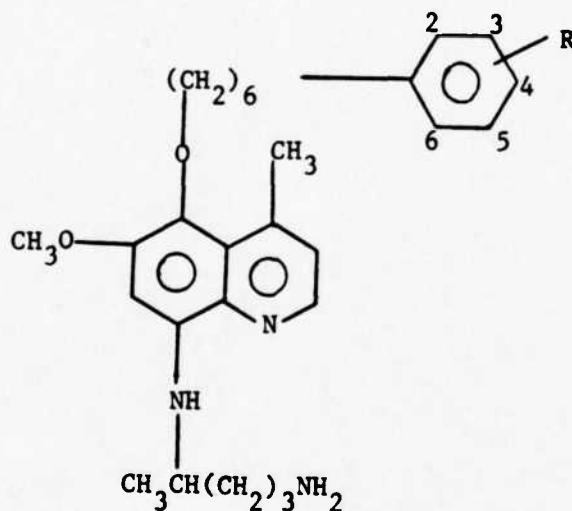
TABLE IV
INFLUENCE OF SUBSTITUENTS ON THE PHENYL GROUP OF
5-[6-(PHENYL)HEXOXY]PRIMAQUINE
BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P.berghei, Mouse)



No.	R	Cures (C), Toxic Deaths (T) or Δ MST							
		Dose, mg/kg							
		5	10	20	40	80	160	320	640
BL 09962	H	5.9	1C	3C	4C	4C	3C	3C	4C
BL 30841	3-Cl	7.5	1C	4C	4C	5C	5C	5C	5C
(BL-48825)									
BL 40448	3-CF ₃		1C	4C	5C	5C	5C	5C	
BL 45137	2,3-Benzo	5.7	2C	5C	5C	5C	5C	5C	

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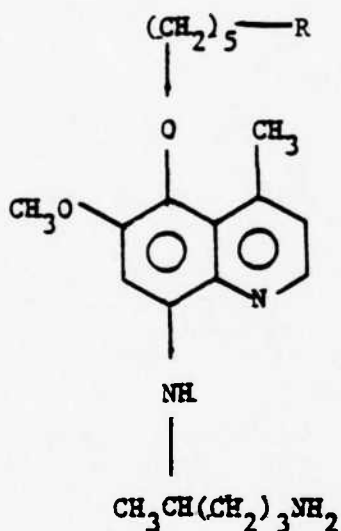
TABLE V
INFLUENCE OF SUBSTITUENTS ON THE PHENYL GROUP OF
5-[6-(PHENYL)HEXOXY]PRIMAQUINE
RADICAL CURATIVE ANTIMALARIAL ACTIVITY
(P. cynomolgi, Rhesus)



No.	R	n	Cures /No. of Animals				
			Dose,mg/kg				
			0.1	0.316	1.0	3.16	10.0
BL 09962	H	6	0/2	4/4	2/2		
BL 30841	3-Cl	6		1/3	3/3		
(BL-48825)							
BL 40448	3-CF ₃	6		2/3	2/2	3/3	
BL 45137	2,3-Benzo	6		0/2	2/2	2/2	

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TABLE VI
5-[5-(HETEROCYCLE)PENTOXY]PRIMAQUINES
BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P. berghei, Mouse)

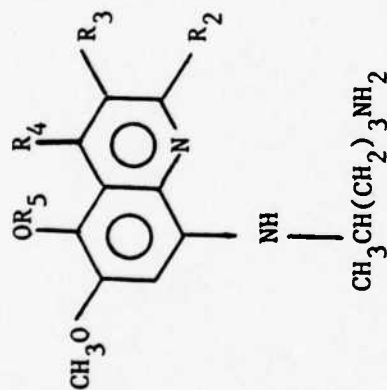


No.	R	Cures (C), Toxic Deaths (T) or Δ MST							
		Dose, mg/kg							
		5	10	20	40	80	160	320	640
BM 01667				5C	5C	5C	3C	2C	0.1
BM 02762									

TABLE VII

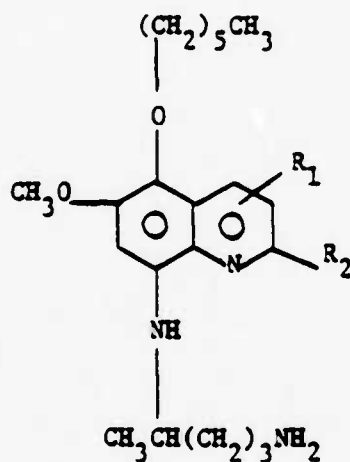
TRISUBSTITUTED PRIMAQUINES

BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY (P.berghei, Mouse)



No.	R ₂	R ₃	R ₄	R ₅	Cures (C), Toxic Deaths (T) or Δ MST						
					Dose, mg/kg						
					5	10	20	40	80	160	320 640
BM 00722	OCH ₃	H	CH ₃	Ph	4.9	1C	2C	4C	4C	4C, 1T	2T 1T
BL 57888	OCH ₃	H	CH ₃	4-FPh	1.2	3.0	3C	5C	5C	1C	13.3 17.1
BM 01210	OCH ₃	H	CH ₃	4-CH ₃ Ph(CH ₂) ₅							
BM 00473	OCH ₃	CH ₃	H	4-FPh			2.7	7.7	1C	5C	5C
BL 58867	OCH ₃	CH ₃	H	3-CF ₃ Ph							
BM 00393	OCH ₃	CH ₃	H	CH ₃ (CH ₂) ₅							
BM 02744	CH ₃	H	CH ₃	3-CF ₃ Ph	1.5	2.9	1C	3C	5C	4C	1.2 1C
BM 01229	CH ₃	H	CH ₃	4-CH ₃ Ph(CH ₂) ₅							

TABLE VIII

EFFECT OF THE 2-CH₃O GROUP ON 5-(ALKOXY)PRIMAQUINESBLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY(P. berghei, Mouse)

No.	R ₁	R ₂	Cures (C), Toxic Deaths (T), Δ MST							
			Dose, mg/kg							
			5	10	20	40	80	160	320	640
BJ 83486	3-CH ₃	H	0.2	8.2	2C	1C	7.6	3T	4T	
BM 00393	3-CH ₃	OCH ₃	2.9	1C	3C	5C	4C	1.2	1C	
BH 89438	4-CH ₃	H	1C	1C	5C	5C	4C	3T	5T	5T
a	4-CH ₃	OCH ₃	I	I	10.5	2C	5C	4C	5T	5T

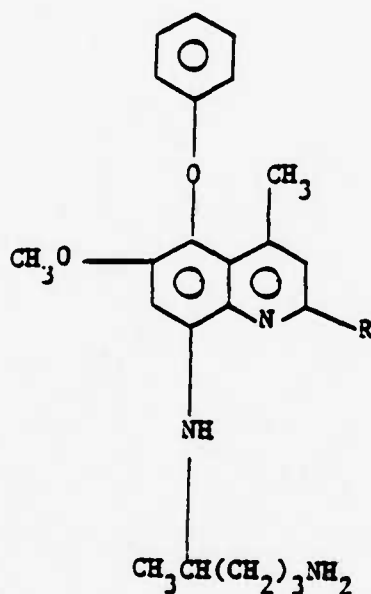
^a

LaMontagne, M.P.; Blumbergs, P.; Smith, D.C.
J. Med. Chem. 1989, 32, 1728

TABLE IX

EFFECT OF THE 2-CH₃O GROUP ON 5-(PHENOXY) PRIMAQUINES

BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P. berghei, Mouse)

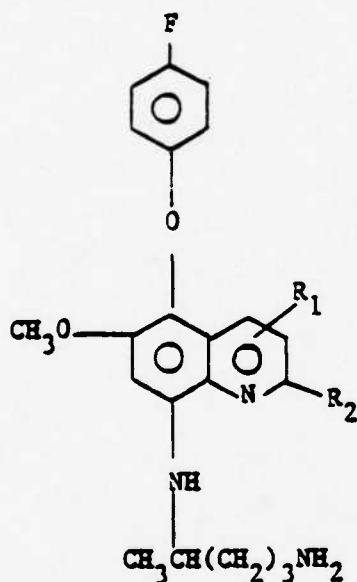


No.	R	Cures (C), Toxic Deaths (T), Δ MST							
		Dose, mg/kg							
		5	10	20	40	80	160	320	640
BJ 44836	H		8.7	4C	3C	4C	4C	3T	2T
BM 00722	OCH ₃				5C		4C		1T

TABLE X

EFFECT OF THE 2-CH₃O GROUP ON 5-(4-FLUOROPHENOXY)PRIMAQUINES

BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P. berghei, Mouse)



No.	R ₁	R ₂	Cures (C), Toxic Deaths (T),							Δ MST	
			Dose, mg/kg								
			5	10	20	40	80	160	320	640	
a	4-CH ₃	H	7.0	3C	4C	5C	5C	5C	4C,1T	3C,2T	
BL 57888	4-CH ₃	CH ₃ O	1.2	3.0	8.0	5C	(10.4) ^b	3C		2T	
BM 00473	3-CH ₃	CH ₃ O			2.7	7.7	1C	5C	5C	5C	

^a

LaMontagne, M.P.; Blumbergs, P.; Strube, R.E.

J. Med. Chem. 1982, 25, 1094.^b Second Evaluation

Contract No. DAMD17-88-C-8106

CHEMISTRY

4-METHYL-5-[5-(R-PHENYL)PENTOXY]PRIMAQUINES

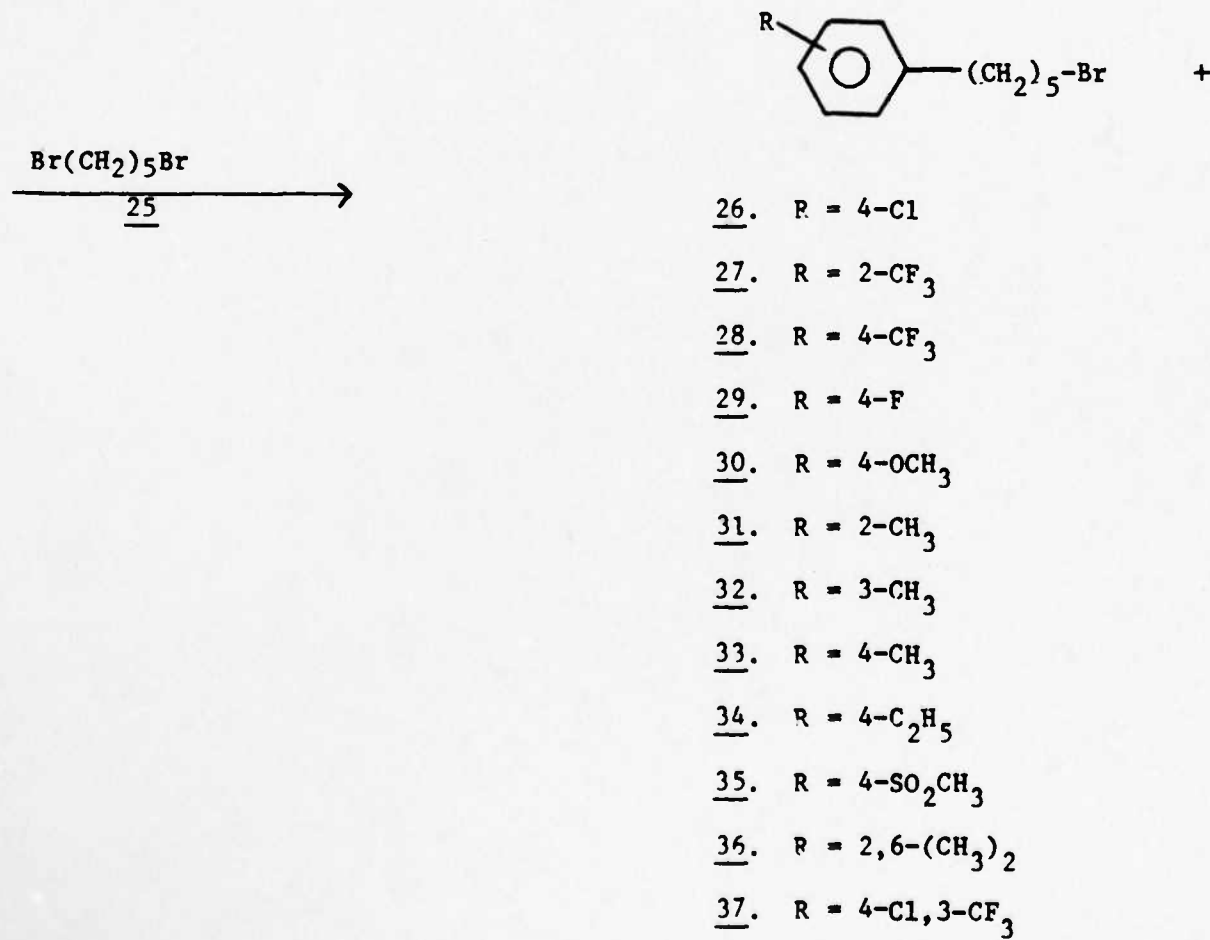
Synthesis of the target compounds (75-86) has been effected as outlined in Scheme 1. Early attempts to make the alkylating agent, 35 was unsuccessful; 35 was subsequently prepared using the alternate route shown in Scheme 2.

The alkylating agents (26-37) were made via an adaptation of the method of Klayman et al.¹ The remaining steps in Scheme 1 were adaptations of those described earlier by Nodiff et al.^{2,3}

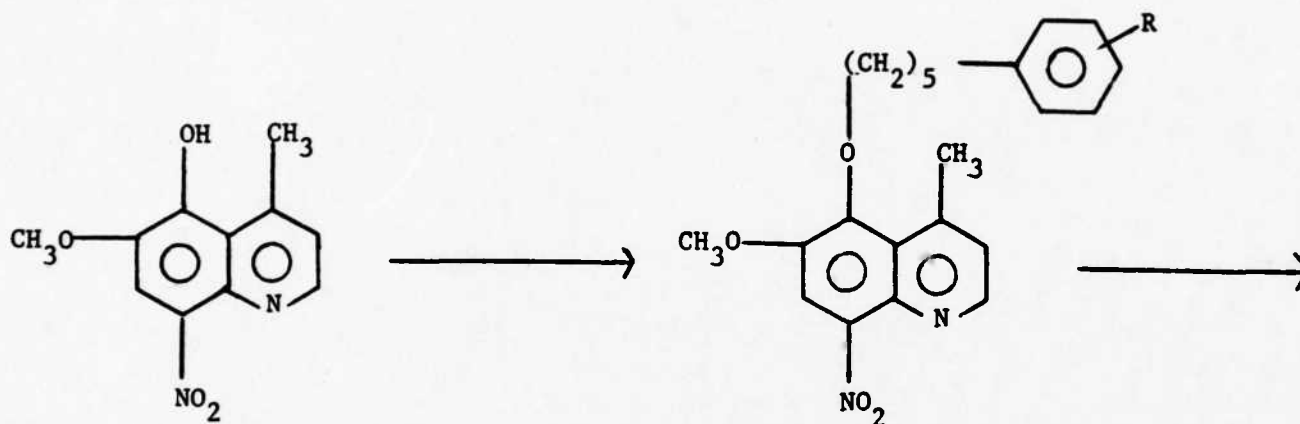
Scheme 1

- | | |
|--|--|
| <u>1.</u> R = 4-Cl | <u>13.</u> R = 4-Cl |
| <u>2.</u> R = 2-CF ₃ | <u>14.</u> R = 2-CF ₃ |
| <u>3.</u> R = 4-CF ₃ | <u>15.</u> R = 4-CF ₃ |
| <u>4.</u> R = 4-F | <u>16.</u> R = 4-F |
| <u>5.</u> R = 4-OCH ₃ | <u>17.</u> R = 4-OCH ₃ |
| <u>6.</u> R = 2-CH ₃ | <u>18.</u> R = 2-CH ₃ |
| <u>7.</u> R = 3-CH ₃ | <u>19.</u> R = 3-CH ₃ |
| <u>8.</u> R = 4-CH ₃ | <u>20.</u> R = 4-CH ₃ |
| <u>9.</u> R = 4-C ₂ H ₅ | <u>21.</u> R = 4-C ₂ H ₅ |
| <u>10.</u> R = 4-SO ₂ CH ₃ | <u>22.</u> R = 4-SO ₂ CH ₃ |
| <u>11.</u> R = 2,6-(CH ₃) ₂ | <u>23.</u> R = 2,6-(CH ₃) ₂ |
| <u>12.</u> R = 4-Cl,3-CF ₃ | <u>24.</u> R = 4-Cl,3-CF ₃ |

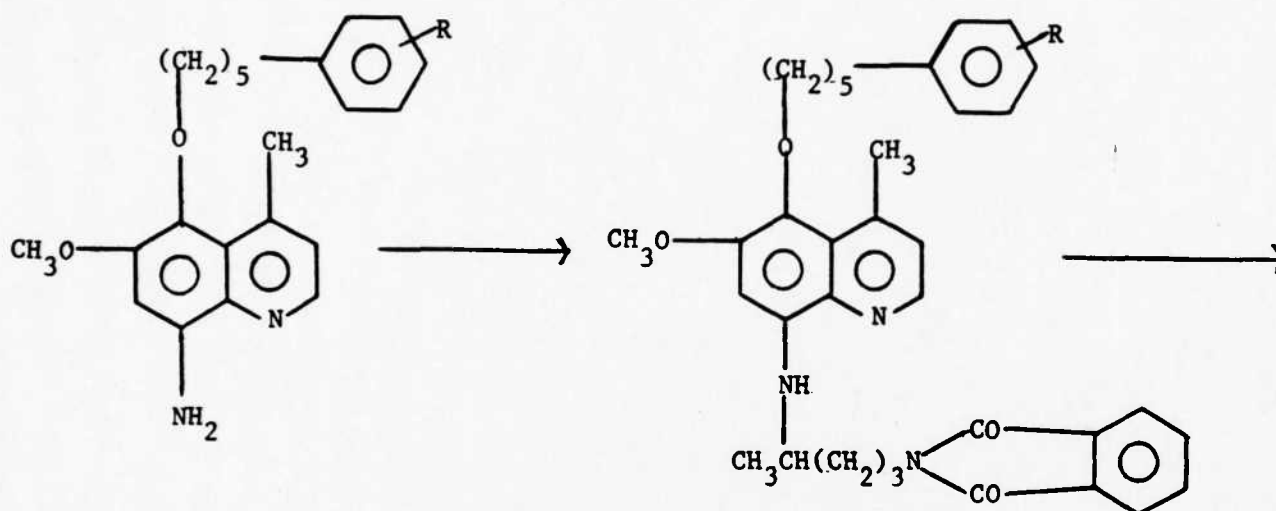
Contract No. DAMD17-88-C-8106

Scheme 1, Continued

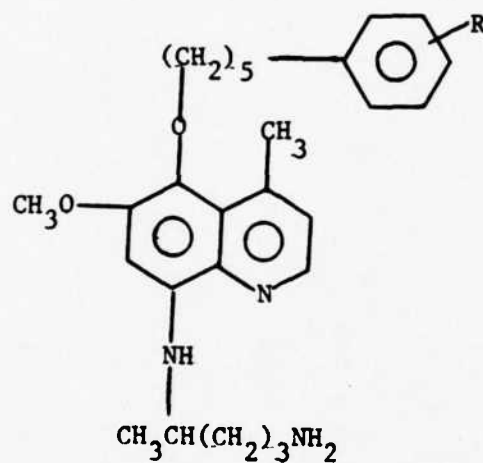
Contract No. DAMD17-88-C-8106

Scheme 1, Continued3839. R = 4-Cl40. R = 2-CF₃41. R = 4-CF₃42. R = 4-F43. R = 4-OCH₃44. R = 2-CH₃45. R = 3-CH₃46. R = 4-CH₃47. R = 4-C₂H₅48. R = 4-SO₂CH₃49. R = 2,6-(CH₃)₂50. R = 4-Cl, 3-CF₃

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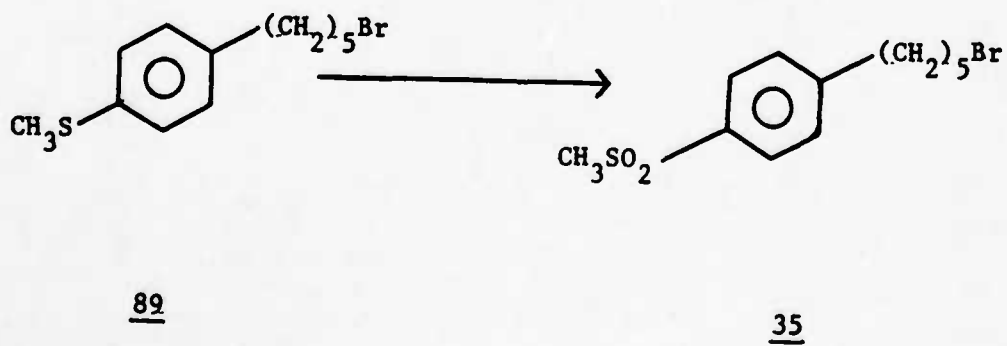
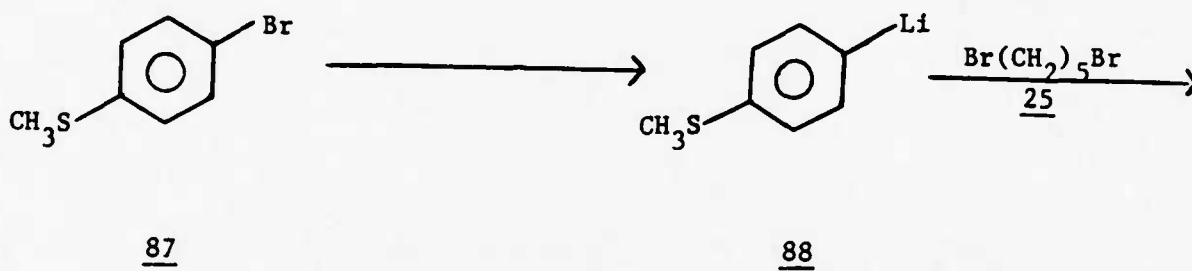
Scheme 1, Continued51. R = 4-Cl52. R = 2-CF₃53. R = 4-CF₃54. R = 4-F55. R = 4-OCH₃56. R = 2-CH₃57. R = 3-CH₃58. R = 4-CH₃59. R = 4-C₂H₅60. R = 4-SO₂CH₃61. R = 2,6-(CH₃)₂62. R = 4-Cl, 3-CF₃63. R = 4-Cl64. R = 2-CF₃65. R = 4-CF₃66. R = 4-F67. R = 4-OCH₃68. R = 2-CH₃69. R = 3-CH₃70. R = 4-CH₃71. R = 4-C₂H₅72. R = 4-SO₂CH₃73. R = 2,6-(CH₃)₂74. R = 4-Cl, 3-CF₃

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Scheme 1, Continued

- 75. $\text{R} = 4\text{-Cl}$
- 76. $\text{R} = 2\text{-CF}_3$
- 77. $\text{R} = 4\text{-CF}_3$
- 78. $\text{R} = 4\text{-F}$
- 79. $\text{R} = 4\text{-OCH}_3$
- 80. $\text{R} = 2\text{-CH}_3$
- 81. $\text{R} = 3\text{-CH}_3$
- 82. $\text{R} = 4\text{-CH}_3$
- 83. $\text{R} = 4\text{-C}_2\text{H}_5$
- 84. $\text{R} = 4\text{-SO}_2\text{CH}_3$
- 85. $\text{R} = 2,6\text{-(CH}_3)_2$
- 86. $\text{R} = 4\text{-Cl}, 3\text{-CF}_3$

Contract No. DAMD17-88-C-8106

Scheme 2

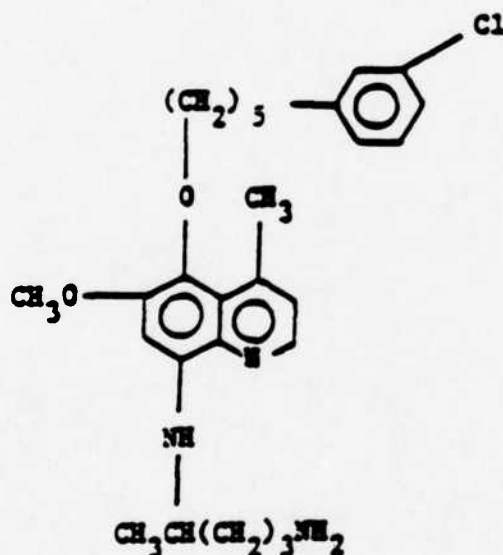
Contract No. DAMD17-88-C-8106

4-METHYL-5-[5-(3-CHLOROPHENYL)PENTOXY]PRIMAQUINE

We have received two disparate sets of blood schizonticidal data (Table XI) for the title compound (BL 50076).

TABLE XI

BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P. berghei, Mouse)

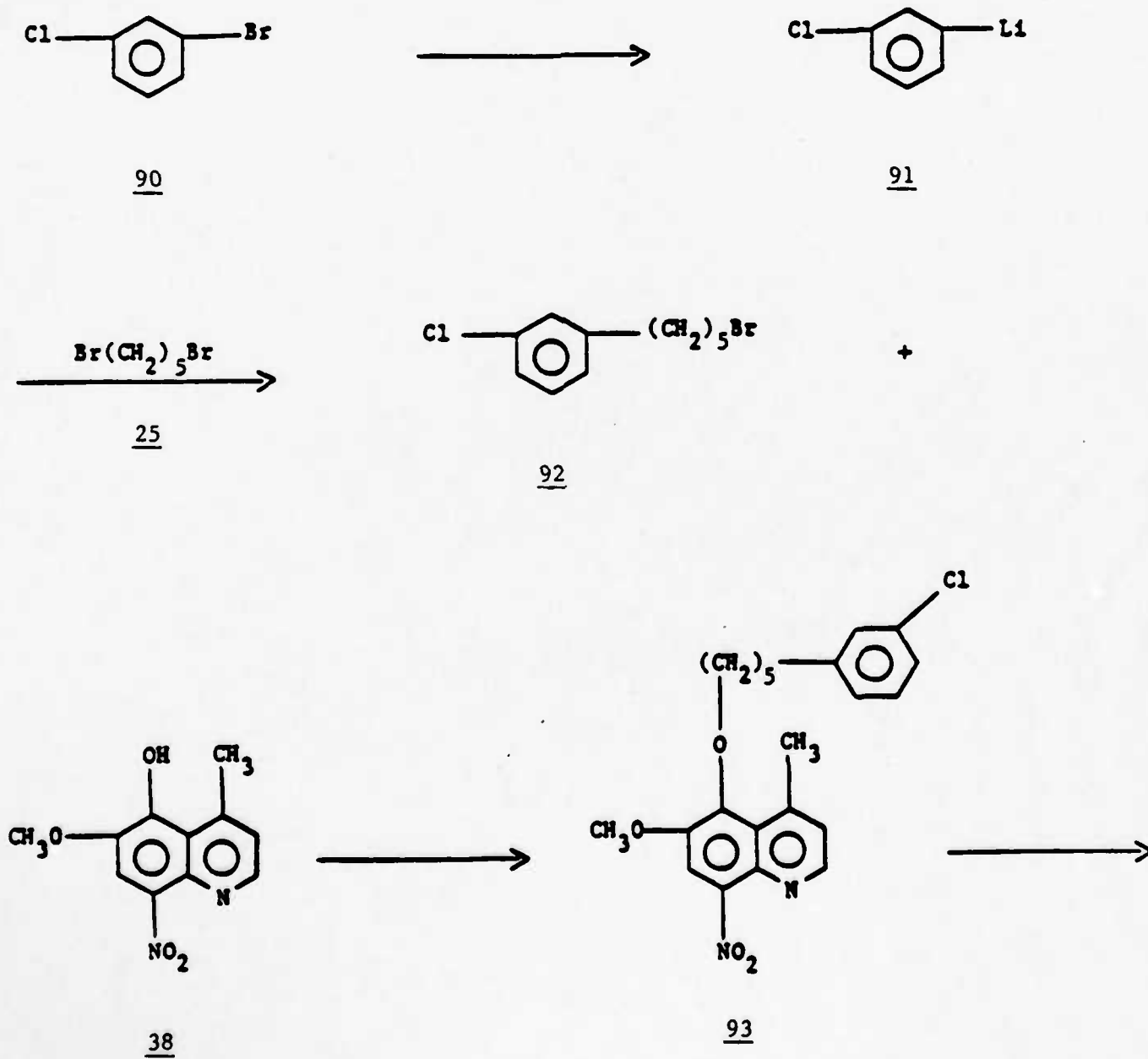


BL 50076

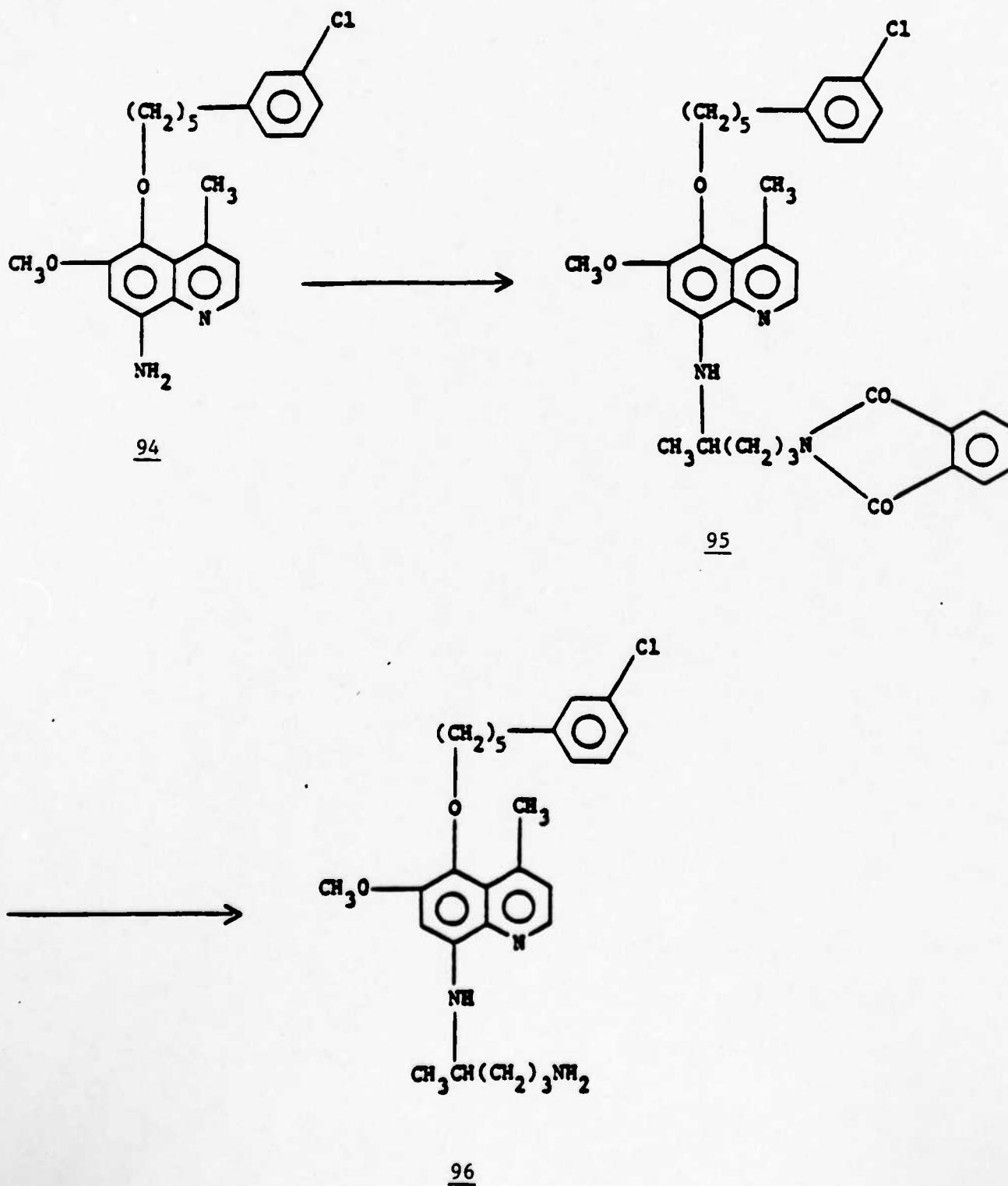
Date	GRP	TST	Cures (C), Toxic Deaths (T) or Δ MST								
			Dose, mg/kg								
			0.04	0.08	0.16	0.32	0.63	1.25	2.5	5	10 20
88019	G70	3						5.2	7.0	7.8	4C 4C
88040	G73	3	4.8	5.4	7.6	3C	5C	5C			

The data obtained on date, 88019, indicated no cures below 10 mg/kg. However, the data for date, 88040 showed multiple cures at the extraordinarily low dose, 0.32 mg/kg. In order to permit confirmatory screening, we prepared an additional quantity of the target compound following Scheme 3.

Contract No. DAMD17-88-C-8106

Scheme 3

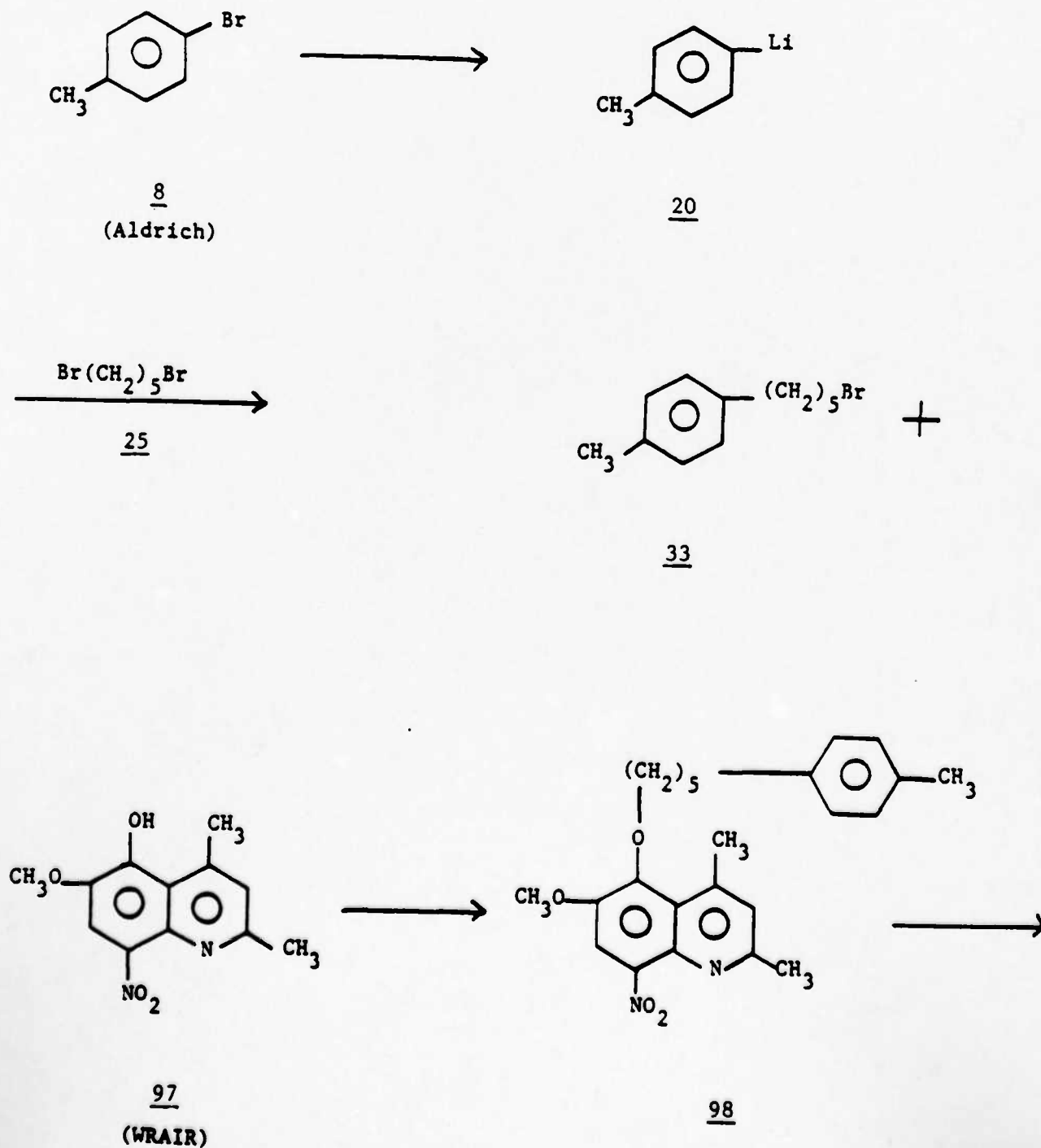
Contract No. DAMD17-88-C-8106

Scheme 3 - Continued

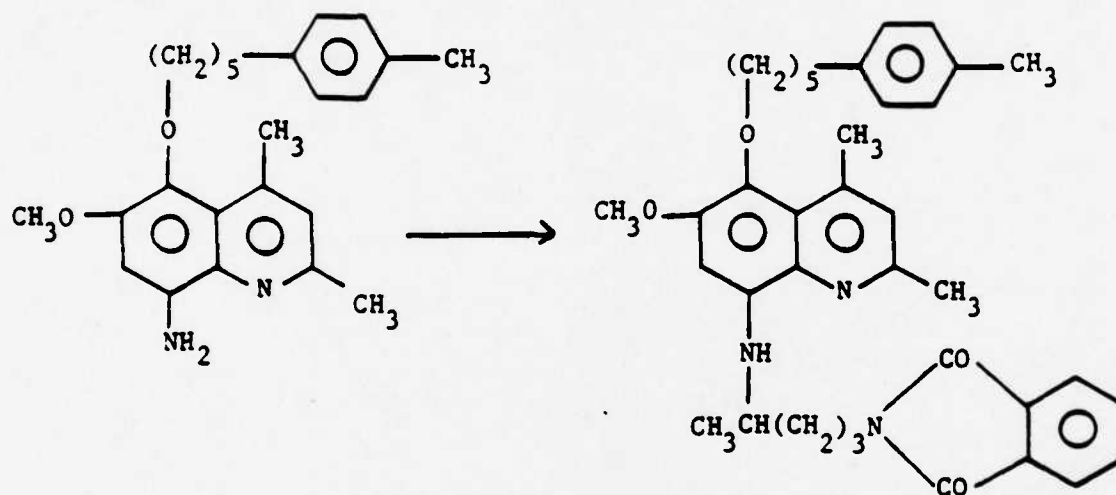
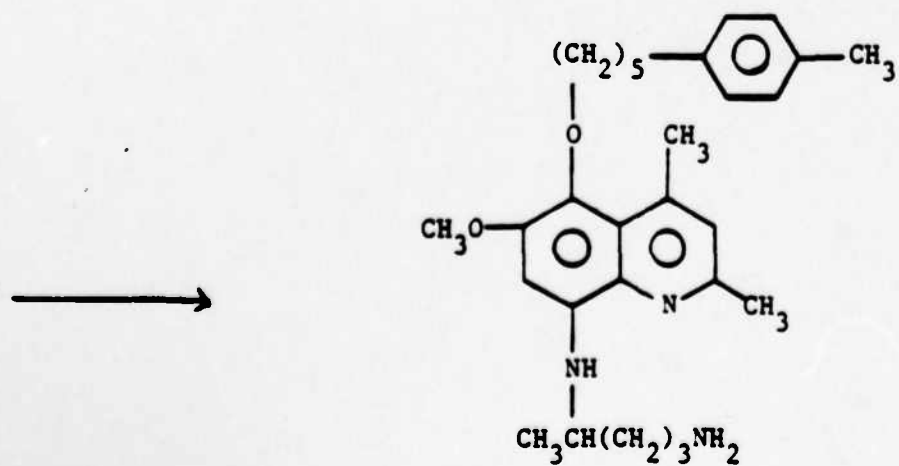
Contract No. DAMD17-88-C-8106

2,4-DIMETHYL-5-[5-(4-METHYLPHENYL)PENTOXY]PRIMAQUINE

The title compound has been synthesized as shown in Scheme 4.

Scheme 4

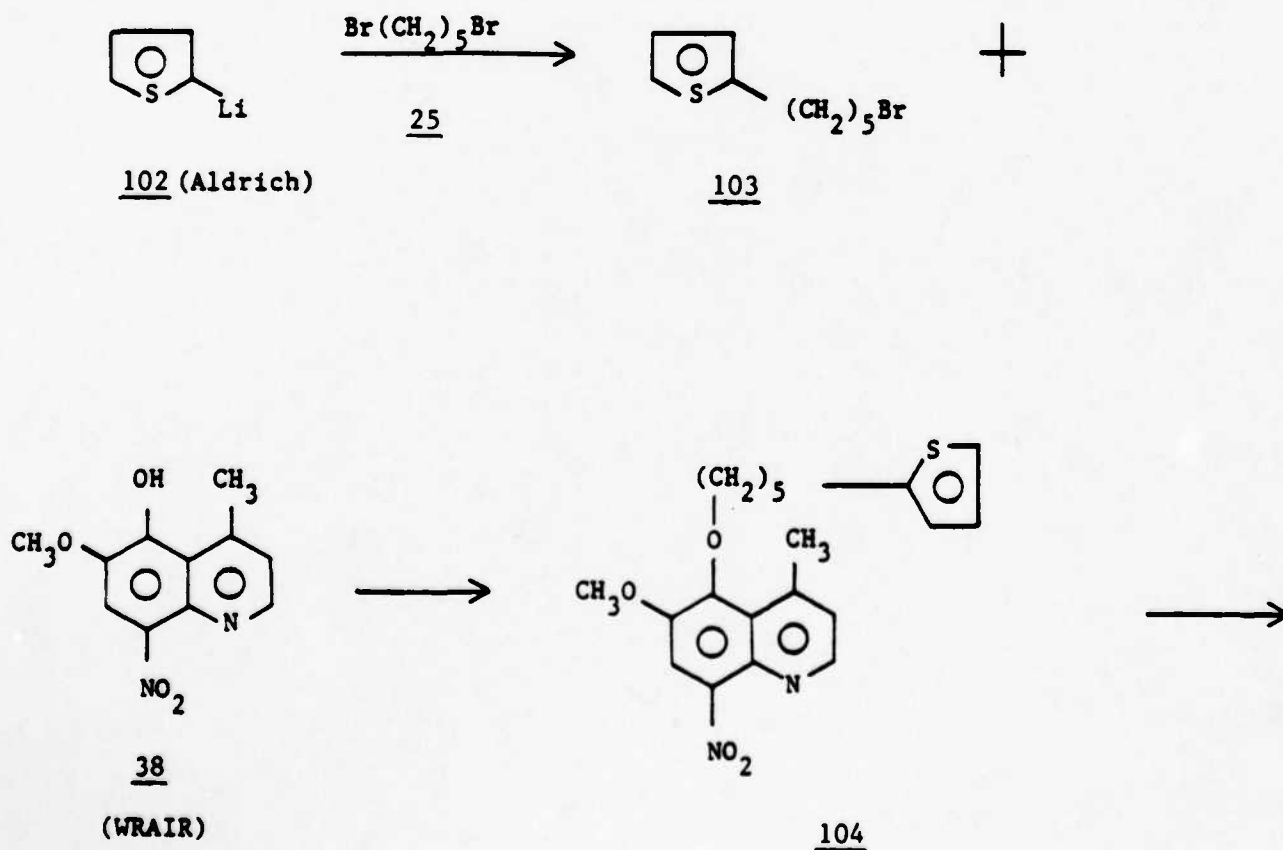
Contract No. DAMD17-88-C-8106

Scheme 4, Continued99100101

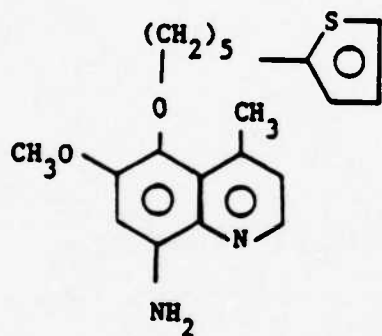
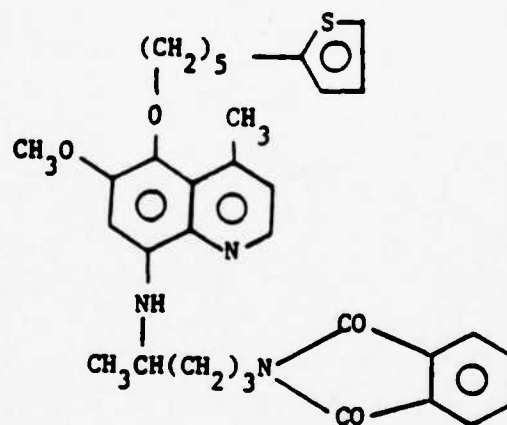
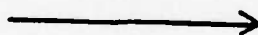
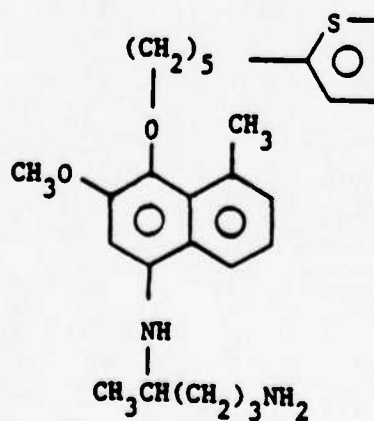
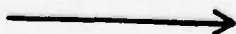
Contract No. DAMD17-88-C-8106

4-METHYL-5[5-(2-THIENYL)PENTOXY]PRIMAQUINE

The title compound was prepared as outlined in Scheme 5.

Scheme 5

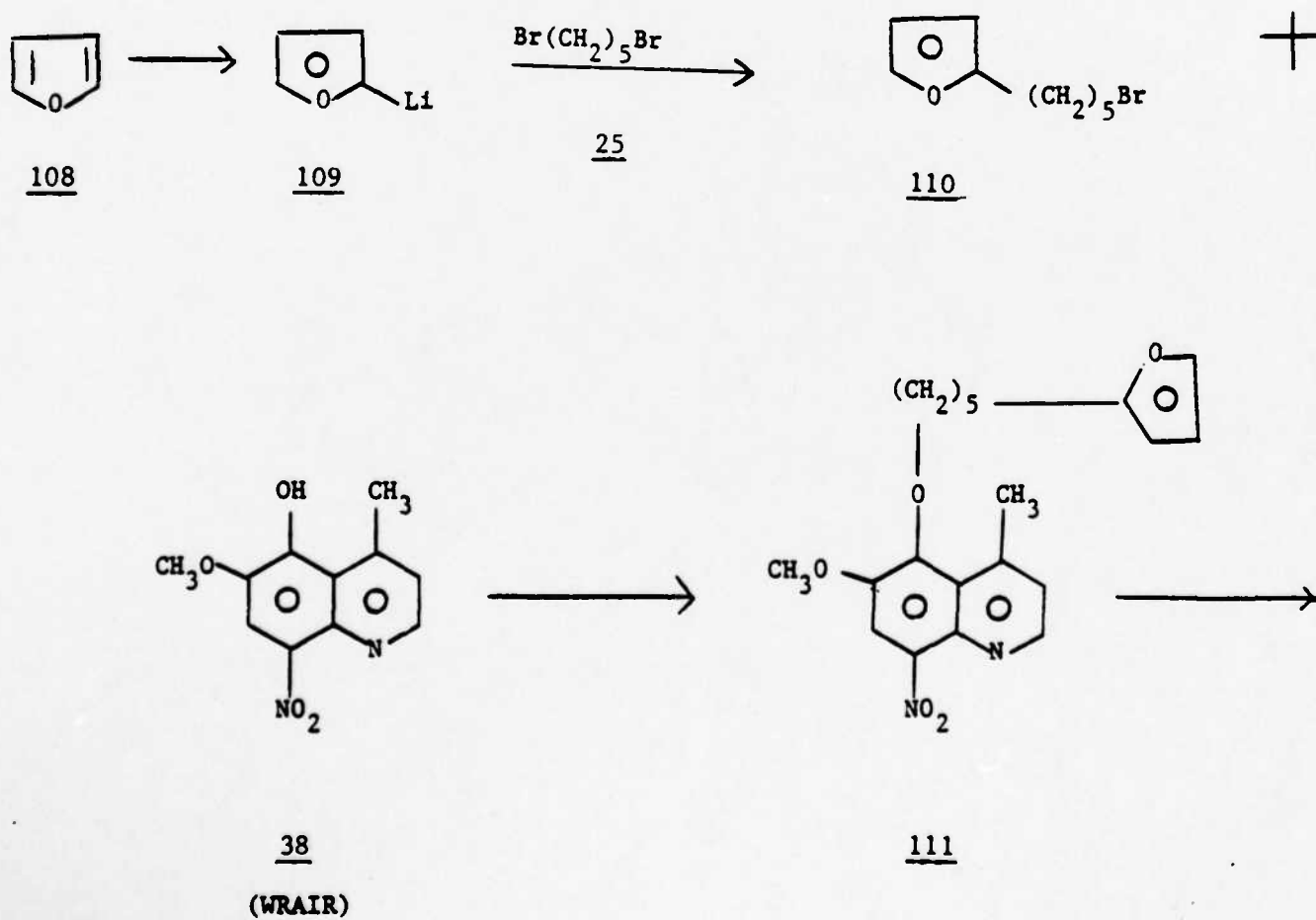
Contract No. DAMD17-88-C-8106

Scheme 5, Continued105106107

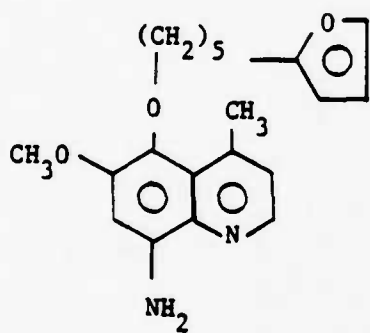
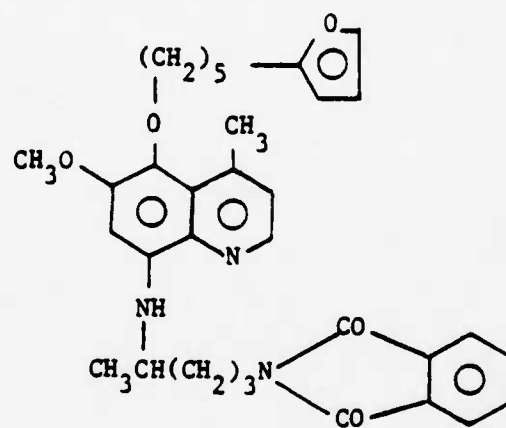
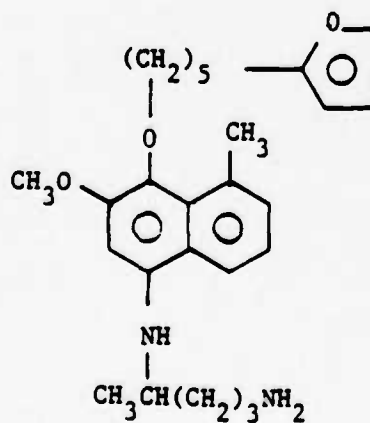
Contract No. DAMD17-88-C-8106

5-[5-(2-FURYL)PENTOXY]-4-METHYLPRIMAQUINE

The title compound was synthesized as shown in Scheme 6.

Scheme 6

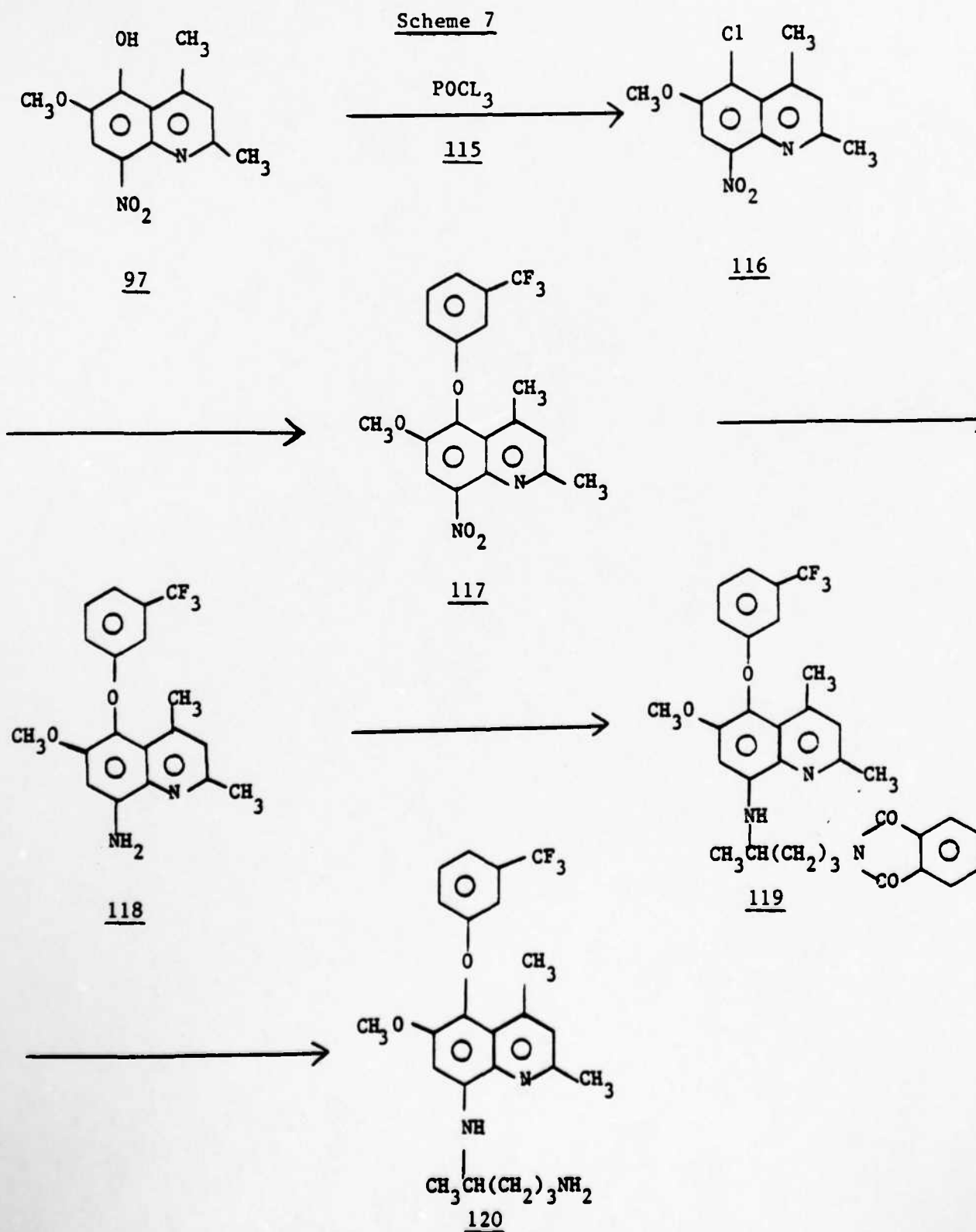
Contract No. DAMD17-88-C-8106

Scheme 6, Continued112113114

Contract No. DAMD17-88-C-8106

2,4-DIMETHYL-5-(3-TRIFLUOROMETHYLPHENOXY)PRIMAQUINE

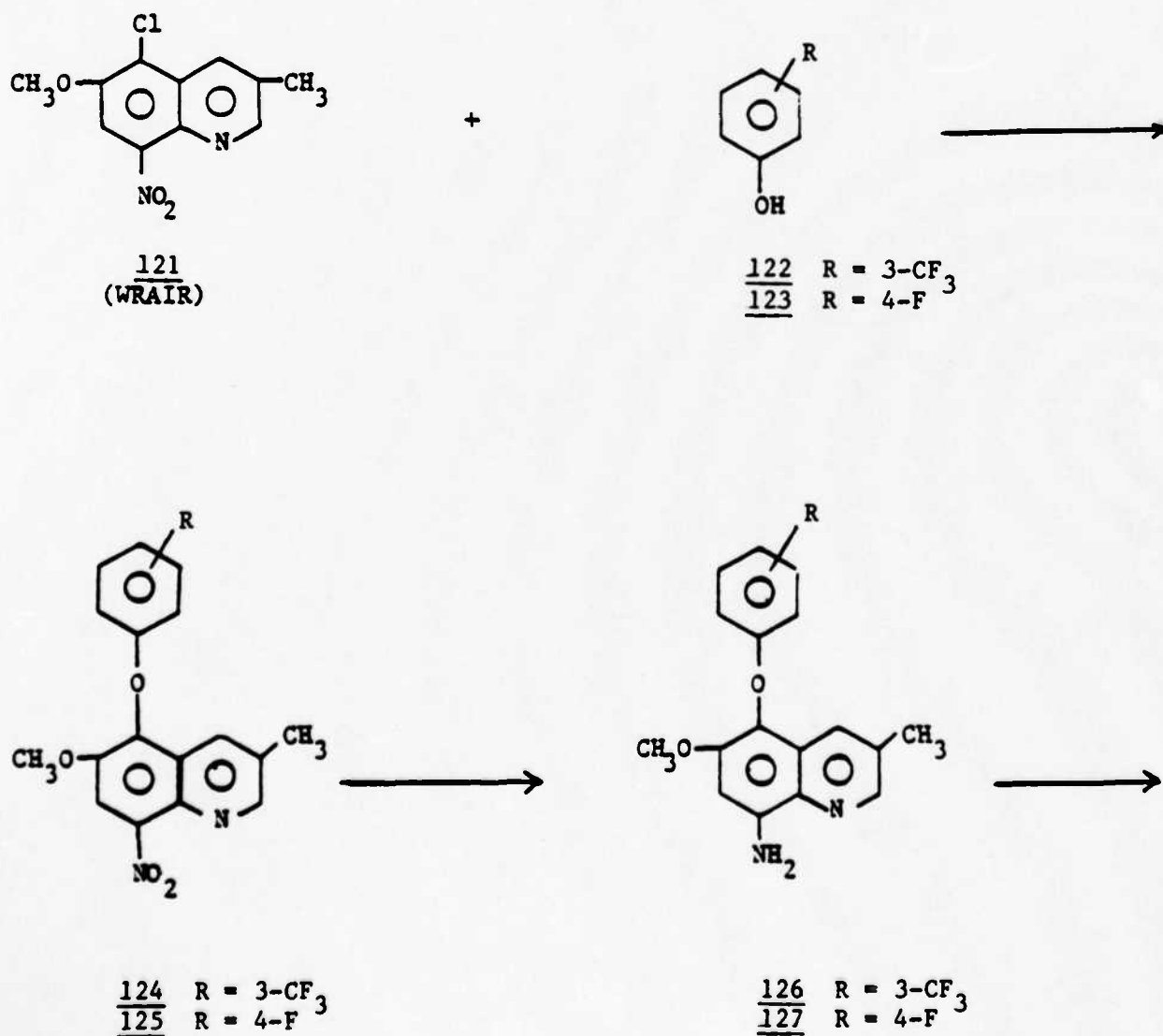
Scheme 7 outlines the synthesis of the target compound.



Contract No. DAMD17-88-C-8106

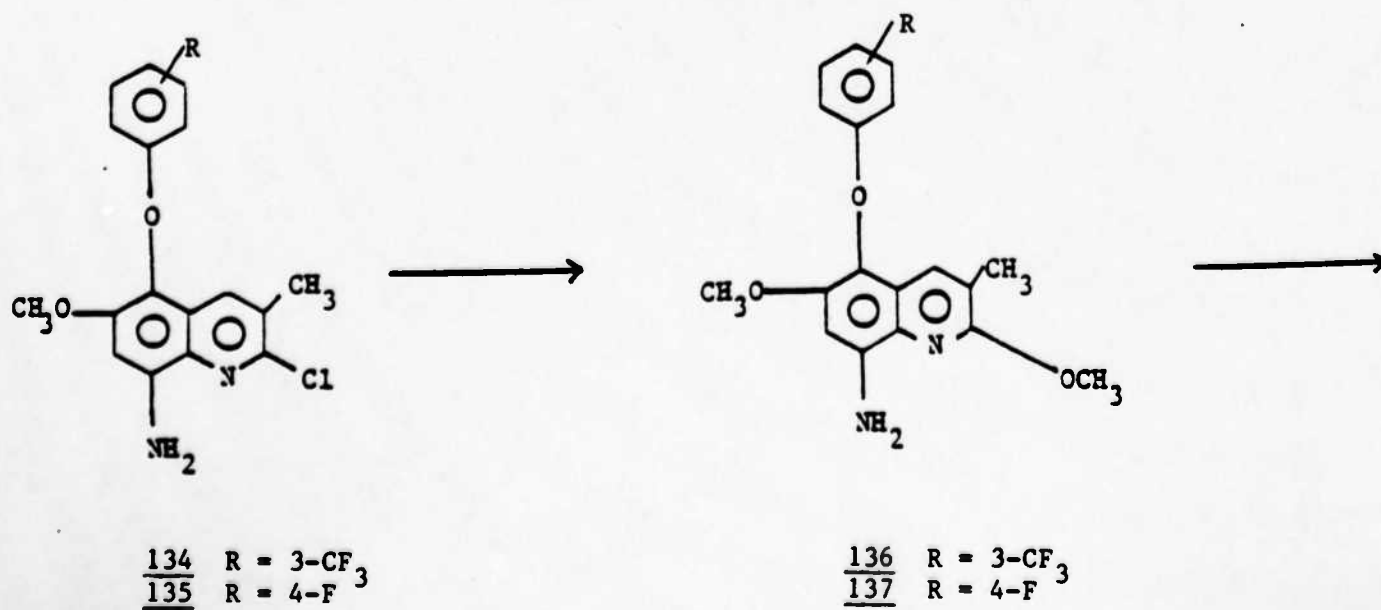
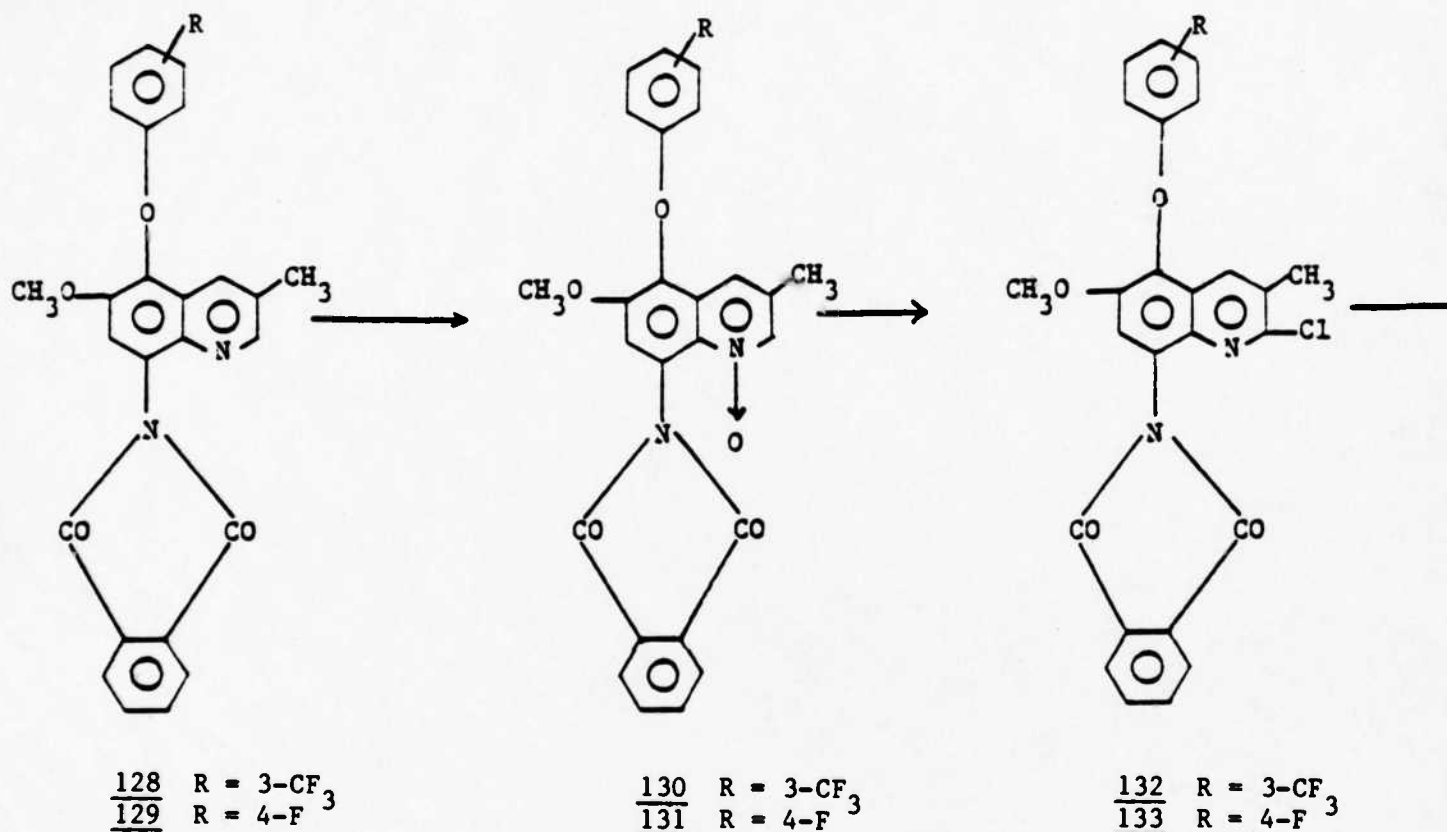
2-METHOXY-3-METHYL-5-(3-TRIFLUOROMETHYLPHENOXY)PRIMAQUINE2-METHOXY-3-METHYL-5-(4-FLUOROPHENOXY)PRIMAQUINE

The target compounds were synthesized, as shown in Scheme 8, via an adaptation of the method of LaMontagne et al⁴.

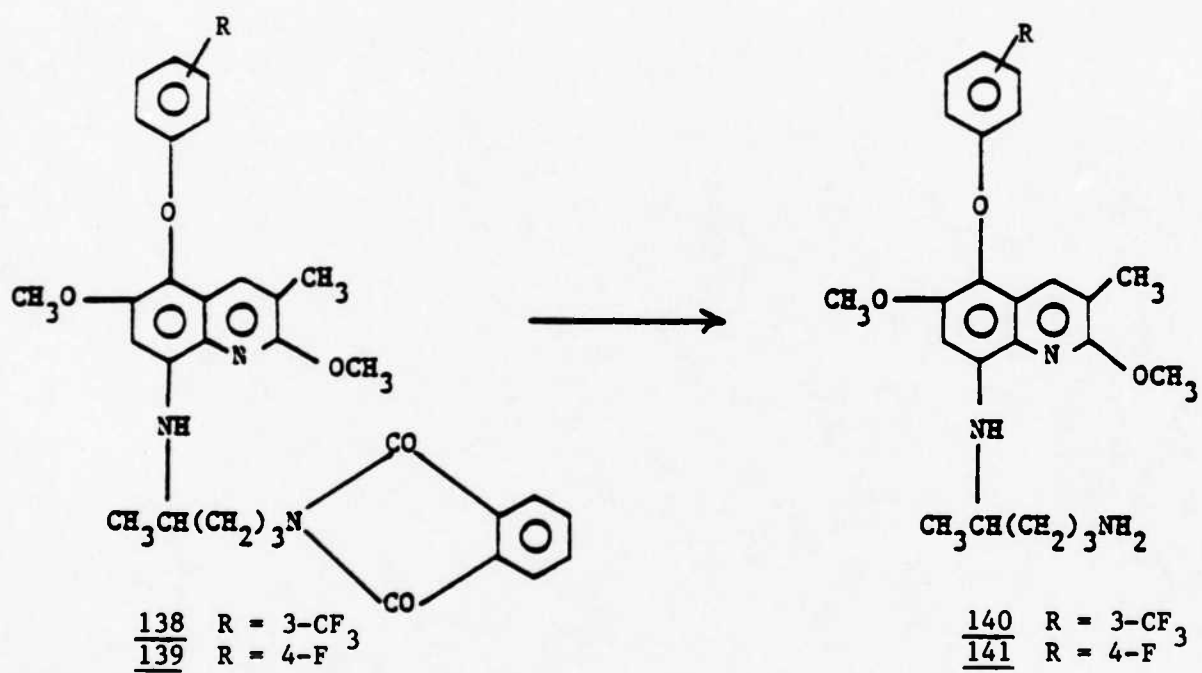
Scheme 8

Contract No. DAMD17-88-C-8106

Scheme 8, Continued



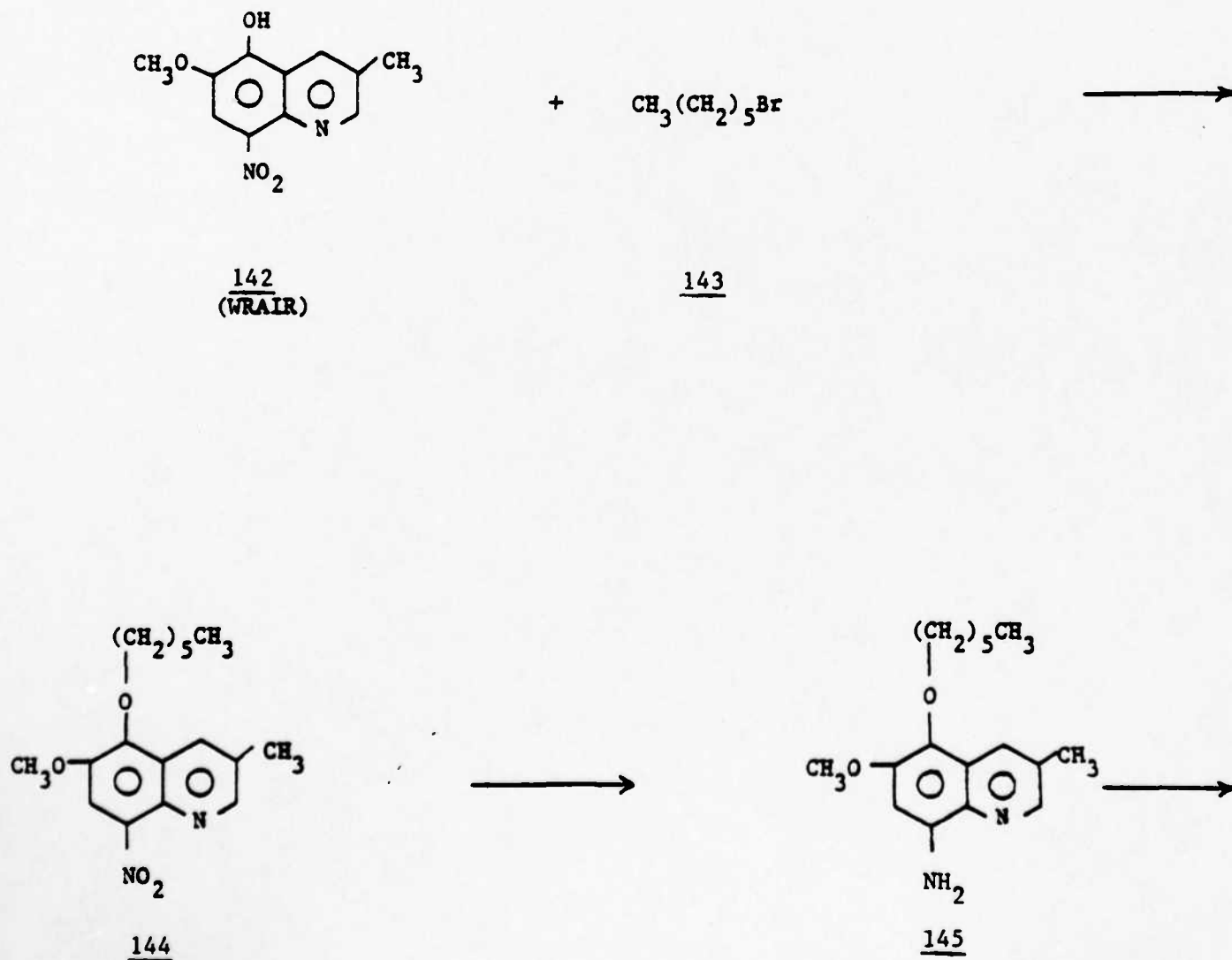
Contract No. DAMD17-88-C-8106

Scheme 8, Continued

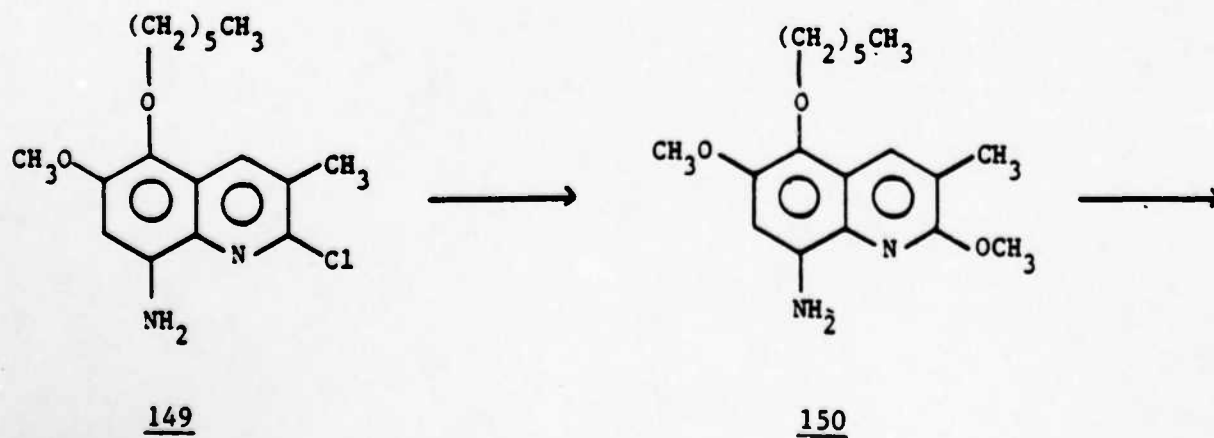
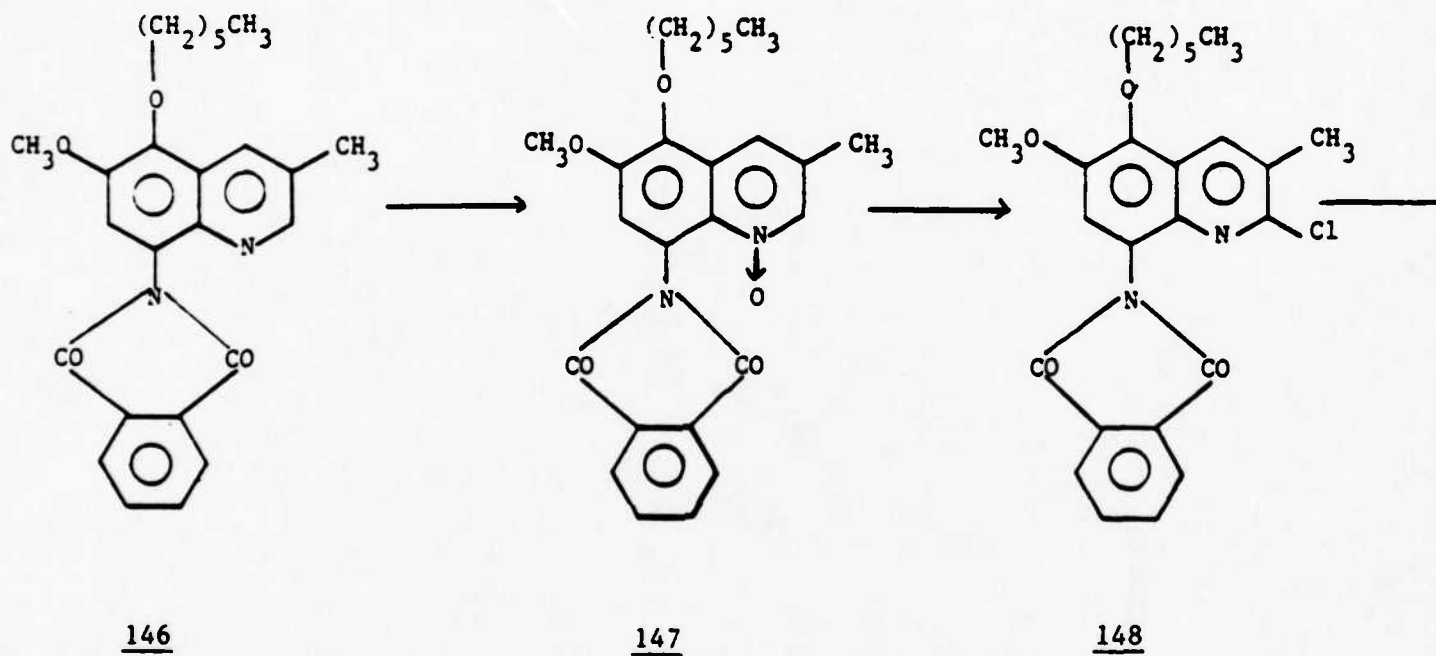
Contract No. DAMD17-88-C-8106

5-(n-HEXOXY)-2-METHOXY-3-METHYLPRIMAQUINE

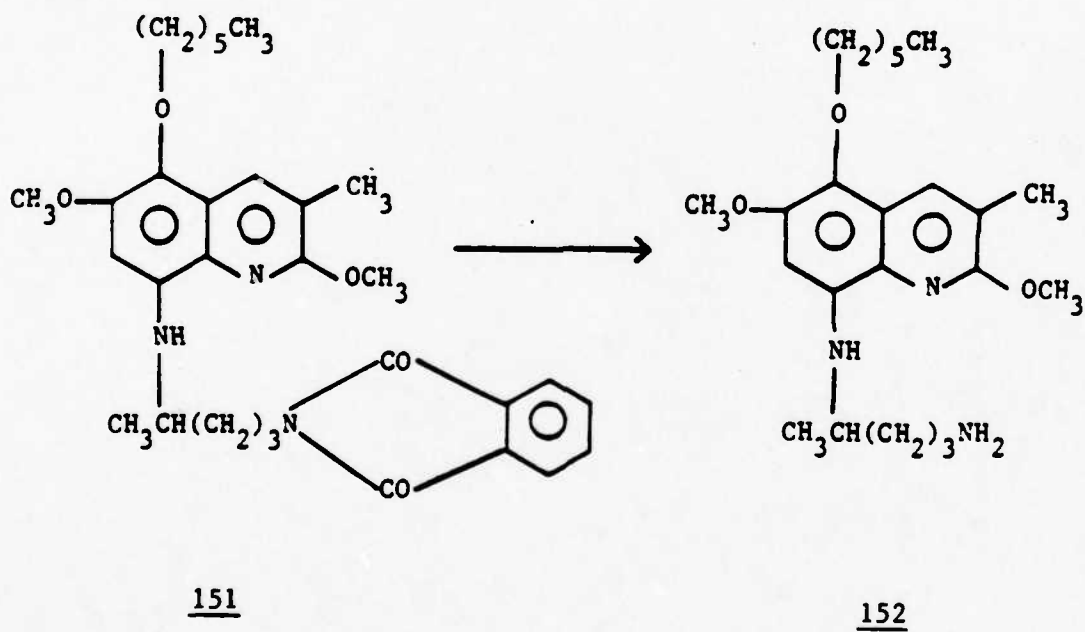
This synthesis was completed, as outlined in Scheme 9, via an adaptation of the method of LaMontagne et al⁴,

Scheme 9

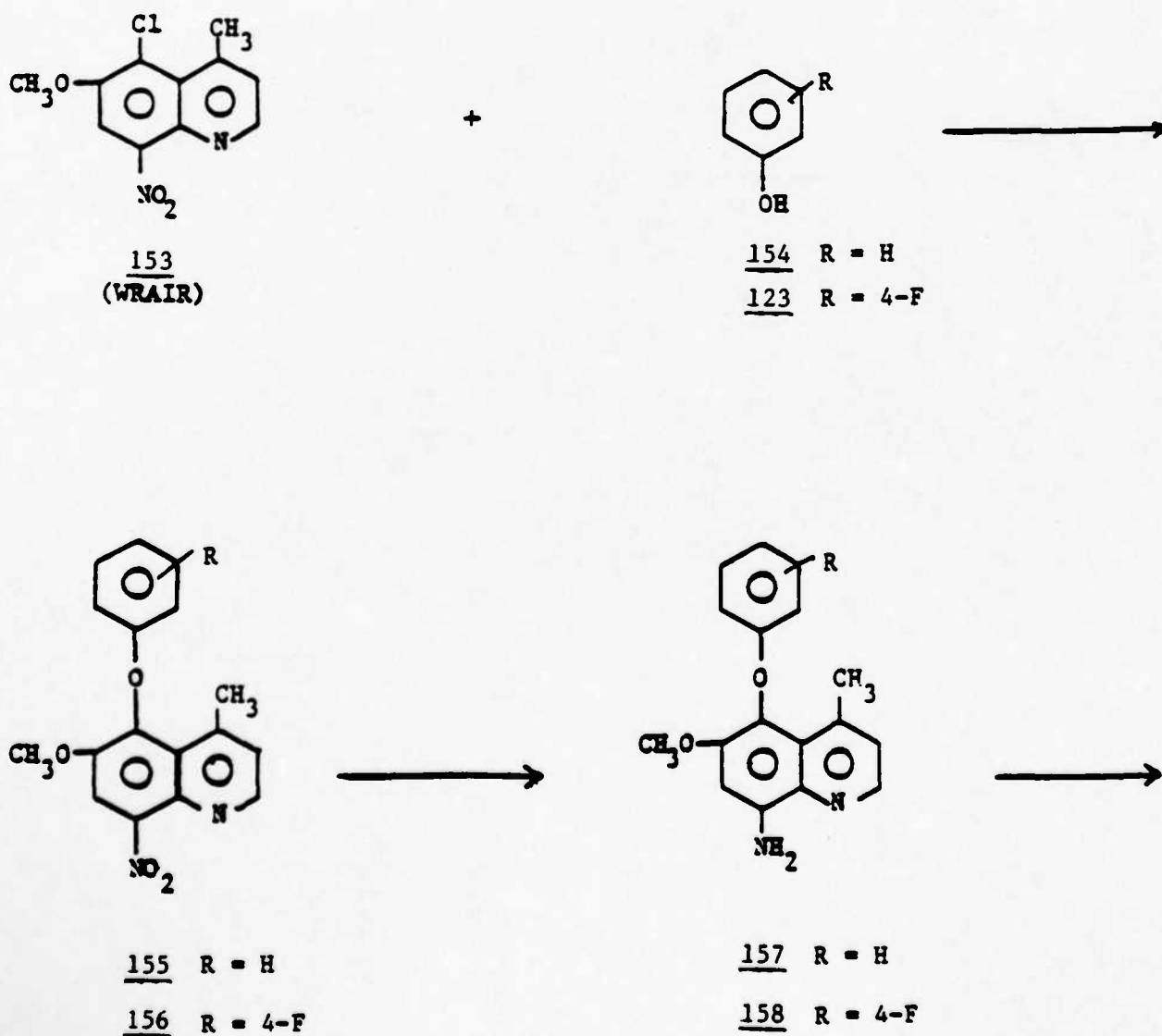
Contract No. DAMD17-88-C-8106

Scheme 9, Continued

Contract No. DAMD17-88-C-8106

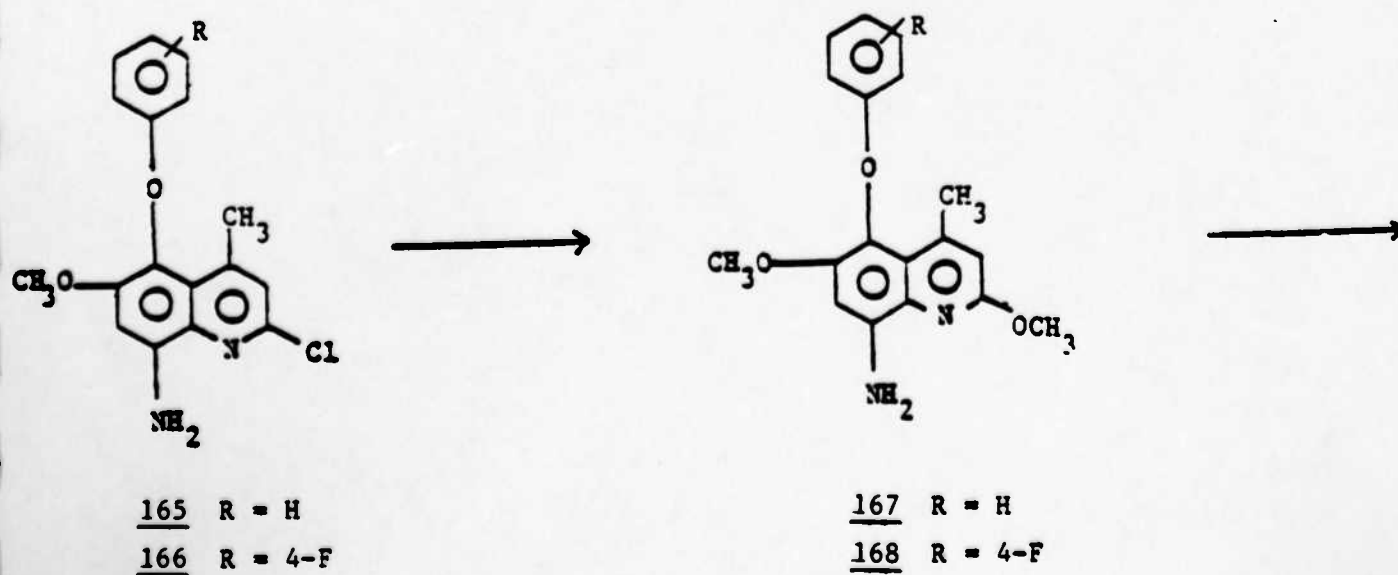
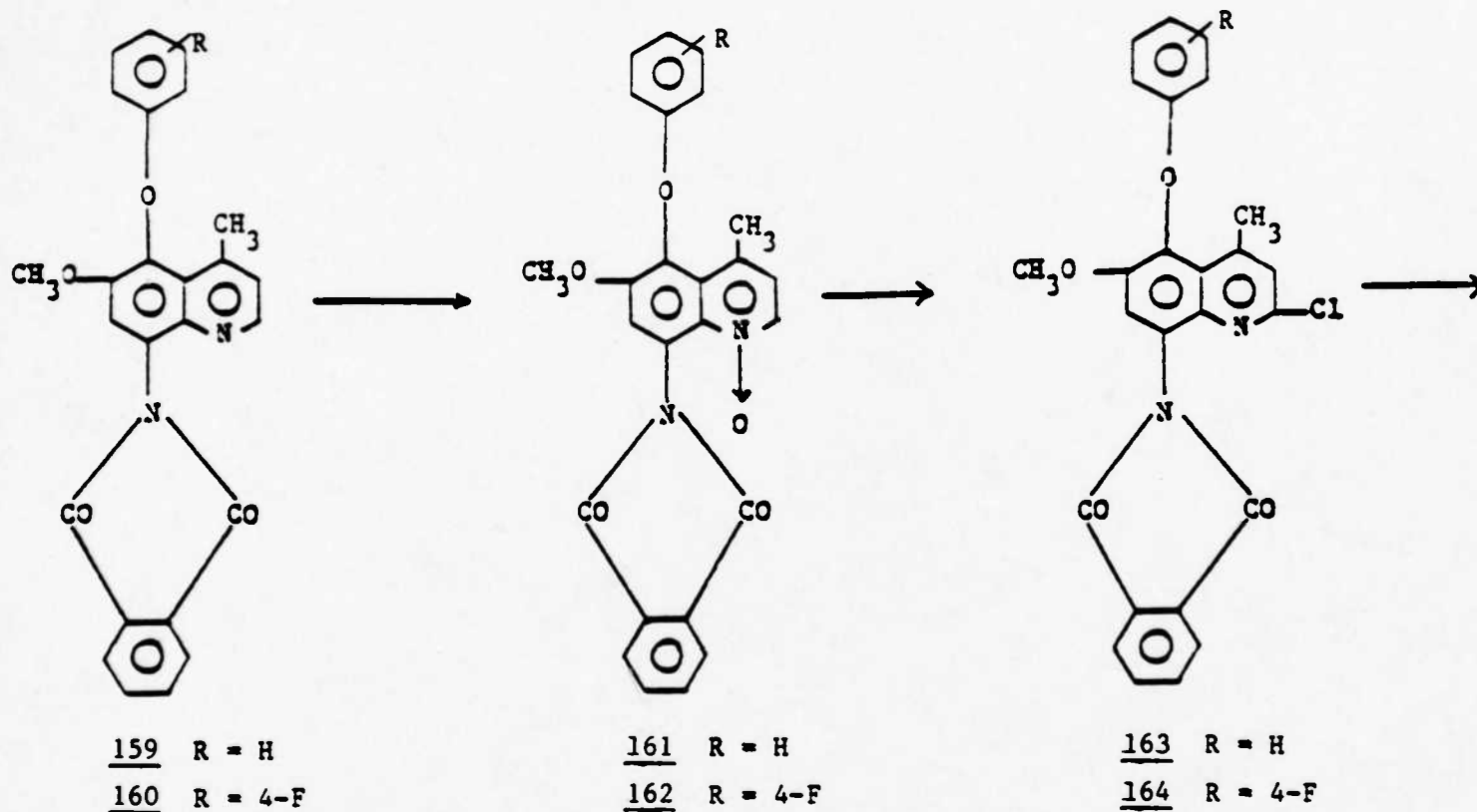
Scheme 9, Continued

Contract No. DAMD17-88-C-8106

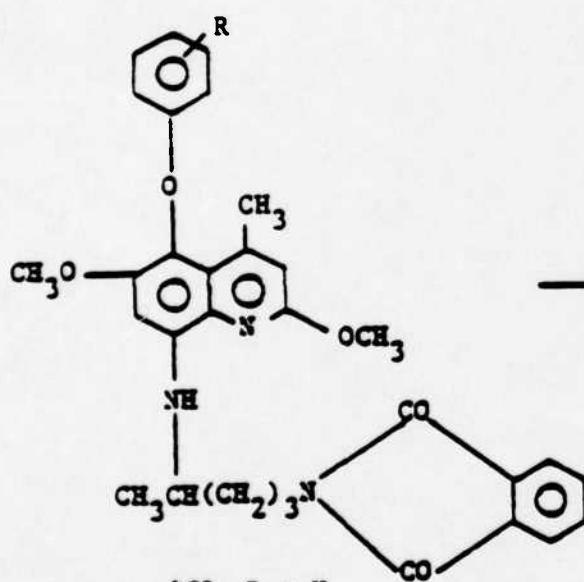
2-METHOXY-4-METHYL-5-PHENOXYPRIMAQUINE2-METHOXY-4-METHYL-5-(4-FLUOROPHENOXY)PRIMAQUINEScheme 10

Contract No. DAMD17-88-C-8106

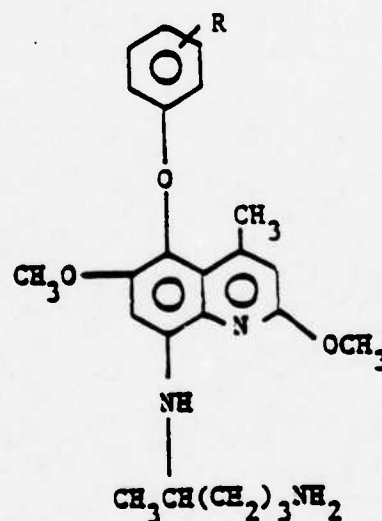
Scheme 10, Continued



Contract No. DAMD17-88-C-8106

Scheme 10, Continued

169 R = H
170 R = 4-F

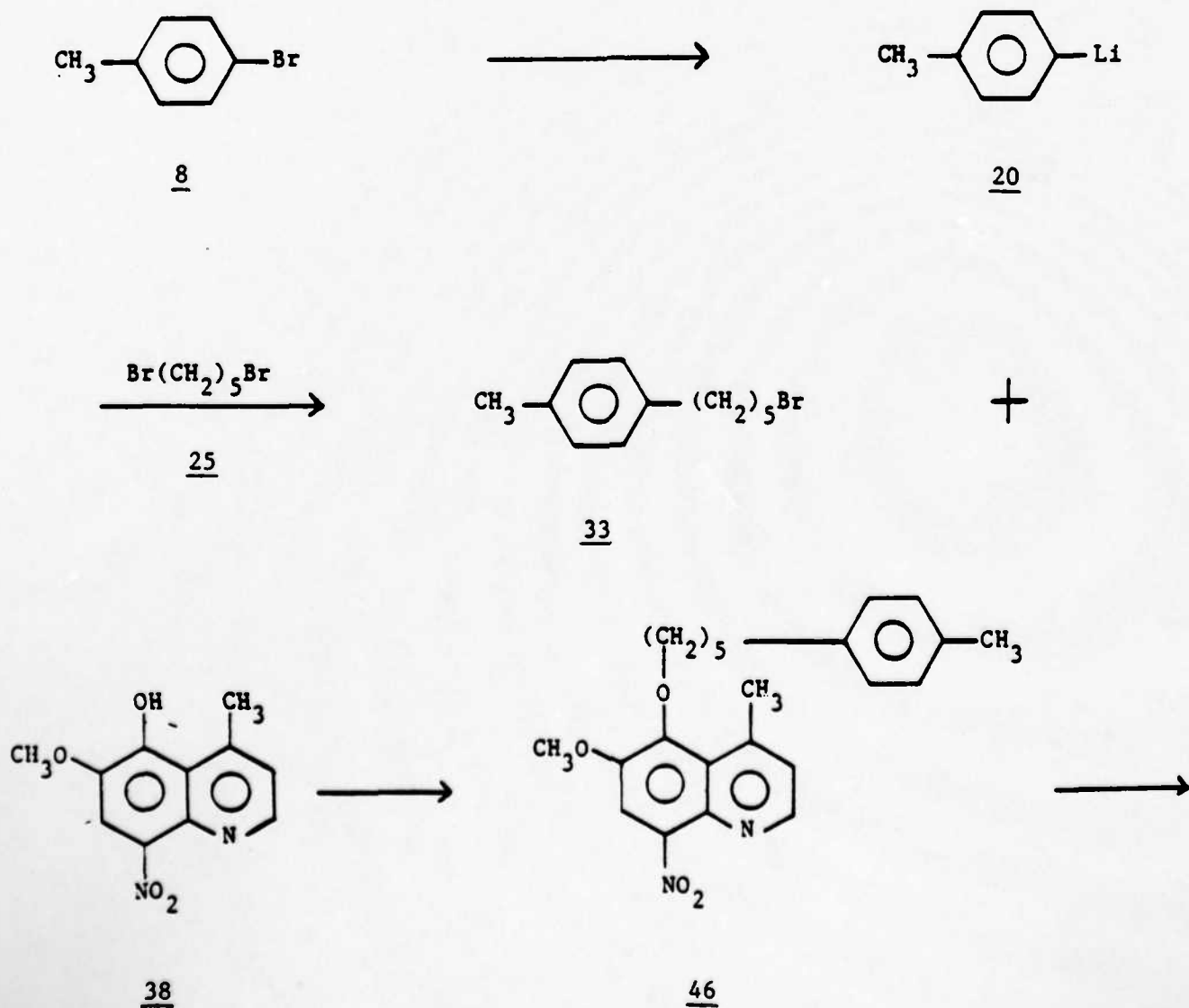


171 R = H
172 R = 4-F

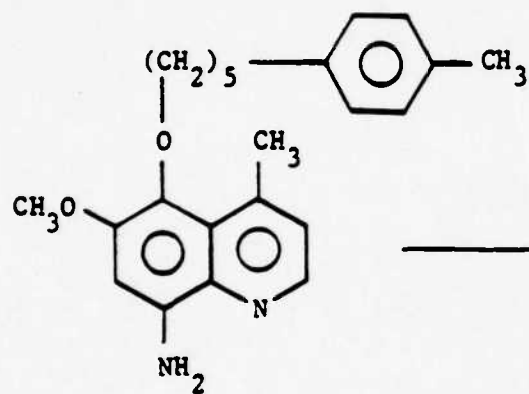
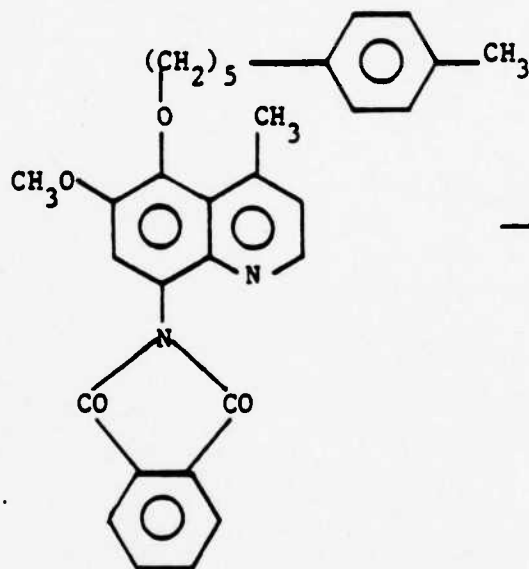
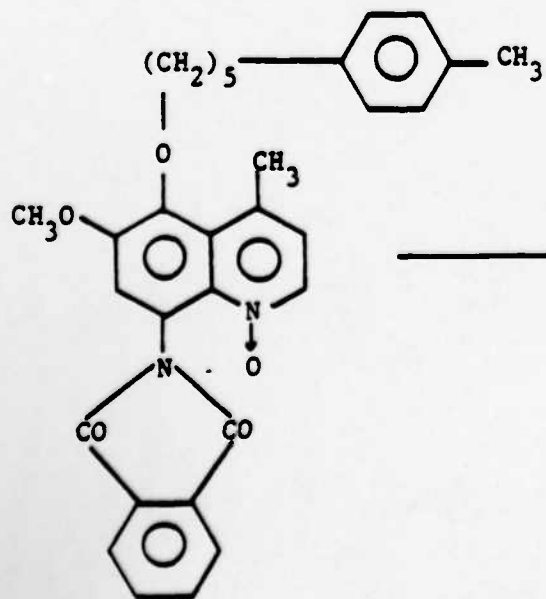
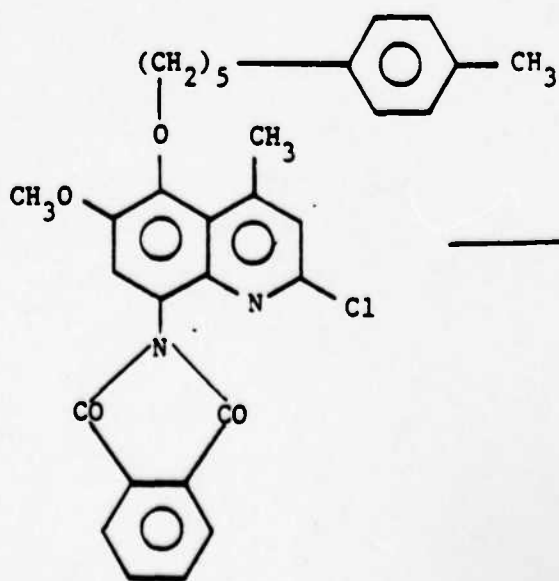
Contract No. DAMD17-88-C-8106

2-METHOXY-4-METHYL-5-[5-(4-METHYLPHENYL)PENTOXY]PRIMAQUINE

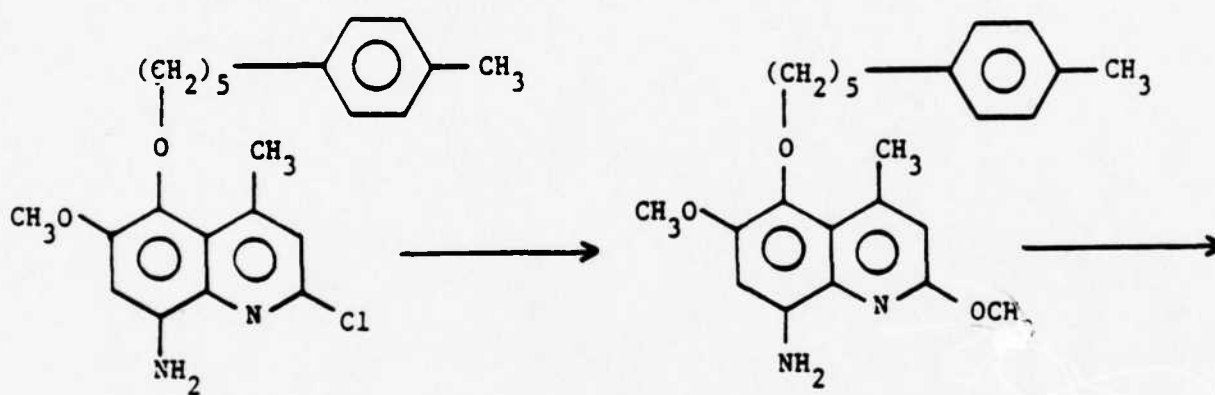
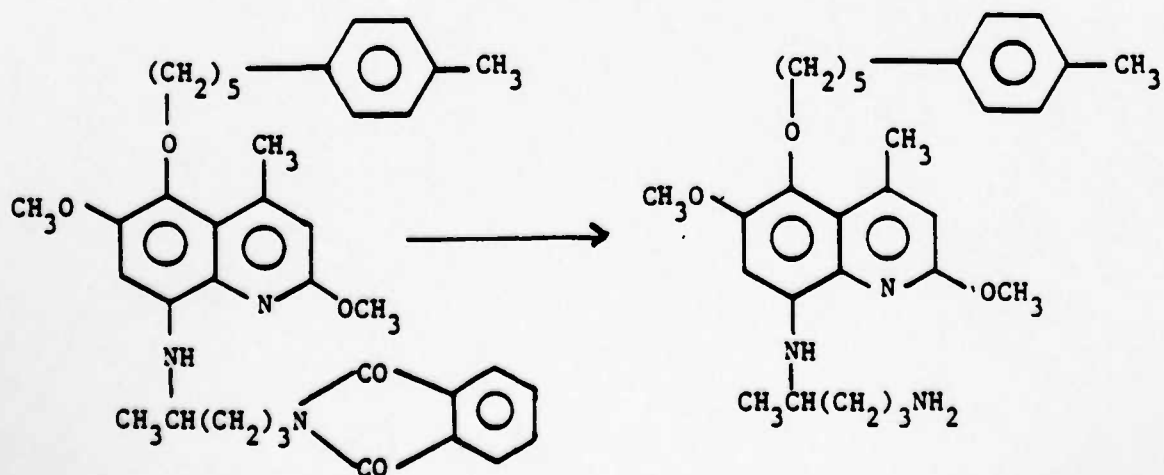
The title compound was prepared as shown in Scheme 11.

Scheme 11

Contract No. DAMD17-88-C-8106

Scheme 11, Continued58173174175

Contract No. DAMD17-88-C-8106

Scheme 11, Continued176177178179

EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Delaware. Infrared spectra were taken on a Perkin-Elmer Model 1420 Spectrophotometer.

1-Bromo-5-(4-chlorophenyl)pentane (26)

To a stirred solution of 1 (Aldrich; 39 g, 0.2 mol) in anhydrous Et_2O (300 ml), at -25°C , under N_2 , was slowly added, during 20 min, a solution of 10 M BuLi in hexane (Aldrich, 20 ml, 0.2 mol) diluted with an additional 10 ml of hexane. The yellow emulsion was stirred at -15°C for 0.5 h, cooled to -35°C , treated with 1,5-dibromopentane (46 g, 0.2 mol) during 10 min and then with THF (200 ml) during 30 min. The resulting white suspension was stirred at -30°C to -15°C for 1 h, allowed to warm to room temperature, slowly poured over dry-ice (200 g) and the yellow solution was added to H_2O (500 ml). The aqueous layer was separated and extracted with Et_2O (4 x 150 ml). The organic layer and the ethereal extracts were combined, washed with 10% Na_2CO_3 and saturated brine, dried (Na_2SO_4) and concentrated to a yellow oil. Fractional distillation gave 22.8 g (44%) of 26, bp $115-116^\circ\text{C}/0.5$ mm; n_D^{23} 1.5430. This material was used without further purification.

5-[5-(4-Chlorophenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (39)

To a stirred mixture of 38 (WRAIR, 11.96 g, 0.05 mol), 26 (13.37 g, 0.05 mol) and HMPA (50 ml), at $115-120^\circ\text{C}$, was added dropwise, during 90 min, a solution of propylene oxide (24 ml) and Et_3N (8 ml). The mixture was heated at $115-120^\circ\text{C}$ for 6h, allowed to cool and extracted with a 1:1 mixture (400 ml) of pet ether ($20-40^\circ\text{C}$) and Et_2O . The extract was washed with 10% NaOH (3 x 75 ml), H_2O (2 x 75 ml), dried (Na_2SO_4) and treated with carbon (Darco G-60). Solvent concentration gave a yellow solid which was filtered, washed with pet ether ($20-40^\circ\text{C}$) and air-dried to give 8.10 g (38%) of 39 which was used without further purification. Crystallization of an aliquot from hexane gave an analytical sample as yellow crystals, mp $77-78^\circ\text{C}$.

Anal. Calcd. for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_4$: C, 63.69; H, 5.59; N, 6.75.

Found: C, 63.74; H, 5.83; N, 6.68

8-Amino-5-[5-(4-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline (51)

A stirred mixture of 39 (6.46 g, 0.016 mol), Fe-filings (8 g), Bu_2O (30 ml), H_2O (100 ml) and HOAc (1.5 ml) was heated at 105-110°C for 3h, allowed to cool and filtered. The filtrate and the residue were extracted with Et_2O (300 ml). The combined extracts were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4), treated with carbon (Darco) and concentrated to a small volume which on cooling and scratching gave a yellow solid. Filtration, washing with hexane and air-drying gave 3.71 g (62%) of 51 as yellow crystals, m.p. 69-71°C. The mother liquor was diluted with hexane (50 ml) and cooled overnight to give another 1.04 g (17%) of 51. The combined material was used without further purification.

5-[5-(4-Chlorophenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (63)

A stirred mixture of 51 (3.27 g, 0.009 mol) and 4-bromo-1-phthalimido-pentane (BPP) (5.23 g, 0.018 mol) was heated at 120-125°C while Et_3N (3 ml) was slowly added during 30 min. After 3.5h at 120-125°C, more BPP (3.42 g, 0.012 mol) and Et_3N (2 ml during 30 min.) were added and heating was continued for 5h. On cooling, the mixture was exhaustively extracted with Et_2O (300 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a dark oil. The oil was pumped at 1.8 mm Hg for 2h, applied to a silica gel column and eluted with CHCl_3 . Concentration of the product eluates gave 4.53 g (89%) of 63 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (75)

A stirred solution of 63 (4.53 g, 0.0076 mol), CHCl_3 (25 ml), EtOH (50 ml) and 95% NH_2NH_2 (3 ml) was heated under reflux for 2h, allowed to cool and filtered. The white residue was washed with EtOH and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (100 ml), and the solution was washed with 20% KOH solution (3 x 50 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a viscous dark yellow oil (2.88 g, 81%). The oil was dissolved in CH_3CN (25 ml) and slowly treated with a hot solution of fumaric acid (0.71 g) in

$\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 V/V, 35 ml). The resulting yellow solid was separated by decantation, washed with CH_3CN (3 x 20 ml), recrystallized from CH_3CN and vacuum dried (1.2 mm Hg, 20°C, 2h) to give 2.60 g (59%) of 75 as a yellow solid, mp 152-153°C (decomp.).

Anal. Calcd. for $\text{C}_{31}\text{H}_{40}\text{ClN}_3\text{O}_6$: C, 63.52; H, 6.88; N, 7.17

Found: C, 63.63; H, 6.84; N, 7.13

1-Bromo-5-(2-trifluoromethylphenyl)pentane (27)

To a stirred mixture of 2 (Aldrich; 22.5 g, 0.1 mol), THF (140 ml) and hexane (60 ml), under N_2 , at an internal temperature of -76°C, was slowly added (25 minutes), 40 ml (0.1 mol) of a 2.5 M solution of BuLi in hexane (Aldrich); the internal temperature remained below -70°C during addition. The dark brown mixture was stirred at -75°C for 30 minutes and treated with 1,5-dibromopentane (23.0 g, 0.1 mol) at a rate which kept the internal temperature below -70°C. The mixture was allowed to rise to room temperature during 1 h, stirred for an additional hour, cooled to 0°C and slowly added to water-ice (400 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organic solutions were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and evaporated to a black oil. Fractional distillation gave 13.24g (45%) of 27 as a colorless oil, bp 90-92°C/0.9 mm; n_D^{25} 1.4855.

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{BrF}_3$: C, 48.83; H, 4.78.

Found: C, 48.91; H, 4.83

6-Methoxy-4-methyl-8-nitro-5-[5-(2-trifluoromethylphenyl)pentoxy]quinoline (40)

To a stirred mixture of 38 (WRAIR)(9.5 g, 0.041 mol), 27 (12.0 g, 0.041 mol) and HMPA (30 ml), at 110-115°C, was added dropwise, during 75 min, a solution of Et_3N (5 ml) and propylene oxide (20 ml). Heating was continued for 6 h at 125-130°C. The mixture was allowed to cool and exhaustively extracted with 400 ml of a 1:1 solution of pet ether (35-60°C) and Et_2O . The combined extracts were washed with 10% NaOH (3 x 100 ml), H_2O (3 x 100 ml), dried (Na_2SO_4), treated with carbon (Darco) and concentrated to a black oil. The oil was pumped for 2 h at room temperature and 0.5 mm and triturated with hexane (15 ml) until solidification occurred. The solid was

filtered, washed with hexane (30 ml) and air-dried to give 6.5 g (36%) of 40 as a yellow solid, mp 56-57°C, which was used without further purification. An aliquot was crystallized twice from hexane to give the analytical sample, mp 60-61°C.

Anal. Calcd. for $C_{23}H_{23}F_3N_2O_4$: C, 61.60; H, 5.17; N, 6.25.

Found: C, 61.86; H, 5.38; N, 6.45.

8-Amino-6-methoxy-4-methyl-5-[5-(2-trifluoromethylphenyl)pentoxylquinoline (52)

A stirred mixture of 40 (6.0 g, 0.0134 mol), Fe - filings (7.5 g), H_2O (100 ml), AcOH (1.5 ml) and Bu_2O (15 ml) was heated at 95-100°C for 2 h, allowed to cool and exhaustively extracted with Et_2O (total, 400 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4), treated with carbon (Darco) and evaporated to a dark yellow oil. After being pumped for 4 h at 0.5 mm, the oil was triturated with hexane (10 ml) at 0°C until a yellow solid appeared; yield 4.28 g (76%), mp 58-59°C. Recrystallization of an aliquot from hexane (2X) gave the analytical sample as yellow crystals, mp 59-60°C.

Anal. Calcd. for $C_{23}H_{25}F_3N_2O_2$: C, 66.01; H, 6.02; N, 6.70.

Found: C, 66.19; H, 6.09; N, 6.46.

6-Methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-[5-(2-trifluoromethylphenyl)pentoxylquinoline (64)

A stirred mixture of 52 (4.0 g, 0.0096 mol) and 4-bromo-1-phthalimido-pentane (BPP) (5.66g, 0.019 mol) was heated at 110-115°C while Et_3N (2.5 ml) was slowly added during 45 min. After 2 h at 110-115°C, more BPP (3.3 g) and Et_3N (0.75 ml during 10 min) were added. Heating was continued for 2 h and additional BPP (1.9 g) was introduced. After 2 h at 120-125°C, final quantities of BPP (1.4g) and Et_3N (0.5 ml) were added and the mixture was heated at 120-125°C for 2 h. On cooling, the mixture was applied to a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave 4.86 g (80%) of 64 as a dark yellow oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(2-trifluoromethylphenyl)pentoxy]quinoline Fumarate (76)

A stirred solution of 64 (4.86 g, 0.0077 mol), CHCl_3 (50 ml), EtOH (100 ml) and 95% NH_2NH_2 (9 ml) was heated under reflux for 3 h, allowed to cool, concentrated and extracted with Et_2O . The extract was washed with 20% KOH (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and evaporated to a yellow oil. The oil was dissolved in CH_3CN (30 ml) and treated with 40 ml of a boiling solution of fumaric acid (0.89g) in MeOH- CH_3CN (1:4 v/v). The resulting precipitate was washed with CH_3CN (3 x 15 ml), crystallized from CH_3CN and vacuum-dried to give 2.37 g (50%) of 76 as a yellow solid, mp 154-155°C (decomp).

Anal. Calcd. for $\text{C}_{32}\text{H}_{40}\text{F}_3\text{N}_3\text{O}_6$: C, 62.02; H, 6.51; N, 6.78.

Found: C, 62.16; H, 6.62; N, 6.50

1-Bromo-5-(4-trifluoromethylphenyl)pentane (28)

This compound was prepared in a manner identical with that described for the 2-isomer (27). The yield of 28, from 22.5 g (0.1 mol) of 3, was 11.08 g (38%); bp 94-96°C/0.8 mm; n_D^{23} 1.4805

6-Methoxy-4-methyl-8-nitro-5-[5-(4-trifluoromethylphenyl)pentoxy]quinoline (41)

This synthesis was identical with that described for the 2-isomer (40). The yield of 41, from 8.78 g (0.0375 mol) of 38, was 8.95 g (53%) as a yellow solid, mp 71-72°C, which was used without further purification. Crystallization of an aliquot from hexane provided the analytical sample, mp 72-73°C.

Anal. Calcd. for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4$: C, 61.60; H, 5.17; N, 6.25.

Found: C, 61.36; H, 5.29; N, 6.40

8-Amino-6-methoxy-4-methyl-5-[5-(4-trifluoromethylphenyl)pentoxy]quinoline (53)

The reduction of 41 was effected essentially as described for the 2-isomer (40). The yield of the 8-amino derivative (53) from 8.42 g (0.0188 mol) of 41 was 6.37 g (81%). Crystallization of an aliquot from hexane afforded the analytical sample, mp 77-78°C.

Anal. Calcd. for $C_{23}H_{25}F_3N_2O_2$: C, 66.01; H, 6.02; N, 6.70.

Found: C, 65.86; H, 6.34; N, 6.66.

6-Methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-[5-(4-trifluoro-methylphenyl)pentoxy]quinoline (65)

Phthalimidoalkylation of 5.85 g (0.014 mol) of 53, carried out as described for the synthesis of 64, gave 4.82 g (54%) of 65 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(4-trifluoro-methylphenyl)pentoxy]quinoline Fumarate (77)

A stirred solution of 65 (4.82 g, 0.0076 mol), $CHCl_3$ (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (6 ml) was heated under reflux for 1 h, allowed to cool and filtered. The white residue was washed with EtOH (5 ml) and the combined filtrate and washings were concentrated to an orange oil. The oil was dissolved in Et_2O (200 ml) and the solution was washed with 25% KOH (3 x 50 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a dark orange oil; yield 3.61 g (94%) after pumping for 1 h at 1 mm/Hg. This base was dissolved in CH_3CN (20 ml) and slowly treated, during 15 min, with 35 ml of a hot solution of fumaric acid (0.83 g) in MeOH- CH_3CN (1:1 v/v). The resulting solid was washed with CH_3CN (2 x 25 ml), crystallized from CH_3CN and dried (3.5 h at 0.5-1.0 mm) to give 2.86 g (61%) of 77 as a yellow solid, mp 155-156°C (decomp.).

Anal. Calcd. for $C_{32}H_{40}F_3N_3O_6$: C, 62.02; H, 6.51; N, 6.78.

Found: C, 61.75; H, 6.81; N, 6.57.

1-Bromo-5-(4-fluorophenyl)pentane (29)

To a stirred mixture of 4-fluorobromobenzene (4) (Aldrich; 35.0 g, 0.20 mol) in anhydrous Et_2O (250 ml), under N_2 , at -40°C, was added dropwise during 30 min., 20 ml of a 10 M solution of BuLi in hexane (Aldrich) diluted with an additional 20 ml of dry hexane. The temperature rose to -30°C during addition and stirring was continued at -30°C for 30 more minutes. The mixture was treated with 1,5-dibromopentane (Aldrich; 46.0 g, 0.20 mol), dropwise, during 10 min., allowed to warm to -10°C, stirred for 20 min., diluted with THF (150 ml), during 30 min., stirred at -10°C for 30 min., and slowly brought

to room temperature. The mixture was slowly poured over crushed dry ice (200 g) and the resulting mixture was carefully added to cold H_2O (500 ml). The aqueous layer was extracted with Et_2O (3 x 200 ml) and the combined extracts and organic layer were washed with 10% Na_2CO_3 (3 x 100 ml), saturated $NaCl$ solution (2 x 200 ml), dried (Na_2SO_4) and concentrated to a pale yellow oil. Fractional distillation gave 18.76 g (38%) of 29 as an oil, bp $128-129^\circ C/3.5$ mm, which was used without further purification.

5-[5-(4-Fluorophenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (42)

To a stirred mixture of 38 (WRAIR; 6.03 g, 0.026 mol), 29 (6.32 g, 0.026 mol) and HMPA (20 ml), at $120-130^\circ C$, was added, dropwise, during 90 min., a solution of propylene oxide (20 ml) and Et_3N (5 ml). The mixture was heated for an additional 5 h, allowed to cool, extracted with Et_2O (300 ml) and Me_2CO to leave 2.26 g of starting material 38. The ether extract was washed with 5% $NaOH$ (3 x 100 ml), H_2O (3 x 100 ml), dried (Na_2SO_4) and evaporated, in vacuo, to a black oil. The oil was placed on a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave a yellow oil which solidified on standing in the refrigerator (4.1 g, 48%). Crystallization from hexane provided an analytical sample as yellow crystals, m.p. $64-65^\circ C$.

Anal. Calcd. for $C_{22}H_{23}FN_2O_4$; C, 66.32; H, 5.82; N, 7.03

Found: C, 66.02; H, 5.85; N, 6.76

8-Amino-5-[5-(4-fluorophenyl)pentoxy]-6-methoxy-4-methylquinoline (54)

A stirred mixture of 42 (7.28 g, 0.018 mol), Fe filings (6 g), H_2O (100 ml), Bu_2O (12 ml) and $HOAc$ (1.5 ml) was heated at $105-110^\circ$ for 1.5 h, allowed to cool and filtered. The solid and the filtrate were extracted with Et_2O and the combined extracts (400 ml) were washed with saturated $NaCl$ solution (3 x 100 ml), dried (Na_2SO_4) and concentrated to a dark oil. The oil was combined with identical material from a similar run which started with 2.5 g (0.0063 mol) of 42. The combined oils were placed on a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave 6.33 g (70%) of 54 as an oil which solidified on standing. This material was used without further purification.

5-[5-(4-Fluorophenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutyl-amino)quinoline (66)

A stirred mixture of 54 (4.18 g, 0.0113 mol) and 4-bromo-1-phthalimido-pentane (BPP) (6.72 g, 0.0226 mol) was heated at 125-130°C while Et₃N (3 ml) was added in small portions during 30 min. After two more hours of heating, additional quantities of BPP (3.36 g) and Et₃N (1 ml) were introduced during 15 min. Heating was continued for 3 h, the mixture was allowed to cool, placed on a silica gel column and eluted with CHCl₃. The eluates were concentrated to give 6.34g (96%) of 66 as a yellow-orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-fluorophenyl)pentoxy]-6-methoxy-4-methyl-quinoline Fumarate (78)

A stirred mixture of 66 (3.68 g, 0.0063 mol), CHCl₃ (25 ml), EtOH (50 ml) and 95% NH₂NH₂ (10 ml) was heated at 85-90°C for 1.5 h, cooled and filtered. The solid was washed with a small amount of EtOH and the combined filtrate and washings were concentrated to an orange oil. This material was dissolved in Et₂O (200 ml), washed with 25% KOH (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na₂SO₄) and concentrated to a dark yellow oil. The oil was dissolved in CH₃CN (15 ml) and slowly treated with fumaric acid (0.6 g) in 30 ml of a boiling solution of MeOH and CH₃CN (1:4). On standing overnight at room temperature, a solid precipitated which was crystallized from CH₃CN to give 1.8 g (50%) of 78 as a yellow solid, m.p. 148-150°C (decomp).

Anal. Calcd. for C₃₁H₄₀FN₃O₆: C, 65.36; H, 7.08; N, 7.38.

Found: C, 64.98; H, 7.16; N, 7.14

1-Bromo-5-(4-methoxyphenyl)pentane (30)

This synthesis was carried out in a manner identical with that described for the preparation of 29. From 37.4 g (0.20 mol) of 5 was obtained 18.0 g (35%) of 30 as a colorless oil, bp 125-127°C/1mm; n_D²⁴ 1.5339. This material was used without further purification.

5-[5-(4-Methoxyphenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (43)

To a stirred mixture of 38 (7.5 g, 0.032 mol), 30 (8.24 g, 0.32 mol) and HMPA (25 ml), at 125-130°C, was added, dropwise during 75 min, a solution of propylene oxide (25 ml) and Et₃N (6 ml). The mixture was heated for an additional 6 h, allowed to cool, extracted with Et₂O (350 ml) and Me₂CO to leave 3.83 g of unreacted starting material 38. The ether extract was washed with 5% NaOH (2 x 75 ml), H₂O (3 x 100 ml), dried (Na₂SO₄) and concentrated to a black oil. The oil was placed on a silica gel column and eluted with CHCl₃. Evaporation of the early eluates returned 4.47 g of the starting material, 30. Subsequent eluates provided 3.51 g (27%) of 43 as a viscous yellow oil which was used without further purification.

8-Amino-5-[5-(4-methoxyphenyl)pentoxy]-6-methoxy-4-methylquinoline (55)

A stirred mixture of 43 (5.0 g, 0.012 mol), Bu₂O (10 ml), H₂O (75 ml), HOAc (1 ml) and Fe filings (5 g) was heated at 110-115°C for 3 h, allowed to cool and filtered. The filtrate and the solid were extracted with Et₂O (300 ml) and the combined extracts were washed with saturated sodium chloride solution (2 x 50 ml), dried (Na₂SO₄) and concentrated in vacuo. The resulting dark solid was placed on a silica gel column and eluted with 1% MeOH in CHCl₃. Concentration of the eluates gave 3.84 g (83%) of 55 as a viscous oil which solidified on standing. This material was used without further purification.

5-[5-(4-Methoxyphenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (67)

A stirred mixture of 55 (3.58 g, 0.0094 mol) and 4-bromo-1-phthalimido-pentane (BPP) (5.58 g, 0.0188 mol) was heated at 120-125°C while Et₃N (2.5 ml) was added during 20 min. The mixture was heated for an additional 3 h, allowed to cool, placed on a silica gel column and eluted with CHCl₃. Concentration of the eluates left 3.32 g, (60%) of 67 as an oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-methoxyphenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (79)

A stirred solution of 67 (4.6 g, 0.0079 mol), CHCl_3 (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (10 ml) was heated under reflux for 2 h, allowed to cool and filtered. The solid was washed with a small amount of EtOH and the combined filtrate and washings were concentrated to a dark orange oil. The oil was dissolved in Et_2O (200 ml), washed with 25% KOH (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a deep yellow oil. The oil was dissolved in CH_3CN (30 ml) and treated with 40 ml of a hot solution of fumaric acid (0.75 g) in MeOH- CH_3CN (1:4). Crystallization of the resulting solid from CH_3CN gave 2.54 g (55%) of 79 as a yellow solid, m.p. 152-153°C (decomp.).

Anal. Calcd. for $\text{C}_{32}\text{H}_{43}\text{N}_3\text{O}_7$; C, 66.07; H, 7.45; N, 7.22.

Found: C, 65.85; H, 7.68; N, 7.08

1-Bromo-5-(2-methylphenyl)pentane (31)

To a stirred solution of 6 (Aldrich; 17.1g, 0.1 mol) in Et_2O (120 ml), under N_2 , at -20°C, was slowly added (25 minutes) 40 ml of a 2.5 M solution of BuLi in hexane (Aldrich). The yellow solution was stirred at -25°C for 30 minutes and treated with 1,5-dibromopentane, 25, (Aldrich; 23.0g, 0.1 mol) followed by THF (60 ml) at a rate which kept the internal temperature below -20°C. The light brown mixture was stirred at -20°C for 1h and allowed to rise to room temperature during 3h. The mixture was slowly added to a bed of dry-ice (120g) and the resulting mixture was poured into H_2O (150 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organic layers were washed with 10% Na_2CO_3 (3 x 100 ml) followed by saturated NaCl solution (3 x 100 ml), dried (Na_2SO_4) and evaporated to a dark brown oil. Vacuum fractional distillation gave 10.4g (43%) of 31 as a colorless oil, bp 104-105.5°C/0.9 mm; n_D^{26} 1.5317.

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{Br}$: C, 59.76; H, 7.11

Found: C, 59.92; H, 6.98

6-Methoxy-4-methyl-5-[5-(2-methylphenyl)pentoxy]-8-nitroquinoline (44)

To a stirred mixture of 38 (WRAIR; 8.2g, 0.035 mol), 31 (8.4g, 0.034 mol) and HMPA (30 ml), at 125°C, was added dropwise, during 3h, a solution of Et₃N (6 ml) and propylene oxide (24 ml). Heating was continued for 2h at 125-130°C. The mixture was allowed to cool and extracted with 500 ml of a 1:1 solution of pet ether (20-40°C) and Et₂O. The combined extracts were washed with 10% NaOH (3 x 100 ml), saturated NaCl solution (3 x 100 ml), dried (Na₂SO₄), treated with carbon (Darco) and concentrated to a dark brown oil. The oil was placed on a silica gel column and eluted with CHCl₃. Evaporation of the yellow eluates gave a red oil which on trituration with hexane, gave 5.8g (42%) of 44, as a yellow solid, m.p., 58-59°C. Recrystallization of an aliquot from hexane-AcOEt (4:1) gave the analytical sample as yellow crystals, m.p. 58-59°C.

Anal. Calcd. for C₂₃H₂₆N₂O₄: C, 70.03; H, 6.64; N, 7.10.

Found: C, 69.81; H, 6.54; N, 7.22.

8-Amino-6-methoxy-4-methyl-5-[5-(2-methylphenyl)pentoxy]quinoline (56)

A stirred mixture of 44 (4.3g, 0.011 mol), Fe-filings (4.3g), H₂O (100 ml), AcOH (1 ml) and Bu₂O (10 ml) was heated at 90-95°C for 4h, allowed to cool and exhaustively extracted with Et₂O (total 500 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (K₂CO₃), treated with carbon (Darco) and evaporated to a yellow oil. The oil was trituated with pet ether (20-40°C) to give 3.8g (96%) of 56 as a yellow solid, mp 55-57°C. This material was used without further purification.

6-Methoxy-4-methyl-5-[5-(2-methylphenyl)pentoxy]-8-(1-methyl-4-phthalimidobutylamino)quinoline (68)

A stirred mixture of 56 (3.5g, 0.0096 mol) and 4-bromo-1-phthalimidopentane (BPP) (3.0g, 0.01 mol) was heated at 125°C while Et₃N (1.5 ml) was slowly added during 30 min. After 2h at 125-128°C, more BPP (3.0g) and Et₃N (1.5 ml during 30 min) were added. Heating was continued for 2h and additional BPP (3.0g) and Et₃N (1.5 ml during 30 min) were introduced and the mixture was heated at 125-128°C for 2h. On cooling, the mixture was extracted with Et₂O (total 250 ml) and the extract was washed with saturated

NaCl solution (2 x 75 ml), dried (Na_2SO_4) and evaporated to an orange oil. The oil was placed on a silica gel column and eluted with hexane-AcOEt (4:1). The orange eluates, on solvent evaporation, gave 6.0g of crude 68 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(2-methylphenyl)pentoxy]quinoline Fumarate (80)

A stirred solution of 68 (6.0g, 0.010 mol), CHCl_3 (25 ml), EtOH (200 ml) and 95% NH_2NH_2 (Eastman; 5 ml) was heated under reflux for 3h., allowed to cool and filtered. The filtrate was concentrated and extracted with Et_2O . The Et_2O extract was washed with 20% KOH (3 x 75 ml), saturated NaCl solution (3 x 75 ml), dried (K_2CO_3) and evaporated to a yellow oil. The oil was placed on a silica gel column and eluted with CHCl_3 -MeOH (from 1:0 to 10:1). The orange eluates, on concentration, gave 3.1g of free base as an oil. The oil was dissolved in CH_3CN (100 ml) and treated with 40 ml of a boiling solution of fumaric acid (0.78g) in MeOH- CH_3CN (1:4 v/v). The resulting precipitate was washed with CH_3CN (30 ml) and vacuum-dried to give 3.0g (53%) of 80 as a yellow solid, mp 134-137°C (decomp.).

Anal. Calcd. for $\text{C}_{32}\text{H}_{43}\text{N}_3\text{O}_6$: C, 67.94; H, 7.66; N, 7.43.

Found: C, 68.16; H, 7.66; N, 7.60.

1-Bromo-5-(3-methylphenyl)pentane (32)

This synthesis was carried out in a manner identical with that described for the preparation of 31. From 17.1g (0.10 mol) of 7, was obtained 12.2g (50%) of 32 as a colorless oil, bp 105.5-107°/0.9 mm; n_D^{24} 1.5283.

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{Br}$: C, 59.76; H, 7.11

Found: C, 59.77; H, 7.06

6-Methoxy-4-methyl-5-[5-(3-methylphenyl)pentoxy]-8-nitroquinoline (45)

This synthesis was identical with that described for the 2-isomer (44). From 10.7g (0.045 mol) of 38, was obtained 45 (13.0g, 73%) as a crude yellow oil. This material was used without further purification.

8-Amino-6-methoxy-4-methyl-5-[5-(3-methylphenyl)pentoxy]quinoline (57)

This reduction of 45 was effected as described for the 2-isomer (44). From 9.2g (0.023 mol) of 45, was obtained 57 (7.9g, 94%) as light yellow crystals, mp. 70-72°C. This material was used without further purification.

6-Methoxy-4-methyl-5-[5-(3-methylphenyl)pentoxy]-8-(1-methyl-4-phthalimidobutylamino)quinoline (69)

Phthalimidoalkylation of 7.9g (0.021 mol) of 57, carried out as described for the synthesis of 2-isomer (68), gave 11.3g (85%) of 69 as a yellow oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(3-methylphenyl)pentoxy]quinoline Fumarate (81)

A stirred solution of 69 (11.2g, 0.019 mol), CHCl_3 (100 ml), EtOH (300 ml) and 95% NH_2NH_2 (Eastman, 12 ml) was heated under reflux for 4h, allowed to cool and filtered. The white residue was washed with EtOH (100 ml) and combined filtrate and washings were concentrated to an orange oil. The oil was extracted with a mixture of Et_2O (250 ml) and 30% KOH (75 ml). The Et_2O solution was separated and washed with saturated NaCl solution (2 x 75 ml), dried (K_2CO_3) and concentrated to give the free base as an orange oil (8.0g, 92%). The oil was dissolved in CH_3CN (150 ml) and treated with 75 ml of a hot solution of fumaric acid (2.1g) in MeOH- CH_3CN (1:4 v/v). The resulting solid was collected, washed with CH_3CN and dried (6 h at 75°C and 0.1 mm Hg) to give 7.4g (69%) of 81 as a yellow solid, mp 140-143°C (decomp.). Anal. Calcd. for $\text{C}_{32}\text{H}_{43}\text{N}_3\text{O}_6$: C, 67.94; H, 7.66; N, 7.43. Found: C, 67.52; H, 7.55; N, 7.44.

1-Bromo-5-(4-methylphenyl)pentane (33)

To a stirred solution of 8 (25.66g, 0.15 mol) in THF (120 ml) and hexane (60 ml) at -40°C, under N_2 , was slowly added, during 40 min, 60 ml (0.15 mol) of a 2.5 M solution of BuLi in hexane (Aldrich). Stirring was continued for 20 min while the temperature was allowed to rise to -10°C and the mixture was then treated with 1,5-dibromopentane (Aldrich; 34.5g, 0.15 mol) during 10 min. After gradual warming to room temperature, the mixture was stirred for

4h, cooled to 0°C and slowly added to water-ice (200 ml). The aqueous layer was extracted with Et₂O (3 x 100 ml) and the combined extracts and organic layer were washed with saturated NaCl solution (2 x 75 ml), dried (Na₂SO₄) and concentrated to a pale yellow oil. Fractional distillation gave 16.2g (45%) of 33 as a colorless oil, bp 102°C/0.8 mm; n_D^{23} 1.5272.

Anal. Calcd. for C₁₂H₁₇Br: C, 59.76; H, 7.11.

Found: C, 59.92; H, 7.13.

6-Methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-nitroquinoline (46)

To a stirred mixture of 38 (WRAIR; 13.75g, 0.059 mol), 33 (14.16g, 0.059 mol) and HMPA (40 ml), at 115-120°C, was added dropwise, during 75 min, a solution of Et₃N (8 ml) and propylene oxide (24 ml). The mixture was heated at 125-130°C for 7 h, allowed to cool and exhaustively extracted with pet ether (20-40°C) and Et₂O (1:1, 400 ml). The combined extracts were washed with 10% NaOH (3 x 100 ml) and the washings were re-extracted with Et₂O (3 x 75 ml). The combined Et₂O solutions were washed with H₂O (3 x 100 ml), dried (Na₂SO₄), treated with carbon (Darco) and concentrated to a dark yellow oil. The oil was pumped at 0.6 mm for 1 h and the resulting semi-solid was vigorously triturated with hexane (15 ml) at 5°C to give a yellow solid. Washing with hexane (2 x 10 ml) gave 12.85g (56%) of 46 as a yellow solid which was used without further purification. Crystallization of an aliquot from hexane provided the analytical sample, m.p. 59-60°C.

Anal. Calcd. for C₂₃H₂₆N₂O₄: C, 70.03; H, 6.64.; N, 7.10.

Found: C, 69.93; H, 6.80; N, 6.99.

8-Amino-6-methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]quinoline (58)

A stirred mixture of 46 (11.70g, 0.030 mol), Fe filings (12g), Bu₂O (30 ml), H₂O (100 ml) and HOAc (1.5 ml) was heated at 115-120°C for 3.5 h, allowed to cool and the supernatant portion decanted. The solid and the decantate were extracted with Et₂O and the combined extracts were washed with saturated NaCl solution (2 x 100 ml), dried (Na₂SO₄), treated with carbon (Darco) and concentrated to a dark oil. The oil was pumped (1mm/Hg) for 3 h at room temperature, cooled to 0°C and vigorously triturated with hexane (20 ml) to give a yellow solid. The solid was washed with hexane to

give 8.73g (81%) of 58 which was used without further purification. Crystallization of an aliquot from hexane afforded the analytical sample as yellow crystals, m.p. 56-57°C.

Anal Calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69.

Found: C, 75.67; H, 7.84; N, 7.63.

6-Methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-(1-methyl-4-phthalimido-butylamino)quinoline (70)

A stirred mixture of 58 (7.12 g, 0.0195 mol) and 4-bromo-1-phthalimido-pentane (BPP) (12.36g, 0.042 mol) was heated at 120-125°C while Et_3N (4 ml) was slowly added during 45 min. After 3h at 120-125°C, more BPP (8.87 g, 0.03 mol) and Et_3N (3 ml during 30 min.) were added and heating was continued for 5h. On cooling, the mixture was exhaustively extracted with Et_2O (300 ml) and the extract was washed with saturated brine (2 x 100 ml), dried (Na_2SO_4) and concentrated to a deep orange oil. The oil was pumped at 1 mm Hg for 1.5 h, applied to a silica gel column and eluted with $CHCl_3$. Concentration of the product eluates gave 11.25 g (99%) of 70 as an orange oil which was pumped at 0.8 mm Hg for 1h and used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5[5-(4-methylphenyl)pentoxy]quinoline Fumarate (82)

A stirred solution of 70 (11.25 g, 0.0194 mol), $CHCl_3$ (50 ml), $EtCH$ (100 ml) and 95% NH_2NH_2 (6 ml) was heated under reflux for 2.5 h, allowed to cool and filtered. The white residue was washed with $EtOH$ and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (250 ml) and the solution was washed with 25% KOH (3 x 75 ml), saturated $NaCl$ solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a viscous yellow oil (6.48 g, 74%). The oil was dissolved in CH_3CN (25 ml) and slowly added to a hot solution of fumaric acid (1.67 g) in CH_3OH-CH_3CN (1:4 v/v, 65 ml). The resulting yellow precipitate was separated by decantation, washed with CH_3CN (3 x 20 ml), recrystallized from CH_3CN and vacuum dried (0.8 mm, 20°C, 2h) to give 5.6 g (51%) of 82 as a yellow solid, mp 153-154 (decomp.)

Anal Calcd. for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43.

Found: C, 67.82; H, 7.75; N, 7.25

1-Bromo-5-(4-ethylphenyl)pentane (34)

To a stirred solution of 10 (Aldrich, 9.25g, 0.05 mol) in THF (30 ml), at -40°C , under N_2 , was slowly added, during 10 minutes, $n\text{-BuLi}$ in hexane (Aldrich, 2.5M, 20 ml, 0.05 mol). The solution was slowly brought to -35°C and stirred at -35°C for 1 hour. A solution of 25 (11.5g, 0.05 mol) in THF (10 ml) was added during 15 min. The mixture was stirred at -35°C for another hour, slowly brought to room temperature, stirred overnight and poured over crushed ice (100g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3x25 ml). The combined organic layers were washed with saturated nace solution (2 x 50 ml), dried (K_2CO_3) and concentrated to a pale yellow oil. The oil was subjected to vacuum fractional distillation and crude 34 (5.82g, 46%), boiling at $110\text{--}112^{\circ}\text{C}$ (1.2 mm of Hg), was collected. This material was used without further purification.

5-[5-(4-Ethylphenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (47)

To a mechanically stirred mixture of 38 (WRAIR), 4.60g, 0.02 mol), 34 (5.00g, 0.02 mol) and HMPA (35 ml), at $105\text{--}110^{\circ}\text{C}$, was added dropwise, during 75 min, a solution of Et_3N (4 ml) and propylene oxide (8 ml). The mixture was heated at $105\text{--}110^{\circ}\text{C}$ for 3 hr, allowed to cool and extracted with a solution of pet.ether ($20\text{--}40^{\circ}\text{C}$) and Et_2O (1:1 v/v, 150 ml), leaving behind a black residue. The organic layer was washed with 10% NaOH solution (3x50 ml). The combined basic wash solutions were re-extracted with a pet.ether ($20\text{--}40^{\circ}\text{C}$)- Et_2O solution (1:1 v/v, 2x50 ml) and the combined organic layers were washed with H_2O (2x50 ml), dried (K_2CO_3), treated with Darco, filtered and concentrated to an oil which on trituration with cold pet.ether ($20\text{--}40^{\circ}\text{C}$, 4 ml) gave 47 as a yellow solid, 4.57g (56%), mp. $53\text{--}54^{\circ}\text{C}$. This material was used without further purification.

8-Amino-5-[5-(4-ethylphenyl)pentoxy]-6-methoxy-4-methylquinoline (59)

A mechanically stirred mixture of 47 (4.00g, 0.0098 mol), Fe-filings (6.0g), Bu_2O (10 ml), H_2O (50 ml) and HOAc (1.0 ml) was heated at $100\text{--}105^{\circ}\text{C}$ for 2h, allowed to cool and filtered. The residue was washed with Et_2O (150 ml) and the filtrate and the washings were combined. The organic layer was separated and the aqueous layer was extracted with Et_2O (2x50 ml).

The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and treated with Darco. Slow solvent evaporation at room temperature produced a yellow solid which was filtered, washed with hexane and air-dried to give 59, 2.05g (55%), mp. 68-69°C. The combined mother liquor and the washings, on cooling (<0°C), gave another crop, 0.75g (20%). The combined material was used without further purification.

5-[5-(4-Ethylphenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (71)

A mechanically stirred mixture of 59 (2.70g, 0.007 mol) and 4-bromo-1-phthalimidopentane (BPP) (3.91g, 0.0132 mol) was heated at 110-115°C while Et_3N (3 ml) was slowly added during 45 min. After 3h at 110-115°C, more BPP (2.25g, 0.0075 mol) and Et_3N (1.5 ml during 5 min.) were added and heating was continued for 4h. More BPP (1.56g, 0.0053 mol) and Et_3N (1 ml during 5 min) were added and heating was continued for 3 hr. TLC (20% EtOAc-hexane) of the reaction-mixture still showed unreacted 59. A final portion of BPP (2.82g, 0.0095 mol) and Et_3N (2 ml during 10 min) were added followed by heating overnight. On cooling, H_2O (50 ml) was added to the flask and the mixture was extracted with Et_2O (2x75 ml). The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was dissolved in $CHCl_3$ (7 ml), applied to a silica column and eluted with 5% EtOAc-hexane. After recovering unreacted BPP, elutant was changed to 10% EtOAc-hexane. Produce eluates were combined and solvent evaporated to give 71 as an orange oil, 3.55g (83%). This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-ethylphenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (83)

A mechanically stirred solution of 71 (3.50g, 0.006 mol), $CHCl_3$ (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (3 ml) was heated under reflux for 1.5h, allowed to cool and filtered. The white residue was washed with $CHCl_3$ (50 ml) and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (100 ml) and the solution was washed with 20% NaOH solution (3x30 ml). The combined basic wash-solutions were re-extracted with Et_2O (2x50 ml) and the combined organic layers were washed with H_2O (2x25 ml), dried (K_2CO_3) and concentrated to a crude yellow oil (2.53g).

The oil was dissolved in CH_3CN (40 ml) and slowly treated with a hot solution of fumaric acid (0.63g) in $\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 v/v, 25 ml). After the yellow precipitate settled, the supernatant liquid was separated and the residue was washed with CH_3CN (3x15 ml) and recrystallized from CH_3CN . Vacuum drying (0.1mm of Hg, 20°C , 2.5h) gave 2.52g (74%) of 83 as a yellow solid, mp $144-146^\circ\text{C}$ (decomp).

Anal. Calcd. for $\text{C}_{33}\text{H}_{45}\text{N}_3$: C, 68.37; H, 7.82; N, 7.25

Found: C, 67.99; H, 7.72; N, 7.20.

1-Bromo-5-[4-(methylthio)phenyl]pentane (89)

To a stirred solution of 87 (Aldrich; 20.3g, 0.1 mol), THF (120 ml) and hexane (60 ml), at -40°C , under N_2 , was slowly added, during 40 min, 40 ml (0.1 mol) of a 2.5 M solution of BuLi in hexane (Aldrich). The stirred white suspension was allowed to warm to -10°C during 20 min and treated, during 10 min, with 1,5-dibromopentane (23.0g, 0.1 mol). The mixture was allowed to warm to room temperature, stirred for 3h, cooled to 0°C and slowly added to water-ice (200 ml). The aqueous layer was extracted with Et_2O (2 x 150 ml) and the combined extracts and organic layer were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a pale yellow oil. The oil was subjected to vacuum fractional distillation. The fraction boiling below $104^\circ\text{C}/2\text{mm}$ was distilled off and the residue was applied to a silica gel column. Elution with hexane and concentration of the eluates gave 7.0g (26%) of 89 as a colorless oil (n_D^{24} 1.5660) which was used without further purification.

1-Bromo-5-[4-(methylsulfonyl)phenyl]pentane (35)

To a stirred solution of 89 (6.4g, 0.023 mol) in CH_2Cl_2 (50 ml), at -5°C to 0°C , was added, during 45 min, a solution of 3-chloroperbenzoic acid (Aldrich, 85%; 9.34g, 0.046 mol) in CH_2Cl_2 (100 ml). The mixture was allowed to warm gradually to room temperature, stirred for 2 h and filtered. The white residue was washed with CH_2Cl_2 (3 x 20 ml) and the combined organic layers were washed with 10% NaHCO_3 (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a viscous oil. Trituration with cold hexane gave 6.0g (86%) of 35 as a white solid, mp $43-44^\circ\text{C}$.

In a similar experiment, the colorless viscous oil was eluted from a silica gel column (EtOAc-Hexane; 1:3 v/v). The product eluates were kept in the freezer overnight and the resulting crystals were washed with hexane and dried in vacuo (2 h, room temp., 0.5 mm) to give the analytical sample, mp 45-46°C.

Anal. Calcd. for $C_{12}H_{17}BrSO_2$: C, 47.21; H, 5.62; O, 10.48

Found: C, 47.16; H, 5.51; O, 10.59

6-Methoxy-4-methyl-5-[5-(4-methylsulfonylphenyl)pentoxy]-8-nitroquinoline (48)

To a stirred mixture of 38 (WRAIR; 1.54g, 0.007 mol), 35 (2.00g, 0.007 mol) and HMPA (20 ml), at 115-120°C, was added dropwise, during 45 min., a solution of Et_3N (2 ml) and propylene oxide (8 ml). Heating was continued for 7h and after cooling, the mixture was exhaustively extracted with ethyl acetate (200 ml). The combined extracts were washed with 10% NaOH solution (3 x 50 ml) and the basic wash solution was re-extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with saturated NaCl solution (3 x 50 ml), dried (Na_2SO_4), concentrated (25 ml) and diluted with hexane (40 ml). On cooling (-5°C) the solution overnight, a yellow solid precipitated which was filtered, washed with hexane and air-dried to give 2.11 g (70%) of 48 as a yellow solid which was used without further purification. Crystallization of an aliquot from ethyl acetate-hexane provided the analytical sample as pale yellow crystals, m.p. 123-124°C.

Anal. Calcd. for $C_{23}H_{26}N_2O_6S$: C, 60.24; H, 5.72, N, 6.11.

Found: C, 60.40; H, 5.97; N, 5.96

8-Amino-6-methoxy-4-methyl-5-[5-(4-methylsulfonylphenyl)pentoxy]quinoline (60)

To a refluxing mixture of 48 (1.45g, 0.0032 mol) in MeOH (80 ml) was added dropwise, during 15 min., a solution of $Na_2S_2O_4$ (2.75g, 0.016 mol) in H_2O (8 ml). After 90 minutes of refluxing, more $Na_2S_2O_4$ (2.75g, 0.016 mol) in H_2O (8 ml) was added during 10 minutes and refluxing was continued for 90 minutes. A final batch of $Na_2S_2O_4$ (1.1g, 0.0063 mol) in H_2O (3 ml) was added, over a period of 5 minutes, followed by refluxing for 45 minutes. After cooling, MeOH was removed on the rotovapor and the reaction

mixture was taken into H_2O (30 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic layers were washed with saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and the solvent was removed to give a yellow residue. This material was combined with material obtained from two similar runs on 0.5g and 1.83g of 48, dissolved in a solution of MeOH- CH_2Cl_2 (5:95 v/v, 25 ml) and filtered through a bed of silica. The filtrate was concentrated to give a crude yellow solid, 2.67g (76%) which was used without further purification.

6-Methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-[5-(4-methylsulfonyl phenyl)pentoxy]quinoline (72)

To a mechanically stirred mixture of 60 (2.60g, 0.0061 mol) and 4-bromo-1-phthalimidopentane (BPP) (3.60g, 0.0122 mol), at 110-115°C, was added Et_3N (3 ml) over a period of 30 minutes. After 3h at 110-115°C, more BPP (3.60g, 0.0122 mol) and Et_3N (2 ml during 15 minutes) were added and heating was continued for 4h. After cooling, the reaction mixture was taken into H_2O (15 ml) and extracted with $CHCl_3$ (3x50 ml). The combined organic layers were dried (Na_2SO_4), concentrated and pumped under vacuum (0.5mm of Hg, 23°C, 2h) to give an oil which was purified by silica-gel-column chromatography (elutant 1% MeOH- $CHCl_3$) to give 2.64g (68%) of 72 as an orange oil. This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(4-methylsulfonylphenyl)pentoxy]quinoline fumarate (84)

A mechanically stirred mixture of 72 (2.60g, 0.004 mol), $CHCl_3$ (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (3 ml) was heated under reflux for 1.5h, allowed to cool and filtered. The white residue was washed with $CHCl_3$ (50 ml) and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (200 ml) and the solution was washed with 20% NaOH solution (3x35 ml). The combined basic wash solutions were re-extracted with Et_2O (2x75 ml) and the combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (Na_2SO_4) and concentrated to a crude yellow oil (1.43g). The oil was dissolved in CH_3CN (15 ml) and slowly treated with a hot solution of fumaric acid (0.33g) in CH_3OH-CH_3CN (1:4v/v, 15 ml). The precipitated yellow solid was collected, washed with CH_3CN (4x15 ml) and

recrystallized from CH_3CN . Vacuum-drying (1.0mm Hg, 4h, 23°C) gave 84 as a yellow solid, 1.06g(42%), mp $134-136^\circ\text{C}$ (decomp).

Anal. Calcd for $\text{C}_{32}\text{H}_{43}\text{N}_3\text{O}_8\text{S}$: C, 61.03; H, 6.88; N, 6.67

Found: C, 61.06; H, 6.85; N, 6.63.

1-Bromo-5-(2,6-dimethylphenyl)pentane (36)

To a stirred solution of 11 (Aldrich, 9.08g, 0.05 mol) in THF (30 ml), at -40°C , under N_2 , was slowly added, during 10 minutes, n-BuLi in hexane (Aldrich, 2.5M, 20 ml, 0.05 mol). The solution was slowly brought to -35°C and stirred at -35°C for 15 min. A solution of 25 (11.3g, 0.05 mol) in THF (15 ml) was added during 5 min. The mixture was stirred at -35°C for 30 min, slowly brought to room temperature, stirred for an additional 3h and poured over crushed ice (100g). The organic layer was separated and the aqueous layer was extracted with Et_2O (3x75 ml). The combined organic layers were washed with saturated NaCl Solution (2x50 ml), dried (K_2CO_3) and concentrated to a pale yellow oil. The oil was subjected to vacuum fractional distillation and crude 36 (4.27g, 34%), boiling at $121.5-122.5^\circ\text{C}$ (0.8mm of Hg), was collected. This material was used without further purification.

5-[5-(2,6-dimethylphenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (49)

To a mechanically stirred mixture of 38 (WRAIR, 3.90g, 0.017 mol), 36 (4.25g, 0.017 mol) and HMPA (30 ml), at $110-115^\circ\text{C}$, was added dropwise, during 80 min, a solution of Et_3N (4 ml) and propylene oxide (8 ml). The mixture was heated at $110-115^\circ\text{C}$ for 5h, allowed to cool and extracted with a solution of pet.ether ($20-40^\circ\text{C}$) and Et_2O (1:1 v/v, 100 ml), leaving behind a black residue. The organic layer was washed with 10% NaOH solution (3x50 ml). The combined basic wash solutions were re-extracted with a pet.ether ($20-40^\circ\text{C}$)- Et_2O solution (1:1 v/v, 2x50 ml). The combined organic layers, on cooling ($0-5^\circ\text{C}$), produced a yellow precipitate which was filtered, dissolved in EtOAc (100 ml), washed with H_2O (2x50 ml), dried (K_2CO_3) and concentrated to an oil which on trituration with cold hexane gave 1.15g (17%) of 49 as a yellow solid, mp $116-117^\circ\text{C}$. The mother liquor was washed with H_2O (2x50 ml), dried (K_2CO_3) and concentrated to an oil which on

trituration with cold hexane gave another batch of 49 as a yellow solid, 2.13g (31%), mp. 115-116°C. The combined material was used without further purification.

8-Amino-5-[5-(2,6-dimethylphenyl)pentoxy]-6-methoxy-4-methylquinoline (61)

A mechanically stirred mixture of 49 (3.27g, 0.008 mol), Fe-filings (5g), Bu_2O (10 ml), H_2O (40 ml) and HOAc (1.2 ml) was heated at 105-110°C for 2.5h, allowed to cool and filtered. The residue was washed with Et_2O (100 ml) and the filtrate and the washings were combined. The organic layer was separated and the aqueous layer was extracted with Et_2O (2x50 ml). The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and treated with Darco. Solvent evaporation produced a yellow oil which on trituration with cold hexane (5 ml), gave 61 as a yellow solid, 2.72g (90%), mp. 96-97°C. This material was used without further purification.

5-[5-(2,6-dimethylphenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutyl-amino)quinoline (73)

A mechanically stirred mixture of 61 (2.70g, 0.007 mol) and 4-bromo-1-phthalimidopentane (BPP) (4.00g, 0.014 mol) was heated at 110-115°C while Et_3N (3 ml) was slowly added during 40 min. After 3h at 110-115°C, more BPP (5.00g, 0.017 mol) and Et_3N (2 ml during 15 min.) were added and heating was continued overnight. On cooling, H_2O (40 ml) was added to the flask and the mixture was extracted with Et_2O (3x50 ml). The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was dissolved in CHCl_3 (10 ml), applied to a silica column and eluted with 5% EtOAc -hexane. After recovering unreacted BPP, elutant was changed to 10% EtOAc -hexane. Product eluates were combined and solvent evaporated to give 73 as an orange oil, 4.20g (100%). This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(2,6-dimethylphenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (85)

A mechanically stirred solution of 73 (4.18g, 0.007 mol), CHCl_3 (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (3.5 ml) was heated under reflux for

1.5h, allowed to cool and filtered. The white residue was washed with CHCl_3 (50 ml) and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (100 ml) and the solution was washed with 20% NaOH solution (3x40 ml). The combined basic wash-solutions were re-extracted with Et_2O (2x50 ml) and the combined organic layers were washed with H_2O (2x30 ml), dried (K_2CO_3) and concentrated to a crude yellow oil (2.87g). The oil was dissolved in CH_3CN (30 ml) and slowly treated with a hot solution of fumaric acid (0.72g) in $\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 v/v, 40 ml). The yellow precipitate was allowed to settle. The supernatant liquid was separated and the residue was washed with CH_3CN (3x10 ml) followed by recrystallization from CH_3CN . Vacuum drying (0.1mm of Hg, 20°C, 4h) gave 2.63g (64%) of 85 as a yellow solid, mp 144-146°C (decomp).

Anal. Calcd. for $\text{C}_{33}\text{H}_{45}\text{N}_3\text{O}_6$: C, 68.37; H, 7.82; N, 7.25

Found: C, 68.08; H, 7.58; N, 7.32

1-Bromo-5-(4-chloro-3-trifluoromethylphenyl)pentane (37)

To a stirred solution of 12 (Aldrich; 25.95g, 0.1 mol) in anhydrous Et_2O (120 ml), under N_2 , at -20°C, was added dropwise, during 20 min, 40 ml of a 2.5 M solution of BuLi in hexane (Aldrich). Stirring was continued for 30 min. and the mixture was then treated, dropwise, during 15 min, with 1,5-dibromopentane (Aldrich; 23.0g, 0.1 mol). The mixture was allowed to warm to 0°C, stirred for 2 h and then treated, at 0°C, during 20 min, with THF (60 ml). After gradual warming to room temperature, the mixture was stirred for 2 h, poured slowly onto crushed dry ice (100g) and carefully added to H_2O (150 ml). The aqueous layer was extracted with Et_2O (3 x 125 ml) and the combined extracts and organic layer were washed with 10% Na_2CO_3 (3 x 100 ml) and saturated NaCl solution (3 x 100 ml), dried (Na_2SO_4) and concentrated to a dark oil. Fractional distillation gave 5.0g (15%) of 37 as an oil, bp 136-138°C/2 mm; n_D^{25} 1.5019.

5-[5-(4-Chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (50)

To a stirred mixture of 38 (WRAIR; 3.49g, 0.015 mol), 37 (4.92g, 0.015 mol) and HMPA (20 ml), at 110-115°C, was added dropwise, during 1 h, a solution of propylene oxide (16 ml) and Et_3N (4 ml). The mixture was heated

at 120-125°C for 4 h and at 135-140°C for 1 h, allowed to cool and extracted with a 1:1 mixture (250 ml) of pet.ether and Et₂O. The extract was washed with 10% NaOH (3 x 100 ml), H₂O (3 x 100 ml), saturated NaCl (2 x 50 ml), dried (Na₂SO₄) and concentrated to give 4.71g (66%) of 50 as a yellow solid which was used without further purification. Crystallization of an aliquot from hexane gave an analytical sample as yellow crystals, mp 91-92°C.

Anal. Calcd. for C₂₃H₂₂ClF₃N₂O₄: C, 57.20; H, 4.59; N, 5.80.

Found: C, 56.99; H, 4.72; N, 5.60

8-Amino-5-[5-(4-chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methylquinoline (62)

A stirred mixture of 50 (6.52g, 0.0135 mol) Bu₂O (15 ml), H₂O (75 ml), Fe filings (6 g) and AcOH (1 ml) was heated at 110-115°C for 2 h, allowed to cool and filtered. The solid and the filtrate were extracted with Et₂O and the combined extracts were washed with saturated NaCl solution, dried (Na₂SO₄), treated with carbon (Darco) and concentrated to an oil. The latter was pumped at room temperature for five hours at 0.2 mm to leave 4.63g (76%) of 62 as a yellow solid which was used without further purification.

5-[5-(4-Chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (74)

A stirred mixture of 62 (1.8g, 0.004 mol) and 4-bromo-1-phthalimido-pentane (BPP) (2.36g, 0.008 mol) was heated at 125-130°C while Et₃N (1 ml) was slowly added during 15 minutes. Heating was continued for 3 h, and the mixture was allowed to cool, placed on a silica gel column and eluted with CHCl₃. Concentration gave 2.34g (88%) of 74 as a viscous yellow oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (86)

A stirred mixture of 74 (1.41g, 0.002 mol), CHCl₃ (20 ml), EtOH (40 ml) and 95% NH₂NH₂ (6 ml) was heated under reflux for 2 h, allowed to cool and filtered. The residue was washed with EtOH (5 ml) and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in Et₂O (100 ml) and the solution was washed with 25% KOH (3 x 30 ml) and saturated

NaCl (2 x 50 ml), dried (Na_2SO_4) and concentrated to a crude dark yellow oil (1.13 g, 100%). This material was dissolved in CH_3CN (10 ml) and slowly treated with a boiling solution of 0.24 g of fumaric acid in 12 ml of a 1:4 v/v solution of MeOH and CH_3CN . The resulting solid was separated by decantation, washed with CH_3CN (3 x 10 ml) and crystallized from CH_3CN to give 0.89g (65%) of 86 as a yellow solid, mp 152-153°C (decomp.).

Anal. Calcd. for $\text{C}_{32}\text{H}_{40}\text{F}_3\text{N}_2\text{O}_6$: C, 58.75; H, 6.01; N, 6.42.

Found: C, 58.52; H, 6.16; N, 6.72.

8-Amino-5-(3-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline (94)

The sequence from 90 to 94 (Scheme 3) was a simple repetition of the one used in our initial synthesis of 94 (Annual/Final Report, USAMRDC Contract No. DAMD17-86-C-6094, February 1988, pp. 90-91).

5-[5-(3-Chlorophenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (95)

A stirred mixture of 94 (9.8 g, 0.025 mol) and BPP (15g, 0.05 mol) was heated at 125-130°C while Et_3N (5 ml) was added dropwise. Additional quantities of BPP (15g) and Et_3N (5 ml) were introduced twice more at 2 h intervals while maintaining the temperature at 125-130°C. The mixture was allowed to cool and extracted with Et_2O . The extract was washed with saturated NaCl, dried (Na_2SO_4), treated with Darco G-60 and concentrated to a brown syrup. This material was diluted with CHCl_3 and passed through a silica gel column. Concentration of the eluates gave 6.6g of 95 as a viscous orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(3-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (96)

The conversion of the phthalimido precursor 95 to 96 was carried out in a manner identical with that described previously (Annual/Final Report, USAMRDC Contract No. DAMD17-86-C-6094, February 1988, pp. 90-91).

2,4-Dimethyl-6-methoxy-5-[5-(4-methylphenyl)pentoxy]-8-nitroquinoline (98)

To a mechanically stirred mixture of 97 (WRAIR, 3.64g, 0.015 mol), 33 (3.53 g, 0.015 mol) and HMPA (25 ml), at 105-110°C, was added dropwise, during 60 min, a solution of Et₃N (3 ml) and propylene oxide (5 ml). The mixture was heated at 105-110°C for 4h, allowed to cool and extracted with a solution of pet. ether (20-40°C) and Et₂O (1:1 v/v, 200 ml), leaving behind a black residue. The extract was washed with 10% NaOH solution (3x75 ml). The combined basic solution was re-extracted with a pet. ether (20-40°C)-Et₂O solution (1:1 v/v, 2x75 ml) and the combined organic layers were washed with H₂O (3x75 ml), dried (K₂CO₃) and concentrated to a black oil. The oil was dissolved in CHCl₃ (5 ml), applied to a silica gel column and eluted with 10% EtOAc in hexane. The product eluates were combined and solvent evaporated to give a thick yellow oil which on vigorous scratching at 0-5°C produced 98 as a yellow solid, 3.25 g (54%), mp 38-39°C. This material was used without further purification.

8-Amino-2,4-dimethyl-6-methoxy-5-[5-(4-methylphenyl)pentoxy]quinoline (99)

A mechanically stirred mixture of 98 (3.00 g, 0.0073 mol), Fe-filings (4 g), Bu₂O (10 ml), H₂O (30 ml) and HOAc (1 ml) was heated at 105-110°C for 1h, allowed to cool and filtered. The residue was washed with Et₂O (150 ml), the filtrate and the washings were combined and the organic layer was separated. The aqueous layer was extracted with Et₂O (2x50 ml) and the combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K₂CO₃), treated with carbon (Darco) and concentrated to a yellow oil. The oil was diluted with pet. ether (20-40°C, 10 ml) and cooled (0°C) overnight. The precipitated solid was filtered, washed with a small volume of pet. ether (20-40°C) and air-dried to give 99 as a yellow solid, 2.30 g (83%), mp 53-55°C. This material was used without further purification.

2,4-Dimethyl-6-methoxy-5-[5-(4-methylphenyl)pentoxy]-8-(1-methyl-4-phthalimidobutylamino)quinoline (100)

A mechanically stirred mixture of 99 (2.20 g, 0.0058 mol), and 4-bromo-1-phthalimidopentane (BPP)(3.44 g, 0.0116 mol) was heated at 100-105°C while Et₃N (2 ml) was slowly added during 20 min. After 3h at 100-105°C, more BPP (3.44g, 0.0116 mol) and Et₃N (2 ml during 10 min.) were added and heating

was continued for 3.5h. A final portion of BPP (1.27g, 0.0043 mol) and Et_3N (1 ml during 5 min) were added followed by heating for 4h. On cooling, the mixture was extracted with Et_2O (200 ml), leaving behind a white residue. The organic layer was washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a dark oil which was subjected to vacuum (1.0 mm Hg, 20°C, 2h). The oil was dissolved in CHCl_3 (4 ml), applied to a silica gel column and eluted with 5% EtOAc in hexane. After the unreacted BPP was recovered, the eluant was changed to 10% EtOAc in hexane. The product eluates were combined and solvent evaporated to give 100 as an orange oil, 3.15g (91%). This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,4-dimethyl-6-methoxy-5-[5-(4-methylphenyl)pentoxyl]quinoline Fumarate (101)

A mechanically stirred solution of 100 (3.12g, 0.0053 mol), CHCl_3 (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (3 ml) was heated under reflux for 1.5h, allowed to cool and filtered. The white residue was washed with CHCl_3 (50 ml) and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (100 ml) and the solution was washed with 20% NaOH solution (3x30 ml), H_2O (1x50 ml), saturated NaCl solution (1x50 ml), dried (MgSO_4) and concentrated to a crude greenish yellow oil (2.13g). The oil was dissolved in CH_3CN (20 ml) and slowly treated with a hot solution of fumaric acid (0.53 g) in $\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 v/v, 20 ml). The yellow precipitate was allowed to settle over a period of 2h. The supernatant liquid was separated and the residue was washed with CH_3CN (2x20ml) followed by recrystallization from CH_3CN . Vacuum-drying (0.5 mm Hg, 20°C, 4h) gave 2.02g (66%) of 101 as a yellow solid, mp 145-147°C (decomp.).

Anal. Calcd. for $\text{C}_{33}\text{H}_{45}\text{N}_3\text{O}_6$: C, 68.37; H, 7.82; N, 7.25

Found: C, 68.48; H, 7.81; N, 7.22

1-Bromo-5-(2-thienyl)pentane (103)

To a stirred solution of 25 (23.00g, 0.10 mol) in THF (100 ml) at -60°C, under N_2 , was slowly added, during 30 min, 100 ml (0.10 mol) of a 1.0 M solution of 2-thienyllithium in THF (Aldrich). Stirring was continued for 1h at -60°C. After gradual warming to room temperature, the mixture was stirred for 2h and slowly poured over a bed of ice (ca. 200g). The organic layer was

separated and the aqueous layer was extracted with Et_2O (2 x 100 ml). The combined organic layer and the extracts were washed with saturated NaCl solution (2 x 75 ml), dried (MgSO_4) and concentrated to a dark oil (23.13g). Fractional distillation gave 12.34g (53%) of 103 as a colorless oil, b.p. $87-88^\circ\text{C}$ (0.7 mm); $n_D^{23} 1.5440$.

Anal. Calcd for $\text{C}_9\text{H}_{13}\text{BrS}$: C, 46.36; H, 5.62.

Found: C, 46.60; H, 5.76

6-Methoxy-4-methyl-8-nitro-5-[5-(2-thienyl)pentoxylquinoline (104)

To a mechanically stirred mixture of 38 (WRAIR; 5.67g, 0.023 mol), 103 (5.32g, 0.023 mol) and HMPA (40 ml), at $115-120^\circ\text{C}$, was added dropwise, during 45 min, a solution of Et_3N (5 ml) and propylene oxide (10 ml). The mixture was heated at $115-120^\circ\text{C}$ for 5 hr, allowed to cool and extracted with a solution of pet. ether ($20-40^\circ\text{C}$) and Et_2O (1:1 v/v, 200 ml). The extract was washed with 10% NaOH solution (3 x 75 ml) and the combined basic washings were re-extracted with pet. ether ($20-40^\circ$) and Et_2O solution (1:1 v/v, 2 x 100 ml). The combined organic layers were washed with H_2O (2 x 100 ml), dried (K_2CO_3), and treated with carbon (Darcon G-60). Solvent evaporation gave 104 as a yellow solid, 5.61g (61%), mp $51-54^\circ\text{C}$. This material was used without further purification.

8-Amino-6-methoxy-4-methyl-5-[5-(2-thienyl)pentoxylquinoline (105)

A mechanically stirred mixture of 104 (5.50g, 0.014 mol), Fe-filings (6g), Bu_2O (15 ml), H_2O (50 ml) and HOAc (1.5 ml) was heated at $105-110^\circ\text{C}$ for 2.5h, allowed to cool and filtered. The residue was well washed with Et_2O (200 ml) and the filtrate and the washings were combined. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 75 ml). The combined organic layers were washed with saturated NaCl solution (2 x 50 ml), dried (K_2CO_3), treated with carbon (Darco G-60), and concentrated to a yellow oil which on trituration with pet. ether ($20-40^\circ\text{C}$, 20 ml), at -20°C , gave 6, as a yellow solid, 4.07g (80%), m.p. $42-44^\circ\text{C}$. This material was used without further purification.

6-Methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-[5-(2-thienyl)pentoxyl]quinoline (106)

A stirred mixture of 105 (4.00g, 0.0108 mol) and 4-bromo-1-phthalimido-pentane (BPP) (6.40g, 0.0216 mol) was heated at 110-115°C while Et₃N (4 ml) was slowly added during 25 min. After 4h at 115-120°C, more BPP (6.40g, 0.0216 mol) and Et₃N (2 ml during 10 min) were added and heating was continued for 4h. A final batch of BPP (1.60g, 0.0054 mol) and Et₃N (1 ml during 5 min) were added and heating was continued for 2h. On cooling, the mixture was extracted with Et₂O (200 ml) leaving behind a grey residue. The extract was washed with H₂O (2 x 75 ml), dried (Na₂SO₄) and concentrated to a black oil. The oil was dissolved in CHCl₃ (12 ml), applied to a silica gel column and eluted with 5% EtOAc in hexane. After recovering the unreacted BPP, the eluting solvent was changed to 10% EtOAc in hexane. Product eluates were combined and concentrated to give 106 as a thick orange-yellow oil, 5.57g (87%). This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(2-thienyl)pentoxyl]quinoline Fumarate (107)

A mechanically stirred mixture of 106 (5.50g, 0.0096 mol), CHCl₃ (35 ml), EtOH (70 ml) and 95% NH₂NH₂ (4 ml) was heated under reflux for 1h, cooled and filtered. The white residue was washed with CHCl₃ (50 ml) and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et₂O (150 ml) and the solution was washed with 20% NaOH solution (3 x 30 ml) and saturated NaCl solution (2 x 50 ml), dried (Na₂SO₄) and concentrated to a yellow oil (3.66g). The oil was dissolved in CH₃CN (25 ml) and slowly treated with a hot solution of fumaric acid (0.93g) in CH₃OH-CH₃CN (1:4 v/v, 40 ml). The precipitated yellow solid was allowed to settle and the supernatant liquid was decanted. The residue was washed with CH₃CN (2 x 50 ml), recrystallized twice from CH₃CN and vacuum dried (1-2 mm, 20°C, 3h) to give 107 as a yellow solid, 3.29g (61%), m.p. 148-150°C.

Anal. Calcd, for C₂₉H₃₉N₃O₆S: C, 62.45; H, 7.05; N, 7.53

Found C, 62.41; H, 7.01; N, 7.51.

1-Bromo-5-(2-furyl)pentane (110)⁵

To a stirred solution of 108 (Aldrich, 6.81g, 0.1 mol) in THF (30 ml), at -30°C, under N₂, was slowly added, during 15 minutes, n-BuLi in hexane (Aldrich, 2.5M, 40 ml, 0.1 mol). The solution was slowly brought to -20°C and stirred at -20°C for 4 hours. A solution of 25 (23.00g, 0.1 mol) in THF (25 ml) was added during 10 min. The mixture was stirred at -20°C for another hour, slowly brought to room temperature, stirred overnight and poured over crushed ice (200g). The organic layer was separated and the aqueous layer was extracted with Et₂O (2x100 ml). The combined organic layers were washed with H₂O (2x50 ml), dried (Na₂SO₄) and concentrated to a pale yellow oil. The oil was subjected to vacuum fractional distillation and crude 110 (7.47g, 34%), boiling at 68-75°C (1mm of Hg), was collected. This material was used without further purification.

5-[5-(2-Furyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (111)

To a mechanically stirred mixture of 38 (WRAIR, 4.00g, 0.017 mol), 110 (3.65g, 0.017 mol) and HMPA (25 ml), at 105-110°C, was added dropwise, during 60 min, a solution of Et₃N (3.5 ml) and propylene oxide (6.5 ml). The mixture was heated at 105-110°C for 2hr, allowed to cool and extracted with a solution of pet.ether (20-40°C) and Et₂O (1:1 v/v, 200 ml), leaving behind a black residue. The organic layer was washed with 10% NaOH solution (3x50 ml). The combined basic wash solutions were re-extracted with a pet.ether (20-40°C)-Et₂O solution (1:1 v/v, 2x75 ml) and the combined organic layers were washed with H₂O (2x50 ml), dried (Na₂SO₄), treated with Darco, filtered and concentrated to give 111 as a yellow solid, 2.5g (40%), mp. 47-49°C. This material was used without further purification.

8-Amino-5-[5-(2-furyl)pentoxy]-6-methoxy-4-methylquinoline (112)

A mechanically stirred mixture of 111 (2.20g, 0.0059 mol), Fe-filings (3.0g), Bu₂O (8 ml), H₂O (30 ml) and HOAc (0.5 ml) was heated at 95-100°C for 2h, allowed to cool and filtered. The residue was washed with Et₂O (100 ml) and the filtrate and the washings were combined. The organic layer was separated and the aqueous layer was extracted with Et₂O (2x50 ml). The combined organic layers were washed with saturated NaCl solution (1x50 ml),

dried (Na_2SO_4), treated with Darco and concentrated to an oil which on trituration with cold hexane produced 112 as a crude greenish-yellow solid, 1.35g (65%), mp 41-42°C. This material was used without further purification.

5-[5-(2-Furyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (113)

A mechanically stirred mixture of 112 (2.73g, 0.008 mol) and 4-bromo-1-phthalimidopentane (BPP) (4.75g, 0.016 mol) was heated at 100-105°C while Et_3N (3 ml) was slowly added during 25 min. After 3.5h at 100-105°C, more BPP (3.24g, 0.011 mol) and Et_3N (2 ml during 15 min.) were added and heating was continued for 2h. More BPP (2.38g, 0.008 mol) and Et_3N (2 ml during 15 min) were added and heating was continued for 2 hr. TLC (40% EtOAc-hexane) of the reaction-mixture still showed unreacted 34. A final portion of BPP (2.38g, 0.008 mol) and Et_3N (1.5 ml during 10 min) were added followed by heating for 4h. On cooling, H_2O (40 ml) was added to the flask and the mixture was extracted with Et_2O (3x100 ml). The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was dissolved in CHCl_3 (8 ml), applied to a silica column and eluted with 10% EtOAc-hexane. Product eluates were combined and solvent evaporated to give 113 as an orange oil, 3.40g (76%). This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(2-furyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (114)

A mechanically stirred solution of 113 (3.36g, 0.006 mol), CHCl_3 (25 ml), EtOH (50 ml) and 95% NH_2NH_2 (3 ml) was heated under reflux for 1h, allowed to cool and filtered. The white residue was washed with CHCl_3 (50 ml) and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (50 ml) and the solution was washed successively with 20% NaOH solution (3x30 ml) and saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a crude yellow oil (2.17g). The oil was dissolved in CH_3CN (20 ml) and slowly treated with a hot solution of fumaric acid (0.59g) in $\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 v/v, 25 ml). The yellow precipitate was allowed to settle overnight. The supernatant liquid was separated and the residue was washed with CH_3CN (3x20 ml) followed by

recrystallization (2X) from CH_3CN . Vacuum drying (0.2mm of Hg, 20°C, 5h) gave 1.95g (60%) of 114 as a yellow solid, mp 145-147°C (decomp).

Anal. Calcd. for $\text{C}_{29}\text{H}_{39}\text{N}_3\text{O}_7$: C, 64.31; H, 7.26; N, 7.76

Found: C, 64.09; H, 7.35; N, 7.80

5-Chloro-2,4-dimethyl-6-methoxy-8-nitroquinoline (116)

A mixture of 12.4g (0.05 mol) of 97 (WRAIR) and 150 ml of POCl_3 (115) (Baker) was heated in a 90° oil bath for 2 hours. On cooling, the mixture was slowly poured over crushed ice (ca. 1kg) and the resulting red solution was carefully basified with conc. NH_4OH to pH10. The brown suspension was filtered and the solid was washed with water, dissolved in CHCl_3 (200ml) and filtered to separate recovered 97 (3.0g). The filtrate was placed on a silica gel column and eluted with CHCl_3 . The yellow eluates were collected and concentrated. Crystallization of the resulting solid from hexane: MeOH gave 9.1g (68%) of 116. Recrystallization from hexane provided the analytical sample as pale yellow needles, mp. 146-148°C.

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{ClN}_2\text{O}_3$: C, 54.05; H, 4.16; N, 10.50.

Found: C, 54.01; H, 4.30; N, 10.25.

2,4-Dimethyl-6-methoxy-8-nitro-5-(3-trifluoromethylphenoxy)quinoline (117)

A mixture of 3-trifluoromethylphenol (Aldrich; 2.2g, 0.013 mol) and KOH (0.9g, 0.013 mol) in 20 ml of 2-ethoxyethanol was heated in a 90° oil bath for 1 hour. The mixture was cooled to 50°C, 116 (3.6g, 0.013 mol) in 2-ethoxyethanol (15 ml) was added all at once and the mixture was heated in a 130° oil bath for 7 hours. On cooling, the resulting solid was collected on a funnel and washed with pet ether (20-40°) to give 4.4g (86%) of 117 as pale brown needles, mp 220-227°C. This material was used without further purification.

8-Amino-2,4-dimethyl-6-methoxy-5-(3-trifluoromethylphenoxy)quinoline (118)

A stirred mixture of 117 (7.1g, 0.018 mol), Fe-filings (11.0g), AcOH (2.5ml), and Bu_2O (15 ml) was heated at 95-110°C for 6 hours, allowed to cool and filtered. The filtrate and residue were extracted with CH_2Cl_2 and the combined extracts (total 400 ml) were washed with saturated NaCl solution

(3x75 ml) and dried (K_2CO_3). The filtrate was treated with carbon and concentrated to a green-gray solid which was washed with pet. ether (20-40°) to yield 4.2g (64%) of 118, mp. 148-153°C. This material was used without further purification.

2,4-Dimethyl-6-methoxy-8-(1-methyl-4-phthalimidobutylamino)-5-(3-trifluoromethylphenoxy)quinoline (119)

A stirred mixture of 118 (4.2g, 0.011 mol) and 4-bromo-1-phthalimidopentane (BPP)(5.0g, 0.017 mol) was heated at 125-130°C while Et_3N (2.5 ml) was added in small portions during 30 minutes. After 2 hours of heating, additional quantities of BPP (5.0g) and Et_3N (2.5 ml) were introduced during 30 minutes and heating was continued for 2 hours. This procedure was repeated two more times. The mixture was allowed to cool, diluted with CH_2Cl_2 (300 ml) and filtered. The filtrate was washed with saturated NaCl solution (2x75 ml), dried (Na_2SO_4) and evaporated to a brown oil. The oil was placed on a silica gel column and eluted with hexane: AcOEt(4:1). The yellow eluates were concentrated to give 10g of crude 119 as a yellow-orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,4-dimethyl-6-methoxy-5-(3-trifluoromethylphenoxy)quinoline Fumarate (120)

A stirred mixture of 119 (10g), $CHCl_3$ (100 ml), EtOH (350 ml), and 95% NH_2NH_2 (Eastman; 10 ml) was heated at reflux for 5 hours, cooled and filtered. The solid was washed with a small amount of EtOH and the combined filtrate and washings were concentrated to an orange oil. This oil was extracted with a mixture of CH_2Cl_2 (300 ml) and 20% KOH (100 ml) and the organic layer was washed with 20% KOH (100 ml), saturated NaCl solution (3 x 75 ml), dried (K_2CO_3) and concentrated to an orange oil (3.4g). The oil was dissolved in CH_3CN (150 ml) and treated with fumaric acid (0.9g) in 20 ml of a boiling solution of MeOH and CH_3CN (1:4). On standing overnight at room temperature, a solid precipitated which was crystallized twice from MeOH: CH_3CN (1:9) to give 2.2g (34% based on 118) of 120 as a yellow solid, mp. 160-163°C (decomp).

Anal. Calcd. for $C_{28}H_{32}F_3N_3O_6$: C, 59.67; H, 5.72; N, 7.46.

Found: C, 59.67; H, 5.84; N, 7.40.

6-Methoxy-3-methyl-8-nitro-5-(3-trifluoromethylphenoxy)quinoline (124)

A mixture of 121 (WRAIR, 12.66g, 0.05 mol), 122 (Aldrich, 8.10g, 0.05 mol), KOH (3.38g) and 2-ethoxyethanol (90 ml) was heated at reflux for 18h, cooled and filtered. The yellow residue was washed with cold EtOH, stirred in acetone (75 ml) and filtered. The acetone filtrate was evaporated to dryness to give a yellow solid (9.1g, 48%). The combined mother liquor and washings, on cooling (0°C), produced another crop (1.74g, 9%) of a yellow solid. The combined material, m.p. 169-170°C, was used without further purification.

8-Amino-6-methoxy-3-methyl-5-(3-trifluoromethylphenoxy)quinoline (126)

A stirred mixture of 124 (10.75g, 0.028 mol), Fe-filings (10g), Bu₂O (40 ml), H₂O (100 ml) and AcOH (1.5 ml) was heated at 115-120°C for 3h, allowed to cool and filtered. The solid and the filtrate were extracted with CHCl₃ (300 ml) and the combined extracts were washed with saturated NaCl solution (2 x 100 ml), dried (K₂CO₃) and concentrated to a small volume. The solution was diluted with pet ether (20-40°C, 100 ml) and cooled (0°C, 2h) with occasional scratching. The resulting precipitate was filtered, washed with pet ether and air-dried to give a greenish solid (7.45 g, 75%), m.p. 110-111°C, which was used without further purification.

6-Methoxy-3-methyl-8-phthalimido-5-(3-trifluoromethylphenoxy)quinoline (128)

A mixture of 126 (7.4g, 0.02 mol), phthalic anhydride (Aldrich, 3.46g, 0.022 mol) and xylene (80 ml) was refluxed for 24h using a Dean-Stark water removal trap. The reaction mixture was cooled (0-5°C) for 1h and filtered. The residue was washed with pet ether (20-40°C) and air-dried to yield 8.30g (82%) of 128 as a greyish white solid, m.p. 234-236°C. This material was used without further purification.

6-Methoxy-3-methyl-8-phthalimido-5-(3-trifluoromethylphenoxy)quinoline-1-oxide (130)

To a mechanically stirred solution of 128 (8.20g, 0.017 mol) in CHCl₃ (80 ml), at 0°C, was added, dropwise, over 20 min, m-chloroperoxybenzoic acid (Aldrich, 85%; 9.68g, 0.45 mol) in CHCl₃ (90 ml). The mixture was slowly brought to room temperature, stirred for an additional 16h, washed with 10%

K_2CO_3 solution (3 x 75 ml), H_2O (2 x 100 ml) and dried (K_2CO_3).

Solvent evaporation gave a yellow mass which on trituration with cold EtOH (15 ml), yielded a yellow solid. This material was filtered, washed successively with cold EtOH and pet ether (20-40°C) and air dried to give 6.23g (74%) of 130 as a pale yellow solid, m.p. 235-238°C (decomp.). The filtrate and washings were combined and cooled below 0°C to produce another crop (0.87g, 10%) of 130. The combined material was used without further purification.

2-Chloro-6-methoxy-3-methyl-8-phthalimido-5-(3-trifluoromethylphenoxy)quinoline (132)

To a cooled (0-5°C) solution of 130 (7.00g, 0.0142 mol) in $CHCl_3$ (100 ml), was added dropwise, over a period of 15 min, phosphorus oxychloride (Aldrich, 21.77g, 0.142 mol, 13.2 ml). The mixture was heated under reflux for 2h, cooled and slowly poured over a bed of ice (100g). The stirred mixture was treated very slowly with 20% KOH solution (ca. 250 ml) to adjust the pH to 10-11. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 x 100 ml). The combined organic layers were washed with H_2O (2 x 100 ml) and dried (K_2CO_3). Solvent evaporation gave 6.50 g (90%) of crude 132, m.p. 240-242°C, which was used without further purification.

8-Amino-2-chloro-6-methoxy-3-methyl-5-(3-trifluoromethylphenoxy)quinoline (134)

A mixture of 132 (6.45g, 0.0126 mol), $CHCl_3$ (15 ml), EtOH (60 ml) and 95% NH_2NH_2 (Eastman, 2.5 ml) was heated under reflux for 2h, allowed to cool and filtered. The white residue was washed with CH_2Cl_2 and the combined filtrate and washings were evaporated to a dark oil. The oil was dissolved in CH_2Cl_2 (100 ml) and washed with 20% KOH solution (3 x 30 ml). The combined basic solution was re-extracted with CH_2Cl_2 (2 x 30 ml) and the combined organic layers were washed with saturated NaCl solution (2 x 50 ml), dried (K_2CO_3) and concentrated to an oil. The oil, on trituration with cold hexane, yielded 134 as a greenish solid, 3.92g (81%). This material was used without further purification.

8-Amino-2,6-dimethoxy-3-methyl-5-(3-trifluoromethylphenoxy)quinoline (136)

A stirred mixture of 134 (3.90g, 0.0102 mol), sodium methoxide (Aldrich, 0.66g, 0.0122 mol) and anhydrous DMF (20 ml) was heated at 90°C for 45 min, cooled and slowly poured over a bed of ice (100g). The mixture was brought to room temperature and extracted with CH_2Cl_2 (3 x 75 ml). The combined extracts were washed with H_2O (2 x 100 ml), dried (K_2CO_3) and concentrated to a dark oil. The oil was dissolved in CH_2Cl_2 , applied to a silica gel column and eluted with CH_2Cl_2 . Concentration of the product eluates gave a yellow oil which on trituration with hexane (10 ml) produced a yellow solid, 2.35g (61%), m.p. 108-110°C. This material was used without further purification.

2,6-Dimethoxy-3-methyl-8-(4-phthalimido-1-methylbutylamino)-5-(3-trifluoromethylphenoxy)quinoline (138)

A stirred mixture of 136 (2.34g, 0.0062 mol) and 4-bromo-1-phthalimidopentane (BPP) (3.67g, 0.0124 mol) was heated at 110-115°C while Et_3N (2.5 ml) was slowly added during 15 min. After 2h at 120-125°C, more BPP (2.75g, 0.0093 mol) and Et_3N (1 ml during 5 min) were added and heating was continued for 6h. On cooling, the mixture was exhaustively extracted with Et_2O (200 ml), leaving behind a white residue. The combined extracts were washed with saturated NaCl solution (2 x 50 ml), dried (K_2CO_3) and concentrated to a yellow oil. The oil was dissolved in CHCl_3 , applied to a silica gel column and eluted with 10% EtOAc in hexane. The product eluates were combined and cooled (0-5°C) to produce 2.20 g (60%) of 138 as a pale yellow solid, m.p. 133-135°C. Eluates containing BPP and the product were combined, concentrated to an oil, reapplied to a silica gel column and eluted with 10% EtOAc in hexane to produce another crop (0.54g, 15%) of 138. The combined material was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-3-methyl-5-(3-trifluoromethylphenoxy)quinoline Fumarate (140)

A stirred solution of 138 (2.64g, 0.0044 mol), CHCl_3 (20 ml), EtOH (40 ml) and 95% NH_2NH_2 (2 ml) was heated under reflux for 2h, allowed to cool and filtered. The white residue was washed with CHCl_3 and the combined filtrate and washings were concentrated to a yellow oil. The oil was

dissolved in Et₂O (100 ml) and the solution was washed with 20% KOH solution (2 x 30 ml), saturated NaCl solution (2 x 50 ml), dried (K₂CO₃) and concentrated to a yellow oil (2.06g, 100%). The oil was dissolved in CH₃CN (15 ml) and slowly treated with a hot solution of fumaric acid (0.52g) in CH₃OH-CH₃CN (1:4 v/v, 25 ml). The precipitated yellow solid was allowed to settle overnight, separated by decantation, washed with CH₃CN (2 x 25 ml), recrystallized from CH₃CN and vacuum dried (1.4mm, 20°C, 2h) to give 1.68 g (65%) of 140 as a beige solid, m.p. 157-158°C (decomp.). The crystallization mother liquor was concentrated to give another batch of solid which on recrystallization produced 0.13g (5%) of 160, m.p. 157-158°C (decomp.).

Anal. Calcd. for C₂₈H₃₂F₃N₃O₇: C, 58.02; H, 5.57; N, 7.25

Found: C, 57.59; H, 5.73; N, 7.00

5-(4-Fluorophenoxy)-6-methoxy-3-methyl-8-nitroquinoline (125)

A mixture of 12.1g (0.11 mol) of 4-fluorophenol (123) (Aldrich) and 6.2g (0.09 mol) of KOH in 27 ml of 2-ethoxyethanol was heated in a 90° oil bath for 1h and treated with 19.0g (0.075 mol) of 5-chloro-6-methoxy-3-methyl-8-nitroquinoline (121), in 2-ethoxyethanol (22 ml), in a single portion. The mixture was heated at 120°C (oil bath temp.) for 2h, cooled with ice-water and filtered. The resulting tan solid was washed successively with H₂O, cold EtOH and pet ether (20-40°) and air dried. Crystallization from MeOH gave 14.2g (58%) of 125 as yellow crystals. The MeOH-insoluble portion was the starting material, 121 (5g). Recrystallization of 125 from MeOH provided the analytical sample as yellow crystals, m.p. 177-179°C.

Anal. Calcd. for C₁₇H₁₃FN₂O₄: C, 62.19; H, 3.99; N, 8.53

Found: C, 62.08; H, 4.26; N, 8.40

8-Amino-5-(4-fluorophenoxy)-6-methoxy-3-methylquinoline (127)

A mixture of 14g (0.04 mol) of 125 and 25g of Fe-filings in 300 ml of H₂O containing 15 ml of Bu₂O and 5 ml of AcOH was heated in a 100°C oil bath for 7h, allowed to cool, and filtered. The filtrate and residue were extracted with Et₂O and the combined extracts (500 ml) were washed with saturated NaCl, dried (K₂CO₃), treated with Darco G-60 and filtered.

Concentration of the filtrate yielded greenish gray crystals which on washing with pet ether (35-60°C) gave 11.8g (93%) of 127 which was used without further purification. Recrystallization of an aliquot from cyclohexane provided the analytical sample as yellow crystals, m.p. 140-141°C.

Anal. Calcd. for $C_{17}H_{15}FN_2O_2$: C, 68.45; H, 5.07; N, 9.39

Found: C, 68.33; H, 5.36; N, 9.48

5-(4-Fluorophenoxy)-6-methoxy-3-methyl-8-phthalimidoquinoline (129)

A mixture of 11.2g (0.037 mol) of 127 and 6.2g (0.042 mol) of phthalic anhydride in 140 ml of xylene was refluxed with a Dean-Stark trap for 20h (0.8 ml of H_2O collected) and allowed to cool to room temperature. The resulting mass was triturated with EtOH, filtered and washed with a small amount of EtOH to give a yellow solid, m.p. 177-180°C. Recrystallization from cyclohexane gave 13g (82%) of 129 as yellow needles, m.p. 180-181°C.

Anal. Calcd. for $C_{25}H_{17}FN_2O_4$: C, 70.09; H, 4.00; N, 6.54

Found: C, 70.25; H, 4.26; N, 6.54

5-(4-Fluorophenoxy)-6-methoxy-3-methyl-8-phthalimidoquinoline-1-oxide (131)

A solution of 12g (0.028 mol) of 129 in 100 ml of $CHCl_3$ was cooled in an ice-water bath and treated with 11.2g (0.055 mol) of m-chloroperoxybenzoic acid (Eastman, 85%) suspended in 60 ml of $CHCl_3$, during 0.5 h. The yellow mixture was stirred at room temperature for 24h and the resulting red solution was washed with 5% $NaHSO_3$ (70 ml), saturated $NaHCO_3$ (75 ml x 3), and saturated $NaCl$ (75 ml x 3), dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the red syrup was triturated with EtOH. The resulting solid was washed with pet ether (20-40°) to give 11.4g (83%) of 131 as a tan solid, m.p. 150-154°C (dec.), which was used without further purification.

2-Chloro-5-(4-fluorophenoxy)-6-methoxy-3-methyl-8-phthalimidoquinoline (133)

To a solution of 131 (10.4g, 0.021 mol) in $CHCl_3$ (200 ml) was added dropwise, over a period of 1h, phosphorus oxychloride (Aldrich, 35g, 0.23 mol, 21 ml). The orange solution was heated under reflux for 2h, cooled and slowly

poured over a bed of ice (300g). The stirred mixture was treated very slowly with 20% NaOH solution to pH 10. The organic layer was separated and the aqueous layer was extracted with CHCl_3 (3 x 100 ml). The combined organic layers were washed with saturated NaHCO_3 solution (3 x 100 ml) and H_2O (3 x 100 ml) and dried (MgSO_4). Solvent evaporation and trituration with EtOH gave 8.8g (95%) of 133 as an off-white solid, m.p. 221-233°C. Crystallization of an aliquot from AcOEt gave the analytical sample as white crystals, m.p. 223-224°C.

Anal. Calcd. for $\text{C}_{25}\text{H}_{16}\text{ClFN}_2\text{O}_4$: C, 64.87; H, 3.48; N, 6.05.

Found: C, 64.57; H, 3.61; N, 5.95.

8-Amino-2-Chloro-5-(4-fluorophenoxy)-6-methoxy-3-methylquinoline (135)

A mixture of 133 (8.7g, 0.018 mol), CHCl_3 (100 ml), EtOH (400 ml) and 95% NH_2NH_2 (Eastman, 20 ml) was heated under reflux for 4.5h, allowed to cool and filtered. The white residue was washed with EtOH. The combined filtrate and washings were evaporated to an orange oil. The oil was treated with 30% KOH solution (100 ml) and the mixture was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with saturated NaCl solution (2 x 75 ml) and dried (K_2CO_3). Solvent evaporation gave 135 as green-yellow solid, 6.3g (100%), m.p. 135-140°C. Crystallization of an aliquot from cyclohexane gave the analytical sample as yellow crystals, m.p. 138-139.5°C.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{ClFN}_2\text{O}_2$: C, 61.36; H, 4.24; N, 8.42.

Found: C, 61.17; H, 4.41; N, 8.36.

8-Amino-2,6-dimethoxy-5-(4-fluorophenoxy)-3-methylquinoline (137)

A stirred mixture of 135 (5.8g, 0.017 mol), sodium methoxide (Aldrich, 1.1g, 0.02 mol) and anhydrous DMF (40 ml) was slowly brought to 80°C over a period of 1h, kept at 80°C for 1h, cooled and slowly poured over a bed of ice (300g). The mixture was brought to room temperature, filtered and the residue was taken into CH_2Cl_2 (250 ml). The organic layer was washed with H_2O (2 x 100 ml), dried (K_2CO_3) and concentrated to a brown oil. The oil was extracted with boiling cyclohexane and cooled to give 137 as yellow crystals, 4.0g (71.5%), m.p. 95-105°C. This material was used without further purification.

2,6-Dimethoxy-5-(4-fluorophenoxy)-3-methyl-8-(1-methyl-4-phthalimidobutyl amino)quinoline (139)

A stirred mixture of 137 (3.9g, 0.011 mol) and 4-bromo-1-phthalimido-pentane (BPP) (5.0g, 0.017 mol) was heated at 120°C while Et₃N (2.5 ml) was slowly added during 30 min. After 2h at 120°C, more BPP (5.0g) and Et₃N (2.5 ml) were added and heating was continued for 2h. This procedure was repeated one more time. On cooling, the mixture was extracted with Et₂O (500 ml). The extract was washed with saturated NaCl solution (3 x 75 ml), dried (K₂CO₃) and concentrated to an orange oil. The oil was applied to a silica gel column and eluted with CHCl₃. Concentration of the product eluates gave 7.7g (93%) of 139 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-5-(4-fluorophenoxy)-3-methylquinoline Fumarate (141)

A stirred solution of 139 (7.7g, 0.014 mol), CHCl₃ (50 ml), EtOH (350 ml) and 95% NH₂NH₂ (20 ml) was heated under reflux for 5h, allowed to cool and filtered. The white residue was washed with EtOH and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in CH₂Cl₂ (250 ml), and the solution was washed with 30% KOH solution (3 x 50 ml), saturated NaCl solution (3 x 75 ml), dried (K₂CO₃) and concentrated to a viscous yellow oil (4.1g, 70%). The oil was dissolved in CH₃CN (70 ml) and slowly treated with a hot solution of fumaric acid (1.1g) in CH₃OH-CH₃CN (1:4 v/v, 150 ml). The resulting yellow solid was separated by decantation, washed with CH₃CN (3 x 20 ml), recrystallized from CH₃CN and vacuum dried (0.1 mm Hg, 60°C, 5h) to give 1.2g (16%) of 141 as beige solid, m.p. 158-160.5°C (decomp.).

Anal. Calcd for C₂₇H₃₂N₃O₇: C, 61.24; H, 6.09; N, 7.93.

Found: C, 61.08; H, 5.75; N, 7.70.

5-(n-Hexoxy)-6-methoxy-3-methyl-8-nitroquinoline (144)

To a mechanically stirred mixture of 142 (WRAIR, 12.00g, 0.051 mol), 1-bromohexane 143 (Aldrich 10.15g, 0.061 mol) and HMPA (50 ml), at 105-110°C, was added dropwise, over a period of 60 min, a solution of propylene oxide (24 ml) and Et₃N (8 ml). The mixture was heated at 105-110°C for another 5 h,

allowed to cool and extracted with a 1:1 mixture (200 ml) of pet ether (20-40°C) and Et_2O . The extract was washed with 10% NaOH solution (3 x 75 ml), H_2O (2 x 75 ml) and dried (K_2CO_3). On cooling (less than 0°C), yellow crystals appeared which were filtered, washed with pet ether (20-40°C) and air-dried to give 12.55 g (77%) of 144, m.p. 86-87°C (Lit.³, m.p. 84-85°C). The mother liquor and the washings were combined and concentrated to give another crop, 1.20g (7%) of 144, m.p. 85-86°C. The combined material was used without further purification.

8-Amino-5-(n-hexoxy)-6-methoxy-3-methylquinoline (145)

A mechanically stirred mixture of 144 (13.70g, 0.0043 mol), Fe-filings (14g), Bu_2O (50 ml), H_2O (100 ml) and HOAc (2 ml) was heated at 105-110°C for 4 h, allowed to cool and filtered. Both the filtrate and the residue were well extracted with CHCl_3 (300 ml). The combined extracts were washed with saturated NaCl solution, dried (K_2CO_3), concentrated to a small volume (ca. 40 ml), diluted with pet ether (20-40°C, 100 ml) and cooled (less than 0°C) overnight. The precipitated solid was filtered, washed with pet ether and air-dried to give 7.56 g (61%) of 145, as a yellow solid, m.p. 66-68°C (Lit.³, m.p. 61-63°C). The mother liquor and the washings were combined, evaporated to dryness and triturated with cold pet ether (20-40°C, 25 ml) to give another crop (2.92g, 24%) of 145 as a yellow solid, m.p. 65-66°C. The combined material was used without further purification.

5-(n-Hexoxy)-6-methoxy-3-methyl-8-phthalimidoquinoline (146)

A mixture of 145 (10.40g, 0.0361 mol) and phthalic anhydride (Aldrich, 5.88g, 0.0397 mol) in xylene (150 ml) was refluxed for 19h using a Dean-Stark water removal trap, cooled to -10° and diluted with pet ether (20-40°C, 75 ml). Vigorous scratching produced a solid which was allowed to settle (30 min), filtered, washed with pet ether and air-dried to give 12.02g (80%) of 146 as a grey-white solid, m.p. 150-151°C. This material was used without further purification.

5-(n-Hexoxy)-6-methoxy-3-methyl-8-phthalimidoquinoline-1-oxide (147)

To a mechanically stirred solution of 146 (11.5g, 0.0275 mol) in CHCl_3 (50 ml) at 0-5°C, was added, dropwise, over 45 minutes, m-chloroperoxybenzoic acid (Eastman, 85%, 11.2g, 0.55 mol) in CHCl_3 (100 ml). The reaction mixture was slowly brought to room temperature, stirred overnight, washed successively with 10% K_2CO_3 solution (3x75 ml), H_2O (1x50 ml) and dried (K_2CO_3). Solvent evaporation at room temperature gave an orange oil which on trituration with cold pet. ether (20-40°C, 25 ml) produced 147 (10.00g, 84%) as a crude yellow solid, mp 169-172°C. This material was used without further purification.

2-Chloro-5-(n-hexoxy)-6-methoxy-3-methyl-8-phthalimidoquinoline (148)

To a magnetically stirred solution of 147 (9.90g, 0.023 mol) in CHCl_3 (100 ml), at 0-5°C, was added, dropwise, over 20 min, phosphorus oxychloride (Aldrich, 34.9g, 0.23 mol, 21.24 ml). The reaction mixture was heated at reflux for 3h, cooled and slowly poured over a bed of ice (200g). The stirred mixture was treated very slowly with 20% NaOH (ca. 300 ml) to adjust the pH to 11-12. The organic layer was separated and the basic aqueous layer was extracted with CHCl_3 (3x100 ml). The combined organic layers were washed with H_2O (3x100 ml), saturated NaCl solution (2x75 ml) and dried (K_2CO_3). Solvent evaporation gave 148 as a yellow-brown solid, 8.8 g (85%), mp 194-196°C. This material was used without further purification.

8-Amino-2-chloro-5-(n-hexoxy)-6-methoxy-3-methylquinoline (149)

A mixture of 148, (5.88g, 0.013 mol), CHCl_3 (20 ml), EtOH (80 ml) and 95% NH_2NH_2 (Eastman, 2.5 ml) was heated under reflux for 3h, allowed to cool and filtered. The white residue was washed with CHCl_3 . The combined filtrate and washings were evaporated to a dark oil. The oil was dissolved in Et_2O (150 ml) and washed successively with 20% KOH solution (3x40 ml), H_2O (1x50 ml) and saturated NaCl solution (2x50 ml). Drying (K_2CO_3) and solvent evaporation gave a yellow oil which on trituration with pet. ether (20-40°C, 10 ml), at -20°C, produced 149 as a yellow solid, 3.60g (86%), mp 73-74°C. This material was used without further purification.

8-Amino-2,6-dimethoxy-5-(n-hexoxy)-3-methylquinoline (150)

A magnetically stirred mixture of 149 (3.00g, 0.0093 mol), sodium methoxide (Aldrich, 1.00 g, 0.019 mol) and anhydrous DMF (20 ml) was heated at 100-105°C for 2h, cooled and slowly poured over a bed of ice (100 g) with stirring. The mixture was brought to room temperature and extracted with CH_2Cl_2 (3x75 ml). The combined organic layers were washed with H_2O (3x50 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was dissolved in CHCl_3 (5 ml) and applied to a silica gel column eluting with 10% EtOAc in hexane. Concentration of the product eluates gave 150 as a yellow oil, 2.38g (80%). This material was used without further purification.

2,6-Dimethoxy-5-(n-hexoxy)-3-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (151)

A stirred mixture of 150 (2.35 g, 0.0074 mol) and 4-bromo-1-phthalimido-pentane (BPP)(4.4g, 0.148 mol) was heated at 115-120°C while Et_3N (2 ml) was slowly added during 30 min. After 3h at 115-120°C, more BPP (2.2g, 0.0074 mol) and Et_3N (1 ml during 10 min.) were added and heating was continued for 4h. On cooling, the mixture was exhaustively extracted with Et_2O (150 ml), leaving behind a white residue. The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a black oil which was dried under vacuum (1.2 mm Hg, 1h, 25°C). The oil was dissolved in CHCl_3 (5 ml), applied to a silica gel column and eluted with 10% EtOAc in hexane. Concentration of the product eluates gave 3.15g (80%) of 151 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-5-(n-hexoxy)-3-methylquinoline Fumarate (152)

A mechanically stirred mixture of 151 (3.10g, 0.006 mol), CHCl_3 (25 ml), EtOH (50 ml) and 95% NH_2NH_2 (Eastman, 3 ml) was heated under reflux for 2.5h, allowed to cool and filtered. The white residue was washed with CHCl_3 and the combined filtrate and washings were evaporated to a yellow oil. The oil was dissolved in Et_2O (100 ml) and the solution was washed with 20% KOH solution (3x30 ml), saturated NaCl solution (2x50 ml), dried (K_2CO_3) and concentrated to a thick yellow oil (1.76g, 75%). The oil was taken into CH_3CN (20 ml) and slowly treated with a hot solution of fumaric

acid (0.51g) in $\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 v/v, 30 ml). The precipitated yellow solid was collected, washed with CH_3CN and recrystallized from CH_3CN . Vacuum-drying (2.0 mm Hg, 4h, 25°C) gave 152 as a yellow solid, 1.72g (57%), mp $152-153^\circ\text{C}$ (decomp.).

Anal. Calcd. for $\text{C}_{27}\text{H}_{41}\text{N}_3\text{O}_7$: C, 62.41; H, 7.95; N, 8.09.

Found: C, 62.22; H, 8.20; N, 8.04.

6-Methoxy-4-methyl-8-nitro-5-phenoxyquinoline (155)

A solution of phenol (154) (11.1g, 0.12 mol), NaOH (4.8 g, 0.12 mol) and EtOH (150 ml) was heated under reflux for 2 h and the solvent was evaporated. To the white residue of sodium phenoxide was added 153 (WRAIR; 25.3g, 0.1 mol) in dioxane (150 ml) and the mixture was heated under reflux for 26 h, allowed to cool, diluted with Me_2CO (200 ml) and filtered. The black residue was washed with Me_2CO (100 ml) and the combined filtrate and washings were concentrated to a dark brown syrup which was extracted with CHCl_3 . The extract was washed with 20% KOH and NaCl solution, dried (Na_2SO_4) and passed through a silica gel column. Concentration gave 21.5g (69%) of 155 as yellow needles, m.p. $150-170^\circ\text{C}$, which was used without further purification (Lit.⁶, m.p. $169-171^\circ\text{C}$).

8-Amino-6-methoxy-4-methyl-5-phenoxyquinoline (157)

A stirred mixture of 155 (29.6g, 0.09 mol) Fe filings (40g), H_2O (300 ml), HOAc (5 ml) and Bu_2O (20 ml) was heated under reflux for 5 h, allowed to cool and filtered. The filtrate and the residue were extracted with Et_2O and the combined extracts were washed with saturated NaCl, dried (Na_2SO_4), treated with Darco G-60 and concentrated, in vacuo, to a yellow-green semi-solid. Trituration of this material with Et_2O gave 12.9g (51%) of 157 as a yellow solid, mp $151-156^\circ\text{C}$, which was used without further purification. Crystallization of an aliquot from hexane-benzene (9:1) (Darco G-60) provided the analytical sample as yellow needles, mp $155-157^\circ\text{C}$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84, H, 5.75; N, 9.99.

Found: C, 72.74; H, 5.88; N, 10.28

6-Methoxy-4-methyl-5-phenoxy-8-phthalimidoquinoline (159)

A mixture of 157 (18.8g, 0.067 mol), phthalic anhydride (10g, 0.067 mol) and xylene (300 ml) was refluxed for 24 h with water collection in a Dean-Stark trap. The mixture was allowed to cool and filtered to give 10.2 g of 159 as a gray solid which melted at 223.5-225°C after washing with xylene. This material was used without further purification. Crystallization of an aliquot from toluene gave the analytical sample as white platelets, mp 225-226.5°C.

Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.82.

Found: C, 73.38; H, 4.42; N, 6.82

6-Methoxy-4-methyl-5-phenoxy-8-phthalimidoquinoline-1-oxide (161)

To a stirred solution of 159 (13.8g, 0.03 mol) in $CHCl_3$ (200 ml), at 2-5°C, was added, during 0.5 h, a solution of 3-chloroperbenzoic acid (Aldrich, 80-85%; 7.3g, 0.03 mol) in $CHCl_3$ (100 ml). The mixture was stirred for 1 h, allowed to warm to room temperature overnight, washed with 5% $NaHSO_3$ (10 ml), dried (Na_2SO_4) and placed on a basic alumina column. Elution with $CHCl_3$ -MeOH (98:2) and concentration of the eluates gave 10g of crude 161. Extraction of this material with hot EtOH and concentration of the extract gave 6.5g (46%) of 161 as yellow crystals, mp 234-237°C. This material was used without further purification.

2-Chloro-6-methoxy-4-methyl-5-phenoxy-8-phthalimidoquinoline (163)

To a stirred solution of 161 (9.7g, 0.02 mol) in $CHCl_3$ (150 ml), at 0°C, was added dropwise, during 15 min, 20 ml (0.2 mol) of $POCl_3$. The solution was heated under reflux for 2 h, allowed to cool, poured over ice and basified with 20% NaOH. The aqueous layer was extracted with $CHCl_3$ and the combined extracts and organic layer were washed with saturated $NaHCO_3$ and H_2O , dried ($MgSO_4$) and concentrated to a yellow syrup. Crystallization from EtOH gave 8.6g (97%) of 163 as pale yellow needles, mp 247-249°C.

Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50; H, 3.85; N, 6.30

Found: C, 67.76; H, 3.88; N, 6.10

8-Amino-2-chloro-6-methoxy-4-methyl-5-phenoxyquinoline (165)

A stirred suspension of 163 (8.3g, 0.01 mol), 95% NH_2NH_2 (20 ml) and EtOH (500 ml) was refluxed for 3 h, allowed to cool and filtered. The white solid was washed with EtOH and CH_2Cl_2 and the combined filtrate and washings were concentrated. The resulting suspension was extracted with CH_2Cl_2 and the extract was washed with 20% NaOH, saturated NaCl solution, dried (K_2CO_3) and concentrated to yellow gum. Crystallization from hot toluene-hexane (1:1) gave 5.6g (99%) of 165 as yellow needles, mp 177.5-179°C.

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$: C, 64.87; H, 4.80; N, 8.90.

Found: C, 64.98; H, 4.86; N, 8.85

8-Amino-2,6-dimethoxy-4-methyl-5-phenoxyquinoline (167)

A solution of 165 (4g, 0.01 mol) in MeOH (50 ml) was added dropwise to a MeONa-MeOH solution (prepared from 0.8g of Na and 150 ml of MeOH) at room temperature and the resulting orange solution was refluxed for 40 h, cooled and concentrated to an orange syrup. The syrup was diluted with CH_2Cl_2 and chromatographed (SiO_2 ; CH_2Cl_2 : MeOH, 100:1). The yellow product eluate was collected, concentrated to a light brown oil and triturated with hexane to provide 2.3g (61%) of 167, m.p. 93-98°C. Crystallization from ethanol provided the analytical sample as pale tan crystals, m.p. 95-97°C.

Anal Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$: C, 69.66; H, 5.85; N, 9.03

Found: C, 70.12; H, 6.09; N, 9.01

2,6-Dimethoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-phenoxyquinoline (169)

A stirred mixture of 167 (2.3g, 0.007 mol) and BPP (5g, 0.016 mol) was heated at 125°C while Et_3N (3 ml) was added, dropwise, during 0.5 h. After 2 h, a second portion of BPP (5g) was added followed by slow introduction of more Et_3N (3 ml). Addition of BPP (5g) and Et_3N (3 ml) was repeated twice more at 2 h intervals. The mixture was allowed to cool and extracted with Et_2O (300 ml). Evaporation of the extract left an oil which was dissolved in a small amount of CH_2Cl_2 , placed on a silica gel column (250g) and eluted with CH_2Cl_2 . The early eluates contained unreacted BPP and were

discarded. Subsequent eluates were combined, concentrated and triturated with EtOH. The resulting solid (2g, m.p. 134-137°C) was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-4-methyl-5-phenoxyquinoline Fumarate (171)

A stirred solution of 169 (3.30g, 0.0063 mol), CHCl_3 (25 ml), EtOH (50 ml) and 95% NH_2NH_2 (4 ml) was heated under reflux for 1h, allowed to cool and filtered. The white residue was washed with CHCl_3 and the combined filtrate and washings were evaporated to an orange oil. The oil was taken into Et_2O (200 ml) and the solution was washed with 20% NaOH solution (3x30 ml), H_2O (1x20 ml), saturated NaCl solution (2x50 ml) and dried (K_2CO_3). Solvent evaporation gave a greenish yellow oil (2.47g) which was dissolved in CH_3CN (20 ml) and slowly treated with a hot solution of fumaric acid (0.73 g) in $\text{CH}_3\text{OH}-\text{CH}_3\text{CN}$ (1:4 v/v, 25 ml). The precipitated yellow solid was separated, washed with CH_3CN (2x20 ml), recrystallized from CH_3CN and vacuum dried (0.8 mm, 20°C, 2h) to give 171 as a yellow solid, 2.47 g (77%), mp 174-176°C (decomp.).

Anal. Calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_7$: C, 63.39; H, 6.50; N, 8.21

Found: C, 63.13; H, 6.64; N, 8.09

5-(4-Fluorophenoxy)-6-methoxy-4-methyl-8-nitroquinoline (156)

A mechanically stirred mixture of 123 (Aldrich, 12.16g, 0.108 mol), potassium hydroxide (6.18g, 0.091 mol) and 2-ethoxyethanol (27 ml) was heated at 90°C for 1 h. 153 (WRAIR, 19.00g, 0.075 mol) in 2-ethoxyethanol (22 ml) was added rapidly and the mixture was heated at 120°C for 1 h followed by cooling at 0°C for 1 h. The precipitate was filtered, washed with cold EtOH and suspended in H_2O (100 ml). After stirring for 5 min, the mixture was filtered and the residue was washed with cold EtOH followed by pet ether (20-40°C). Air-drying gave 19.92 g (81%) of 156 as a yellow solid, m.p. 179-181°C (Lit.⁷, m.p. 183.5-185°C). This material was used without further purification.

8-Amino-5-(4-fluorophenoxy)-6-methoxy-4-methylquinoline (158)

A mechanically stirred mixture of 156 (19.90g, 0.067 mol), Fe filings (20g), Bu₂O (75 ml), H₂O (150 ml) and HOAc (2 ml) was heated at 110-115°C for 5 h, allowed to cool and filtered. The filtrate was extracted with Et₂O (200 ml) and the combined extracts were washed with saturated NaCl solution (2 x 75 ml), dried (MgSO₄) and concentrated to a small volume. The precipitated solid was filtered, washed with hexane and air-dried to give 2.71 g (15%) of 158 as a yellow solid, m.p. 147-148°C (Lit.⁷, m.p. 144.5-145.5°C). The residue from the reaction mixture was stirred with CHCl₃ (250 ml) for 5 min and filtered. The filtrate was washed with saturated NaCl solution (2 x 75 ml), dried (K₂CO₃), treated with Darco and evaporated to give another crop of 158, m.p. 147-148°C (12.33g, 68%). The combined material was used without further purification.

5-(4-Fluorophenoxy)-6-methoxy-4-methyl-8-phthalimidoquinoline (160)

A mixture of 158 (15.00g, 0.05 mol) and phthalic anhydride (Aldrich; 8.18g, 0.055 mol) in xylene (200 ml) was refluxed for 20 h using a Dean-Stark water removal trap. The reaction mixture was cooled (0-5°C) for 1 h and filtered. The residue was washed with pet ether (20-40°C) and air-dried to yield 17.30g (80%) of a greyish white solid, m.p. 214-215°C (Lit.⁸ m.p. 213-215°C). The mother liquor was diluted with pet ether (20-40°, 100 ml) and cooled (0°C) overnight. The precipitated solid was filtered, washed with pet ether (20-40°C) and air-dried to give another crop (2.17 g, 10%) of 160 as a greyish white solid m.p. 213-214°C. The combined material was used without further purification.

5-(4-Fluorophenoxy)-6-methoxy-4-methyl-8-phthalimidoquinoline-1-oxide (162)

To a mechanically stirred solution of 160 (17.00g, 0.04 mol) in CHCl₃ (100 ml) at 0°C, was added, dropwise over 15 min, m-chloroperbenzoic acid (Aldrich, 85%; 16.10g, 0.08 mol) in CHCl₃ (160 ml). The mixture was slowly brought to room temperature, stirred for an additional 16 h, washed with 10% K₂CO₃ solution (3 x 100 ml), H₂O (2 x 100 ml) and dried (K₂CO₃). Solvent evaporation gave a yellow mass which on trituration with cold EtOH (20 ml), yielded a yellow solid. It was filtered, washed with cold EtOH, pet

ether (20-40°C) and air-dried to give 17.09g (97%) of 162 as a pale yellow solid, m.p. 223-225°C (decomp.)(Lit.⁸, m.p. 241-243°C). This material was used without further purification.

2-Chloro-5-(4-fluorophenoxy)-6-methoxy-4-methyl-8-phthalimidoquinoline (164)

To a cooled (0-5°C) solution of 162 (17.00g, 0.038 mol) in CHCl_3 (225 ml), was added dropwise, over a period of 15 min, phosphorus oxychloride (Aldrich, 58.64g, 0.38 mol, 35.7 ml). The orange solution was heated under reflux for 2.5 h, cooled and slowly poured over a bed of ice (200g). The stirred mixture was treated very slowly with 20% KOH solution (ca. 650 ml) to adjust the pH to 10-11. The organic layer was separated and the aqueous layer was extracted with CHCl_3 (2 x 200 ml). Combined organic layers were washed with H_2O (2 x 250 ml) and dried (MgSO_4). Solvent evaporation and air drying gave 15.00g (85%) of 164 as a pale yellow solid, m.p. 228-230°C (decomp.) (Lit.⁸, m.p. 234-236°C). This material was used without further purification.

8-Amino-2-chloro-5-(4-fluorophenoxy)-6-methoxy-4-methylquinoline (166)

A mixture of 164 (15.00g, 0.0324 mol), CHCl_3 (30 ml), EtOH (120 ml) and 95% NH_2NH_2 (Eastman, 5 ml) was heated under reflux for 3 h, allowed to cool and filtered. The white residue was washed with EtOH and CHCl_3 and the combined filtrate and washings were evaporated to an orange oil. The oil was treated with 20% KOH solution (60 ml) and the mixture was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with saturated NaCl solution (2 x 75 ml) and dried (K_2CO_3). Solvent evaporation gave a greenish-yellow solid, 9.29g (86%), m.p. 145-146°C (Lit.⁸, m.p. 150-152°C). This material was used without further purification.

8-Amino-2,6-dimethoxy-5-(4-fluorophenoxy)-4-methylquinoline (168)

A stirred mixture of 166 (3.81g, 0.0115 mol), sodium methoxide (Aldrich, 0.90g, 0.017 mol) and anhydrous DMF (25 ml) was slowly brought to 80°C over a period of 45 min, kept at 80°C for another 15 min, cooled and slowly poured over a bed of ice (150g). The mixture was brought to room temperature, filtered and the residue was taken into CH_2Cl_2 (150 ml). The organic

layer was washed with H_2O (2 x 50 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was applied to a silica gel column and eluted with CH_2Cl_2 . Concentration of the product eluates gave a yellow oil which on trituration with hexane (5 ml) produced a yellow solid, 2.37g (64%), m.p. 91-92°C (Lit.⁸, m.p. 93-95°C). This material was used without further purification.

2,6-Dimethoxy-5-(4-fluorophenoxy)-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (170)

A stirred mixture of 168 (3.50 g, 0.011 mol) and 4-bromo-1-phthalimido-pentane (BPP) (6.50g, 0.022 mol) was heated at 105-110°C while Et_3N (3 ml) was slowly added during 15 min. After 4 h at 120-125°C, more BPP (4.00g, 0.0135 mol) and Et_3N (1.5 ml during 10 min) were added and heating was continued for 5 h. On cooling, the mixture was exhaustively extracted with Et_2O (150 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (K_2CO_3) and concentrated to an orange oil. The oil was applied to a silica gel column and eluted with $CHCl_3$. Concentration of the product eluates gave 4.1 g (71%) of 170 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-5-(4-fluorophenoxy)-4-methyl-quinoline Fumarate (172)

A stirred solution of 170 (1.79g, 0.0033 mol), $CHCl_3$ (15 ml), $EtOH$ (30 ml) and 95% NH_2NH_2 (1.5 ml) was heated under reflux for 1h, allowed to cool and filtered. The white residue was washed with $EtOH$ and the combined filtrate and washings were evaporated to a yellow oil. The oil was dissolved in Et_2O (100 ml) and the solution was washed with 20% KOH solution (2 x 25 ml), saturated NaCl solution (2 x 25 ml), dried (K_2CO_3) and concentrated to a yellow oil (1.36g, 99%). The oil was dissolved in CH_3CN (10 ml) and slowly treated with a hot solution of fumaric acid (0.39g) in CH_3OH-CH_3CN (1:4 v/v, 15 ml). The resulting yellow solid was collected, washed with CH_3CN (2 x 20 ml), recrystallized from CH_3CN and vacuum dried (1 mm, 20°C, 6h) to give 1.27g (72%) of 172 as a yellow solid, m.p. 167-169°C (decomp.).

Anal Calcd. for $C_{27}H_{32}FN_3O_7$: C, 61.24; H, 6.09; N, 7.94

Found: C, 61.04; H, 6.27; N, 8.12

6-Methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-phthalimidoquinoline (173)

A mixture of 58 (15.00g, 0.0412 mol), phthalic anhydride (Aldrich, 6.70g, 0.0453 mol) and xylene (150 ml) was refluxed, using a Dean-Stark trap, for 3.5 h, cooled (0-5°C) for 0.5 h and filtered. The residue was washed with pet. ether (20-40°C, 125 ml) and air-dried to give 15.70 g (77%) of 173 as a grey-white solid, mp 148-149°C. The combined filtrate and washings, on cooling (0°C) overnight, gave another crop (2.72g 13%) of 173, mp 147-148°C. A small portion of the combined material was recrystallized from EtOAc (Darco) to give the analytical sample, mp 149-150°C.

Anal. Calcd. for $C_{31}H_{30}N_2O_4$: C, 75.28; H, 6.11; N, 5.67

Found: C, 75.13; H, 6.48; N, 5.61

6-Methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-phthalimidoquinoline-1-oxide (174)

To a mechanically stirred solution of 173 (17.40g, 0.0352 mol) in $CHCl_3$ (70 ml), at 0-5°C, was added, dropwise, over 30 min, *m*-chloroperoxybenzoic acid (Eastman, 85%, 14.29g, 0.0704 mol) in $CHCl_3$ (80 ml). The mixture was slowly brought to room temperature, stirred for an additional 24 h, washed with 10% K_2CO_3 solution (3x75ml), H_2O (1x50 ml), 10% $NaHSO_3$ solution (2x50 ml), saturated NaCl solution (1x50 ml) and dried (K_2CO_3). Solvent evaporation at room temperature produced a dark yellow oil which on trituration with cold EtOH (0-5°C, 25 ml) gave a yellow solid. This material was filtered, washed with pet. ether (20-40°C, 25 ml) and air-dried to give 10.88g (61%) of 174 as a crude yellow solid, mp 164-166°C. This material was used without further purification.

2-Chloro-6-methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-phthalimidoquinoline (175)

To a cooled (0-5°C) solution of 174 (10.80g, 0.021 mol) in $CHCl_3$ (100 ml), was added dropwise, over a period of 20 min, phosphorus oxychloride (Aldrich, 32.44g, 0.21 mol, 19.72 ml). The mixture was heated under reflux for 1.5h, cooled (0-5°C) and slowly poured over a bed of ice (200g). The stirred mixture was treated very slowly with 20% NaOH solution (ca. 250 ml) to adjust the pH to 10-11. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2x100 ml). The combined organic layers were

washed with H_2O (2x100 ml), saturated NaCl solution (2x100 ml) and dried (K_2CO_3). Solvent evaporation gave a thick yellow oil which on trituration with cold Et_2O (20 ml) gave a yellow solid. The solid was filtered, washed with pet. ether (20-40°C, 25 ml) and air-dried to give 9.10 g (81%) of 175 as a crude yellow solid, mp 118-120°C. This material was used without further purification.

8-Amino-2-chloro-6-methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxylquinoline (176)

A mixture of 175 (9.00g, 0.017 mol), $CHCl_3$ (40 ml), EtOH (60 ml) and 95% NH_2NH_2 (Eastman, 4 ml) was heated under reflux for 2h, cooled and filtered. The white residue was washed with $CHCl_3$ and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in CH_2Cl_2 (200 ml) and washed with 20% NaOH solution (2x50 ml). The combined basic solution was re-extracted with CH_2Cl_2 (2x75 ml) and the combined organic layers were washed with H_2O (1x50 ml), sat. NaCl solution (2x75 ml) and dried (K_2CO_3). Solvent evaporation gave a dark oil which on trituration with pet. ether (20-40°C, 15 ml) at -20°C produced 176 as a crude greenish yellow solid, 6.30g (93%). This material was used without further treatment in the next step.

8-Amino-2,6-dimethoxy-4-methyl-5-[5-(4-methylphenyl)pentoxylquinoline (177)

A mixture of 176 (5.18g, 0.013 mol), sodium methoxide (Aldrich, 1.05g, 0.0194 mol) and anhydrous DMF (20 ml) was heated at 90°C. More sodium methoxide (a total of 2.03g, 0.038 mol) was added at 2h intervals while heating was continued for 8h. After cooling, the dark mixture was slowly poured over a bed of ice (100g) with stirring. The precipitated semi-solid was separated, washed with H_2O and dissolved in CH_2Cl_2 (100 ml). The organic layer was washed with H_2O (2x100 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was dissolved in $CHCl_3$ (5 ml), applied to a silica gel column and eluted with $CHCl_3$. Concentration of the product eluates gave an oil which on cooling (-20°C) and scratching produced 177 as a greenish-yellow solid, 2.35g (46%), mp 46-48°C. This material was used without further purification.

2,6-Dimethoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-(4-phthalimido-1-methylbutylamino)quinoline (178)

A stirred mixture of 177 (2.30g, 0.0058 mol) and 4-bromo-1-phthalimido-pentane (BPP) (3.46g, 0.0116 mol) was heated at 110-115°C while Et₃N (2 ml) was slowly added during 10 min. After 2h at 110-115°C, more BPP (2.22 g, 0.0074 mol) and Et₃N (1ml during 5 min) were added and heating was continued for another 2h followed by addition of more BPP (1.00 g, 0.0034 mol) and Et₃N (1 ml during 5 min). After additional heating for 3h, the mixture was cooled and exhaustively extracted with Et₂O (100 ml), leaving behind a white residue. The combined organic layers were washed with saturated NaCl solution (2x50 ml), dried (K₂CO₃), concentrated to a black oil and vacuum-dried (1mm, 20°C, 1h). The oil was dissolved in CHCl₃ (5 ml), applied to a silica gel column and eluted with 5% EtOAc-hexane initially, followed by 10% EtOAc-hexane. Product eluates were combined and solvent evaporated to give 178 as a yellow oil, 2.85g (80%). This material was used without further purification.

8-(4-Amino-1-methylbutylamino)-2,6-dimethoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]quinoline Fumarate (179)

A solution of 178 (2.84g, 0.0047 mol), CHCl₃ (30 ml), EtOH (60 ml) and 95% NH₂NH₂ (Eastman, 3 ml) was heated under reflux for 1.5 h, cooled and filtered. The white residue was washed with CHCl₃ (50 ml) and the combined filtrate and the washings were concentrated to an orange oil. The oil was dissolved in Et₂O (100 ml) and the solution was washed with 20% NaOH solution (3x30 ml), H₂O (1x50 ml), saturated NaCl solution (1x50 ml) and dried (MgSO₄). Solvent evaporation gave a greenish-yellow oil (2.10 g) which was dissolved in CH₃CN (25 ml) and slowly treated with a hot solution of fumaric acid (0.51g) in CH₃OH-CH₃CN (1:4v/v, 20 ml). The precipitated yellow solid was allowed to settle overnight, filtered, and washed with CH₃CN (30 ml). The solid was recrystallized from CH₃CN and vacuum-dried (1 mm, 20°C, 3h) to give 179 as a yellow solid, 2.0g (72%), mp 149-151°C (decomp.).

Anal. Calcd. for C₃₃H₄₅N₃O₇: C, 66.53; H, 7.61; N, 7.05

Found: C, 66.65; H, 7.83; N, 7.00

CONCLUSIONS

1. In earlier work, we prepared a series of 5-[ω -(phenyl)alkoxy]primaquines which combined low acute toxicity with excellent blood schizontocidal and radical curative activity. During the present contract period we have raised the blood schizontocidal activity of this series even higher by attaching various substituents to the terminal phenyl group. Although blood data are incomplete and radical data are unavailable, the most promising compounds, to date, seem to be the 2-CF₃ and 4-CH₃ derivatives (BL 54967 and BL 55820 in Table III).
2. We have also discovered that a terminal phenyl can be replaced by a heterocycle, like 2-thienyl (BM 01667 in Table VI), with almost no change in blood schizontocidal therapeutic index. Radical data are unavailable.
3. Although screening data are too sparse for SAR correlation, it would seem that addition of a third substituent to position 2 of a 3,5- or 4,5-disubstituted primaquine lengthens the synthesis considerably without therapeutic benefit (Tables VII - X).

Final judgment of the compounds prepared during this contract period must await the completion of blood schizontocidal screening and the arrival of radical curative data.

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