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SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS, TREATMENT AND PROPHYLAXIS

ANNUAL REPORT

By

A. Markovac
D.J. Dagli
A.B. Ash
C.L. Stevens

February 1988

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

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FIELD	GROUP	SUB-GROUP
07	03	
06	01	

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2,2-Di(or tri)aryl-1-dimethylamino(or amino)methyl-ethylenes. Modified 8-aminohexylamino-6-methoxy-4-methylquinolines.

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The program is directed at the preparation of improved antileishmanial and antitrypanosomal drugs. During the past year 14 target compounds were submitted for testing against L. donovani, T. rhodesiense and T. cruzi. Two candidate antileishmanials are modified 8-aminoquinolines. Twelve compounds were directed primarily against T. cruzi., all modified Wellcome Research Laboratories structures. These included: four 2,2-diaryldimethyl (or dihydro)aminomethylethylenes, one 2,2'-diarylaminomethyl-2-hydroxyethane, two 2,2'-diarylamidoximinoethylenes, four 1,2,2-triaryldimethyl (or dihydro)aminomethylethylenes and one 1,1,2-triaryl-aminomethyl-2-hydroxyethane.

Keywords: methylenes; ethylenes; ethanes

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FOREWORD

The work described herein was performed under Contract No. DAMD17-84-C-4210 for the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Walter Reed Army Medical Center. This Progress Report covers the 12-month period ending August 31, 1987.

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

ACKNOWLEDGMENT

The work was performed under the general direction of Dr. C.L. Stevens, Principal Investigator. Dr. A. Markovac served as Associate Investigator and Dr. D.J. Dagli as Senior Research Chemists with Dr. A.B. Ash as Program Manager.

The timely advice and assistance of Dr. Robert R. Engle, the COTR, is gratefully acknowledged.

TARGET COMPOUNDS SUBMITTED

THREE YEARS: 9/01/84 TO 8/31/87

CONTRACT NO. DAMD17-84-C-4210

SNL NO.	ASI CODE NO.	BOTTLE NO.	WALTER REED NO.	EXPERIMENTAL ANNUAL REPORT PAGE NO.
		First Year (9/1/84 - 8/31/85)		
109	DJD-06-44	BK99121	253904	29
110	DJD-06-59A	BL00432	254019	31
111	DJD-06-81	BL03808	254238	34
112	DJD-06-99	BL05571	254391	36
113	AM-04-12	BL07691	254588	37
114	DJD-06-126	BL07682	254589	38
115	DJD-06-134	BL08401	254642	40
116	DJD-06-152	BL09533	254731	42
117	AM-04-20	BL09524	254729	43
		Second Year (2/1/85 - 8/31/86)		
118	KW-08-188	BL12503	254959	31
119	KW-08-211B	BK12790	254985	31
120	DJD-06-210	BL18247	255426	33
121	AM-04-28	BK40799	255566	36
122	DJD-06-268	BL19333	255593	37
123	DJD-06-270	BL19324	255594	37
124	RK-04-154	BL19315	255595	42
125	DJD-06-288	BL20336	255664	43
126	DJD-06-293	BL20345	255665	43
127	DJD-06-295	BL20354	255662	46
128	DJD-07-27	BL21780	255784	47
129	DJD-07-32	BL22205	255810	50
130	DJD-07-44	BL24003	255931	51

TARGET COMPOUNDS SUBMITTED (Continued)

SNL NO.	ASI CODE NO.	BOTTLE NO.	WALTER REED NO.	EXPERIMENTAL ANNUAL REPORT PAGE NO.
		Third Year (9/1/86 to 8/31/87)*		
131	DJD-07-51	BL24012	255934	41
132	DJD-07-65	BL27862	256122	43
133	DJD-07-66	BL27853	256123	43
134	DJD-07-89	BL31768	256541	46
135	DJD-07-94	BL31777	256539	46
136	DJD-07-97	BL31759	256540	46
137	DJD-07-107	BL33137	256599	49
138	DJD-07-107A	BL33146	256600	49
139	DJD-07-117	BL35828	256782	51
140	DJD-07-118	BL35837	256780	53
141	DJD-07-123	BL35846	256781	53
142	DJD-07-128	BL35855	256779	53
143	DJD-07-153	BL45066	257305	57
144	DJD-07-161	BL48405	257566	59

*This Report

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SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS

TREATMENT AND PROPHYLAXIS

1. INTRODUCTION AND BACKGROUND

Work performed under prior contract (1) will be reviewed first in general terms, followed by the approach taken under the current contract (2,3). Both contracts were targeted toward the two title parasites.

1.1 Prior Contract Work

Under the six and one-half year prior contract (1), a total of 56 target candidate drugs were submitted in several structural categories: 15 analogs of active leishmaniacide WR 6,026, 8-[(6-diethylaminohexyl)amino]-6-methoxy-4-methylquinoline, three 7-aminoquinolines, two 3-aminoquinolines, one 4-amino-2,6-substituted-pyridine, 20 aryl/heterocyclic bis(amidoximes) and bis(amidines), four clinical bis(amidines) together with the four bis(amidoxime) analogs of the clinical drugs, and HOE 668 plus six structural modifications.

Promising new leads against L. donovani were obtained in the 8-aminoquinolines series by some 15 modifications of the basic WR 6,026 structure, largely by incorporating additional methoxy groups in the 2- and/or 5-position, as well as various side chain modifications of WR 6,026. Significant reductions in toxicity were achieved in a number of instances while retaining a high degree of activity; none were as active as WR 6,026, however.

Another successful result was the acquisition of new candidate trypanosomiacides with a high degree of activity against T. rhodesiense. The drugs are effective administered both PO as well as SC and possess excellent toxicity characteristics. For example, 2,6-bis(4-amidoximinophenyl)-4-methylpyridine, WR 248,936, is active at 0.83 mg/kg, both PO and SC, with a minimum toxic dose of 424 mg/kg or higher, respectively. On the other hand, no compounds active against the refractory T. cruzi, "Chagas disease", indigenous to South and Central America, were found and more attention was directed to this problem under the current contract.

1.2 Work Under the Current Contract

Work under the current contract, initiated September 1, 1984, represents a continuation and extension of work performed under the prior contract. The structures of all 36 compounds prepared to-date under the three-year current contract are shown in Figure 1.

In the first year (2), nine compounds were prepared. Seven of these represented a continuation of prior phases of work: four modifications of the 8-aminoquinoline leishmaniacide, WR 6,026, two new bis(amidoximes) and one new bis(amidine) as candidate tryanosomiacides, and one bis(pyridylhydrazide) as a leishmaniacide (4, Peters, 1981).

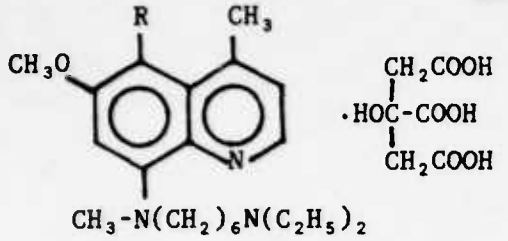
Also in the first year, a new effort was initiated against forms of the refractory Trypanosoma cruzi. Thus McCabe and co-workers at Stanford University (5, 1983) stated that "Chagas disease, caused by infections of T. cruzi, affects millions of people in Central and South America and, at present, no chemotherapeutic agent has been accepted as completely effective for its treatment." Our literature search revealed a 1982 paper (6a) [and related patents (6b,6c)] by a group of workers at Wellcome Research Laboratories in England who described a series of 1,1-bis(aryl)-3-dimethylaminomethylethylenes which were active orally in mice against a Peruvian strain of T. cruzi. As a result, the first example of new congeners of the Wellcome compounds were prepared in the first year.

In the second year 11 of the 13 compounds were Wellcome type compounds and the other two candidate drugs were candidate leishmaniacides (new 8-aminoquinolines).

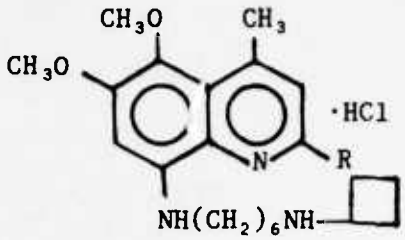
In the third year, the first 12 of the 14 submissions were related to the Wellcome structures. No additional examples of these are planned and the balance of the contract work will be targeted against strains of leishmaniasis, including the two 8-aminoquinoline submitted at the end of the current (third) year.

FIGURE NO. 1

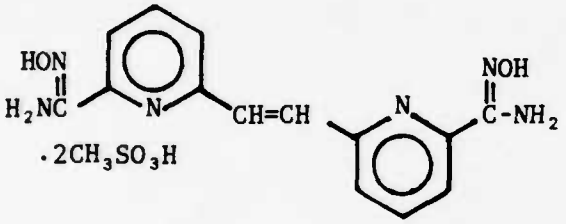
COMPOUNDS PREPARED UNDER THE CURRENT CONTRACT
(1 September 1984 - 31 August 1985)
Year No. 1 (9)



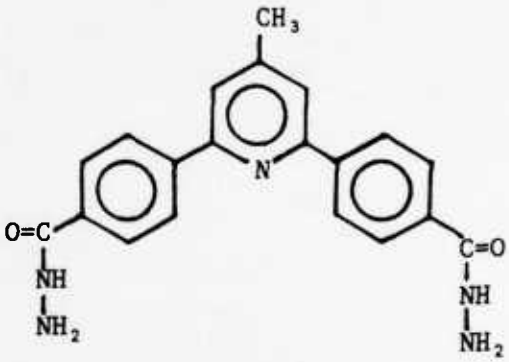
SNL-109, R = H, 10 g, DJD-06-44, WR 253904
SNL-111, R = OCH_3, 12 g, DJD-06-81, WR 254238



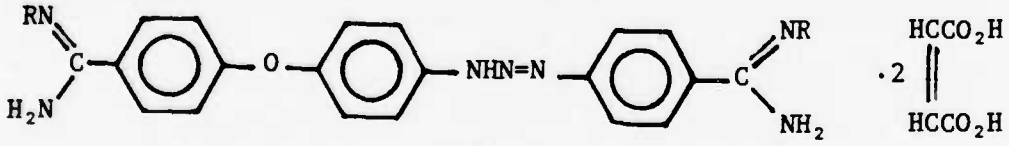
SNL-112, R = H, 11 g, DJD-06-99, WR 254391
SNL-114, R = OCH_3, DJD-06-126, WR 254589



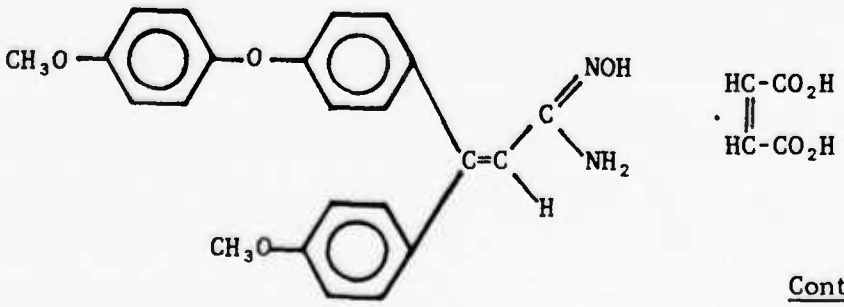
SNL-110, 9 g, DJD-06-59A, WR 254019



SNL-113, 7 g, AM-04-12, WR 254588



SNL-115, R = OH, 10 g, DJD-06-134, WR 254642
SNL-116, R = H, 4.5 g, DJD-06-152, WR 254731



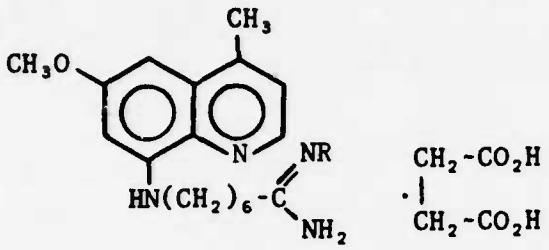
Continued

SNL-117, 4.5 g, AM-04-20, WR 254729

FIGURE 1, Continued

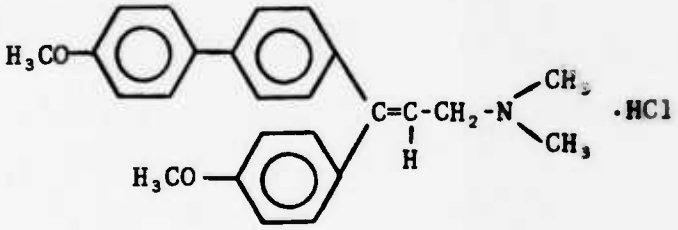
(1 September 1985 to 30 August 1986)

Year No. 2 (Y3)



SNL-118, R = OH, 5 g, KW-08-118, WR 254959

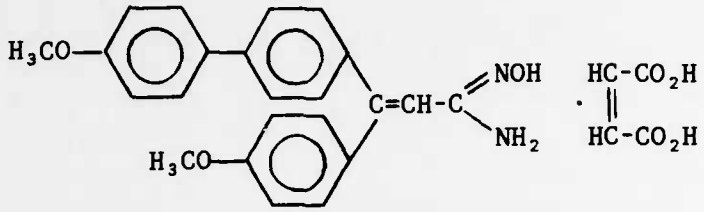
SNL-119, R = H, 6 g, KW-08-211B, WR 254985



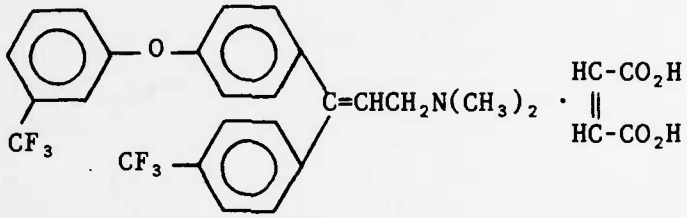
SNL-120, 4.5 g, DJD-06-210, WR 255426

FIGURE 1, Continued

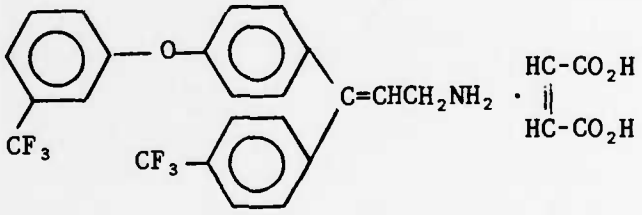
Year No. 2 (Continued)



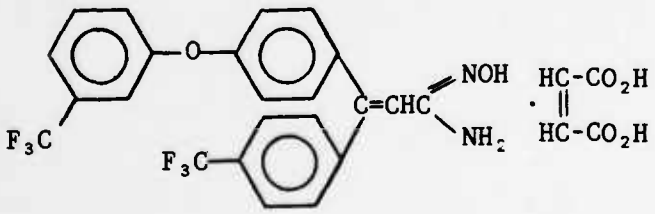
SNL-121, 5 g, AM-04-28, WR 255566



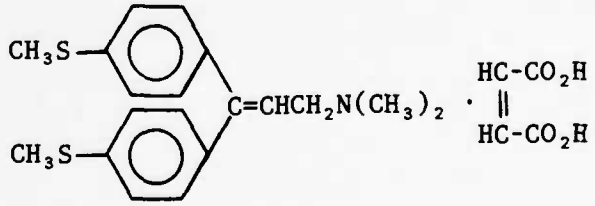
SNL-122, 7.5 g, DJD-06-268, WR 255593



SNL-123, 10 g, DJD-06-270, WR 255594



SNL-124, 5 g, RK-04-154, WR 255595

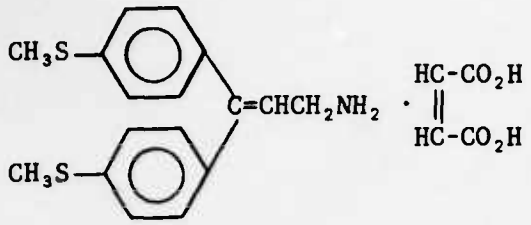


SNL-125, 4.5 g, DJD-06-288, WR 255664

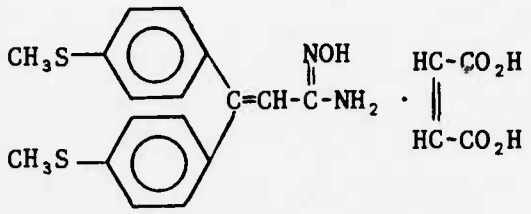
Continued

FIGURE 1, Continued

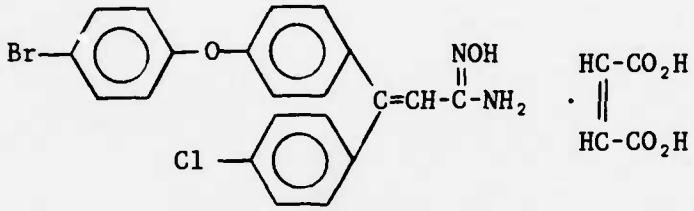
Year No. 2 (Continued)



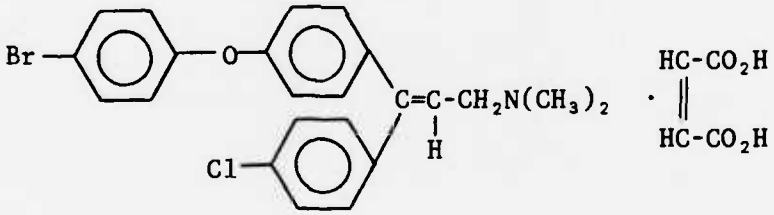
SNL-126, 4 g, DJD-06-293, WR 255665



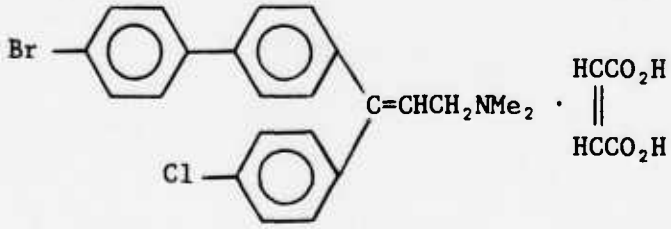
SNL-127, 4 g, DJD-06-295, WR 255662



SNL-128, 7.5 g, DJD-07-27, WR 255784



SNL-129, 6.5 g, DJD-07-32, WR 255810



SNL-130, 4.5 g, DJD-07-44, WR 255931

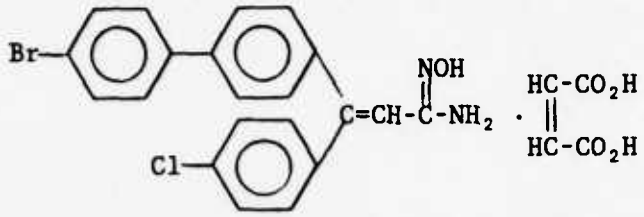
Wellcome Research Laboratories 353C

(As Tartrate salt)

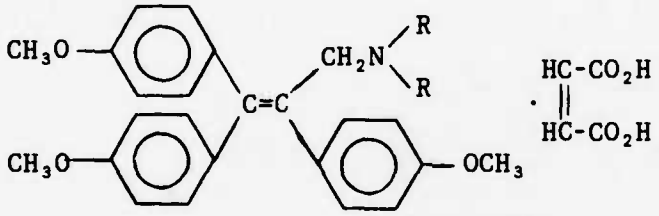
FIGURE 1, Continued

September 1, 1986 to 31 August 1987

Year No. 3 (14)



SNL-131, 4.5 g, DJD-07-51, WR 255934



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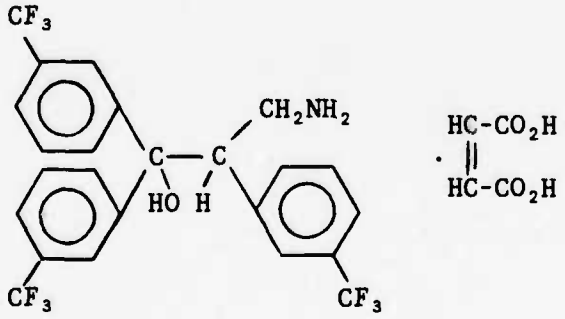
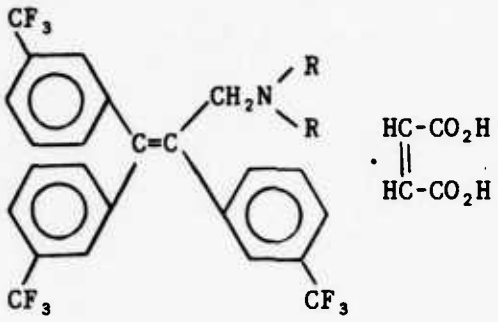
SNL-133, R = H, 5.8 g, DJD-07-66, WR 256123



SNL-134, 3.5 g, DJD-07-89, WR 256541

FIGURE 1, Continued

Year No. 3 (Continued)



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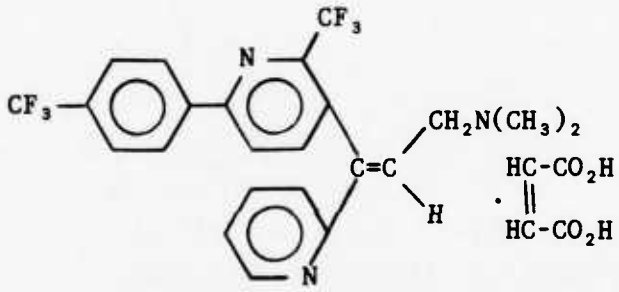
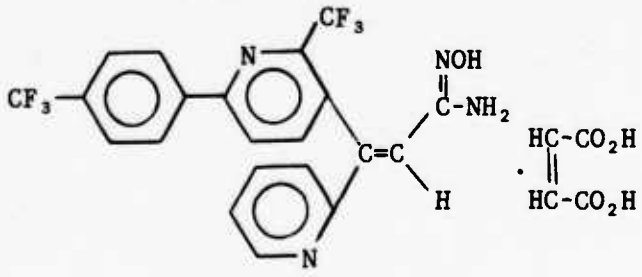
SNL-136, R = H, 4.5 g, DJD-07-97, WR 256540



SNL-137, Isomer A, 4.5 g, DJD-07-107, WR 256599

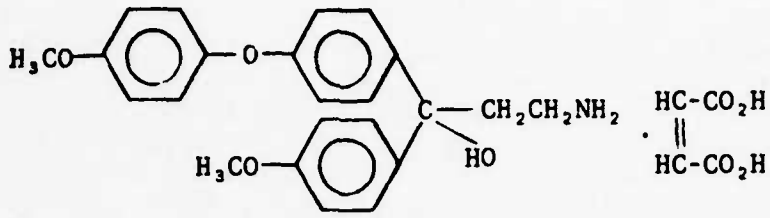
SNL-138, Isomer B, 8.5 g, DJD-07-107A, WR 256600



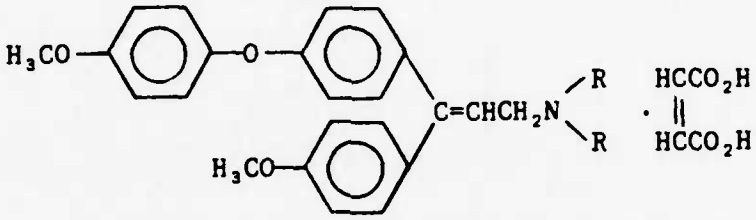
SNL-139, 10 g, DJD-07-117, WR 256782

FIGURE 1, Continued

Year No. 3 (Continued)



SNL-140, 3.5 g, DJD-07-118, WR 256780



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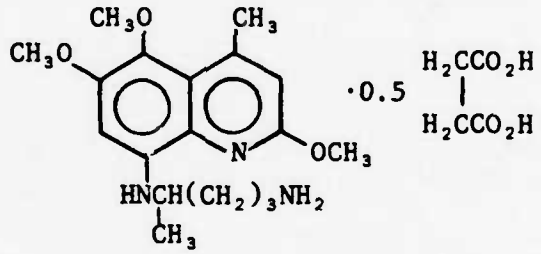
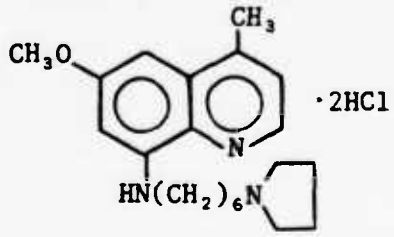
SNL-142, R = H, 5 g, DJD-07-128, WR 256779



SNL-143, 5.5 g, DJD-07-153, WR 257305



SNL-11, 5 g, DJD-07-161, WR 257566

2. DISCUSSION OF WORK COMPLETED. BIOLOGICAL RATIONAL AND DATA.

The 36 compounds submitted in the past three years of the current contract are shown in Figure 1, pages 3-9. These compounds will be discussed briefly, both in terms of the biological rationale leading to their preparation, as well as the activity data available at this writing. Biological data for the 56 target compounds submitted under the prior contract were summarized in the Final Summary Report (1) and portions of the data for these early compounds will be tabulated herein for comparative purposes.

The 22 compounds submitted in the first two years under the current contract were presented and discussed in two Annual Reports (2,3). The 14 compounds prepared and submitted in the past year will be presented and discussed, particularly in terms of synthesis and structure inasmuch as no biological data are yet in hand.

2.1 Leishmaniacides (8-Aminoquinolines)

The major effort has been directed at modified 8-aminoquinolines. Thus, under the current contract in the past two years, six new examples were prepared: SNL-109, 111, 112, 114, 118 and 119 (see Figure 1). The rationale for their preparation is the high activity of WR 6026 against L. donovani (Hanson) represented by a Glucantime index of 474 (IM) and 708 (PO). The available biological data are shown in Table 1.

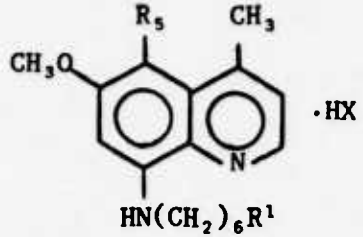
8-N^1-CH_3 Blocking Group: - The pair of 8-N^1-CH_3 blocked compounds, SNL-109 and 111, represent the use of a blocking N-methyl group to prevent the metabolic conversion of the drug to a 5,8- or a 7,8-iminoquinone in order to assess the impact upon the activity and/or toxicity relative to the parent compounds. Referring to Table 1, no data are yet available for SNL-109 which is WR 6026 containing a 8-N^1 blocking methyl group. However, SNL-111, which bears the toxicity-inducing (usually) 5-methoxy group (see data for WR 226,292), shows a minimum toxic dose of 832 mg/kg and a 100% suppression of parasites at 52 mg/kg (lowest dose tested). While the data are limited, the results are nevertheless promising.

8-N^6-Cyclobutyl Side Chain Group: - Similarly, in the case of analogs bearing a cyclobutyl side-chain group (Table 1), the original compound, SNL-07, showed both promising activity and reduced toxicity relative to WR 6026. Accordingly, in the case of SNL-112, the activating but toxicity-inducing 5-methoxy group was again added; no data are yet available. However, some data are available for SNL-114, the 2-methoxy derivative, which shows 100% suppression of parasites at a dosage of 52 mg/kg, coupled with a sharply reduced toxicity (high minimum toxic dose of 832 mg/kg). Data at dose levels below 52 mg/kg are required to explore this promising lead further.

TABLE 1

ANTILEISHMANIAL ACTIVITY OF ANALOGS OF WR 6026 (IN PART)

L. donovani, hamster (Hanson) (IM)



SNL No.	WR No., Bottle No.	R^1	R_5	Other Groups	Min. Curative Doses, % Suppression mg/kg/day (x4)		Min. Toxic Dose	Glucantime Index, G
	6,026	$-NEt_2$	H	—	99.6/0.20	84/0.05	52	474
	226,292	$-NEt_2$	$-OCH_3$	—	100/0.20	68/0.05	>13 <52	401
17(a)	242,896	$-NEt_2$	H	$2-OCH_3$	99.5/13	56/0.81	208(6/6T)	33
108(a)	254,123	$-NEt_2$	$-OCH_3$	$2-OCH_3$	100/52(a)		208(6/6T)	7(a)
				8-N^1-Blocked Analogs				
109(a)	253,904	$-NEt_2$	H	$8-N^1-CH_3$				
111	254,233	$-NEt_2$	$-OCH_3$	$8-N^1-CH_3$	100/52(a)		832(6/6T)	1(a)
				Cyclobutyl Sidechain Analogs				
07(a)	239,374	$-NH-C_4H_7$	H	—	99.2/0.81	74/0.20	208(6/6T)	188,174
112	254,391	$-NH-C_4H_7$	$-OCH_3$	—				
114	254,589	$-NH-C_4H_7$	H	$2-OCH_3$	100/52(a)		832(6/6T)	1(a)
				Amidoximino/Amidino Sidechain Groups				
118	254,959	$-C(NH_2)=NOH$	H	—	50/52		52, Non Toxic	
119	254,985	$-C(NH_2)=NH_2$	H	—				

(a) Prepared under prior Contract No. DAMD17-78-C-8001.

8-N^6-Amidoximino/Amidino Sidechain Groups: - The most recent modifications of WR 6026 are SNL-118 and 119 in which the exterior 8-amino group is replaced by an amidoximino and amidino group, respectively. No data are yet available.

Other: - Another candidate leishmaniacide of a different structural category is represented by 2,6-bis(4-hydrazidophenyl)-4-methylpyridine, SNL-113 (Fig. 1). This was prepared based on a suggestion by Peters and associates (4) who noted that the antituberculosis drug isoniazid had a remissive effect (tissue culture and animals) against L. mexicana, and a salutary clinical result in limited cases. While the clinical result was discounted later, the hydrazido group may be worth exploring as new leads are relatively scarce.

2.2 Trypanosomiacides (T. rhodesiense)

The early effort (1) was directed at exploring the effect of a wide variety of bis(amidines) and bis(amidoximes), primarily against T. rhodesiense (Rane/Ager).

Bis(amidoximes) and bis(amidines): - As reported in detail in the earlier work under the prior contract (1), considerable success against L. rhodesiense was achieved with a number of the title compounds as shown in Table 2 (for structures, see Figure 2). Thus a number of compounds were active (SC) over a range of 0.11 to 0.83 mg/kg and SNL-28 (WR 248,396), 2,6-bis-(4-amidinophenyl)-4-methyl-pyridine dihydrochloride, was curative (PO) at 1.66 mg/kg.

In the current program, the preparation of 1,2-ethylene-bis-(6-amidoximino-2-pyridyl), SNL-110 (Fig. 1), was based on the high activity against T. rhodesiense exhibited by the closely-related 2-amidoximino-6-(4-amidoximinostyryl)pyridine (SNL-36), WR 249,238, which gave a minimum curative dose of 6.55 mg/kg (x 1), both SC and PO (1). SNL-110 (WR 254,019) was curative (4/5C) at 26.5 mg/kg but it was inactive at 13 mg/kg (SC, no oral data). Also the new submissions, SNL-115 and 116 are triazene structures (Fig. 1) relating to the commercial drug diminazene(berenil) in terms of containing a phenoxy grouping; no data are available on these as yet.

TABLE 2

ANTITRYPANOSOMAL DATA. SELECTED BIS(AMIDOXIMES) AND BIS(AMIDINES)[a]

AO = Bis(amidoxime), AM = Bis(amidine)

SNL No.	For Structures, see Figure 2, next page: WR or BN No.	Type Cpd.	T. rhodesiense Rane/Ager, five mice (SC): Min. Curative Dose	100% Curative Dose(5/5C)	Min. Toxic Dose	Rane,[b] five mice, Min. Toxic Dose
			mg/kg(x1)			
			A. Bis(aryl) Heterocycles			
28	248,396	AO	0.83(5C)	0.83	>424	
29	248,535	AM	0.11(1C)	0.42	424	160(1T)
47	249,698	AM	0.21(2C)	0.83	424	640(5T)
54	250,262	AM	0.21(2C)	0.83	106	160(4T)
107	252,070	AM	0.11(1C)	0.42	106,212	NA
			B. HOE 668, SNL-77 and Thio Analog SNL-96			
77	245,720	AM	0.11(2C)	0.83	424	>640(0T)
96	251,336	AM	0.83(4C,5C)	0.83	212	
			C. Commercial Drugs and Bis(amidoxime) Analogs			
			Pentamidine Dimethanesulfonates			
63	250,385	AO	0.83 (1C)	1.66	106	640(4T)
64	4,931	AM	0.83 (2C)	1.66	106	640(5T)
			Diminazene (Berenil) Dimaleates			
67	250,483	AO	0.11 (1C)	0.83	212	
68	27,800	AM	0.01 (1C)	0.11	106	160(3T)

a) From prior Contract No. DAMD17-78-C-8001.

b) *P. berghei* antimalarial test.

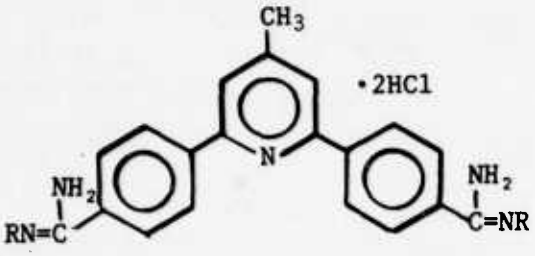
FIGURE 2

SELECTED ACTIVE ANTITRYPANOSOMAL STRUCTURES

From Prior Contract (1)

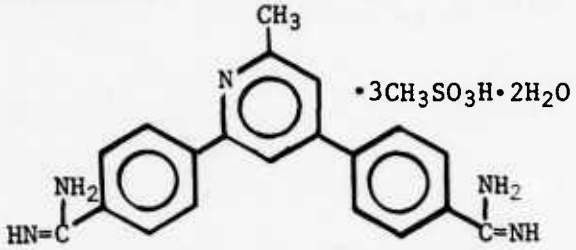
(T. rhodesiense, See Table 2, Section 2.2)

A. Bis(aryl) Heterocycles

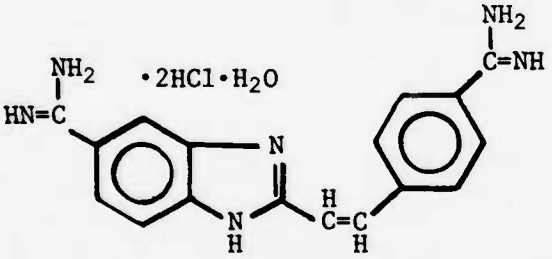


SNL-28, R = OH, WR 248,396, KW-II-98A

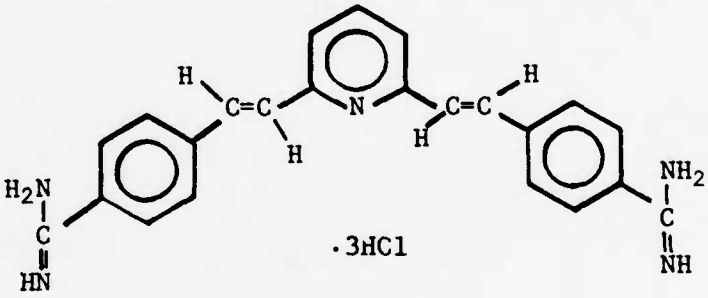
SNL-29, R = H, WR 248,535, KW-II-109A



SNL-54, WR 250,262, DJD-04-41

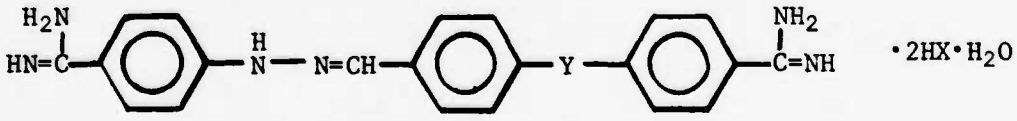


SNL-47, WR 249,698, KW-III-91A



SNL-107, WR 252,070, DJD-06-03

B. HOE 668 (SNL-77) and a Thio Analog (SNL-96)



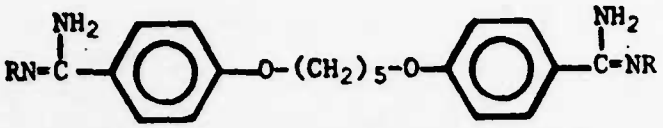
SNL-77, Y = O, WR 245,720, 2HX = Dimaleate, DJD-04-151

SNL-96, Y = S, WR 251,336, 2HX = Dihydrochloride, DJD-04-243

Continued

FIGURE 2 (Continued)

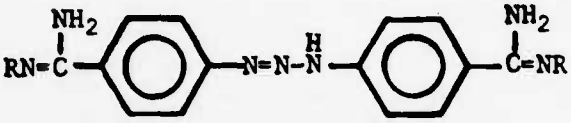
C. Commercial Bis(amidines) and their Bis(amidoxime) Analogs



SNL-63, R = OH, WR 250,385 $\cdot 2HCl \cdot 0.5H_2O$, DJD-04-59

SNL-64, R = H, WR 4,931 $\cdot 2HCl$ (Pentamidine), DJD-04-63

WR 4,931, Commercial: Pentamidine Diisethionate



SNL-67, R = OH, WR 250,483 ·Dimaleate, DJD-04-94

SNL-68, R = H, WR 27,800 ·Dimaleate (Diminazene; Berenil), DJD-04-95

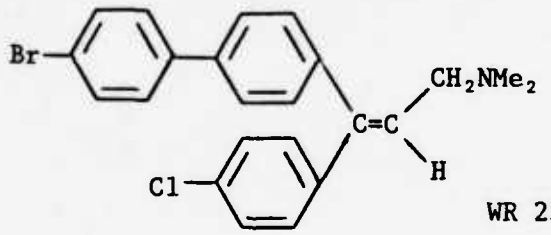
WR 27,800, Commercial: Diminazene(Berenil) Diaceturate

Some 16 of the title bis(amidoximes) and bis(amidines) were tested against T. cruzi (Ager); none were active. The results, in part, led to the work discussed below directed specifically against T. cruzi (5,6).

2.3 Trypanosomiacides (T. cruzi)

As we noted earlier, and in our original proposal dated March 1984, "Chagas' disease", caused by infections of T. cruzi, affects millions of people in Central and South America. McCabe and co-workers (5) at Stanford University state that, "at present, no chemotherapeutic agent has been accepted as completely effective for its treatment. Nifurtimox and benznidazole are being used to treat human diseases but they are limited in application by significant side effects. It is controversial as to whether or not nifurtimox or benznidazole is curative."

In vie of this, coupled with the fact the compounds reported above in section 2.2 were active only against T. rhodesiense, our attention was focused on candidate drugs which might be effective against South and Central American forms of trypanosomiasis. A 1982 paper (6a) by a group of workers at Wellcome Research Laboratories in England describe a powerful antitrypanocide which is effective orally against the refractory T. cruzi. Compound 353C cured 90% of T. cruzi



WR 255931

353C, tartrate salt; SN:-130, maleate salt

(Peruvian)-infected mice orally at a weekly dosage of 25 mg/kg. Compound 353C was one of the most active of the 130 1,1-diaryl-3-aminoprop-1-enes prepared by Wellcome (6a) and covered in two patents (6b and 6c). Structures related to 353C were prepared by Wellcome from the proper diaryl ketone and, for example, dimethylaminoethyl-triphenylphosphonium halide using the Wittig reaction.

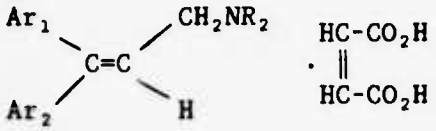
Accordingly, compound 353C and 10 other modified 1,1-diaryl structures were prepared in this laboratory as shown in Figure 3. These modifications are all new compounds to our best knowledge: Three of these are essentially intermediates in that they are primary amines, i.e., those where R = H: SNL-123, -126 and -142. As a further structural modification, two 1,1,2-triaryl-2-dimethylaminomethyl-ethylenes and their primary amine precursors were prepared; these four compounds are shown in Figure 4.

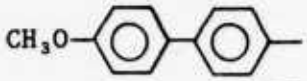
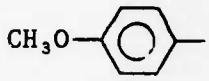
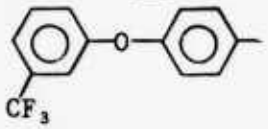
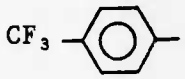
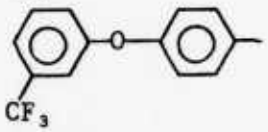
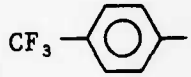
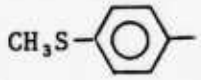
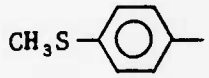
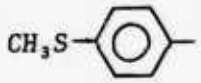
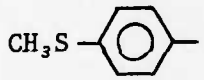
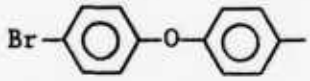
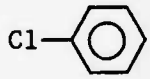
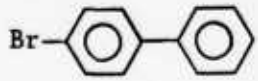
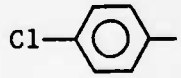
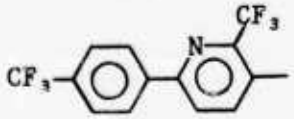
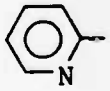
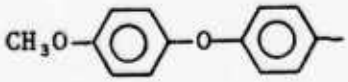
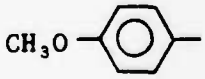
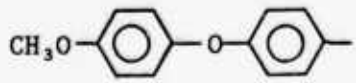
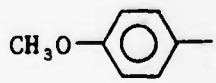
Inasmuch as the 3,3-diarylacrylonitriles were readily accessible from the intermediate 3-hydroxy-3,3-diarylpropionitriles, the nitrile group was converted to the amidoximine group in a number of cases. Seven 1,1-diaryl-2-(amidoximino)ethylenes were prepared as shown in Figure 5.

No test data are available for any of the Wellcome type compounds (Figure 3 and 4) prepared in the course of this work against T. cruzi and/or other South American strains of trypanosomiasis. However, one modified structure, SNL-131, an amidoxime, shown in Figure 5, gave 20% suppression against T. cruzi at 100 mg/kg and the compound was non-toxic at 400 mg/kg (recent 12/87 data).

FIGURE 3

1,1-DIARYL-2-(DIMETHYLAMINOMETHYL)ETHYLENES (11)

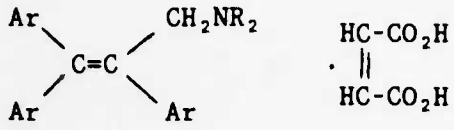


WR No. (SNL No.)	Ar_1	Ar_2	R
255,426 (120) (a)			CH_3
255,593 (122)			CH_3
225,594 (123)			H
255,664 (125)			CH_3
255,665 (126)			H
255,810 (129)			CH_3
255,931 (130) (b)			CH_3
256,599 (137) (c) } 256,600 (138) (d)			CH_3
256,781 (141)			H
256,779 (142)			H

(a) HCl Salt
(b) Burrough Welcome Compound 353C
(c) Isomer A
(d) Isomer B

FIGURE 4

1,1,2-TRIARYL-2-(DIMETHYLAMINOMETHYL)ETHYLENES (4)



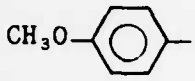
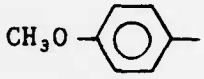
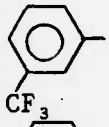
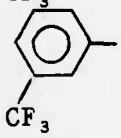
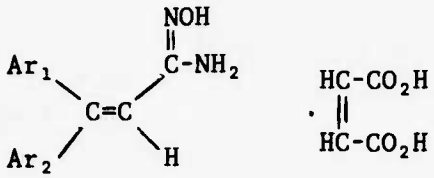
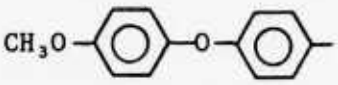
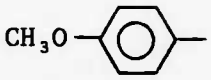
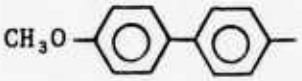
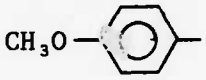
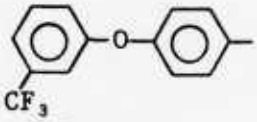
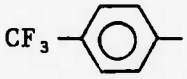
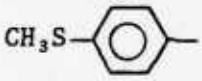
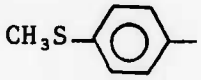
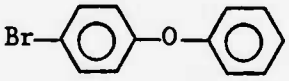
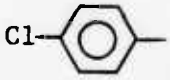
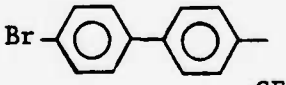
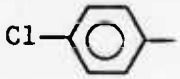
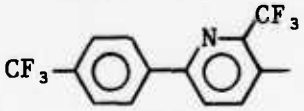
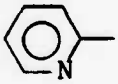
WR No. (SNL No.)	Ar	R
256,122 (132)		CH_3
256,123 (133)		H
256,539 (135)		CH_3
256,540 (136)		H

FIGURE 5

1,1-DIARYL-2-(AMIDOXIMINO)ETHYLENES (7)



WR No. (SNL No.)	Ar_1	Ar_2
254,729 (117)		
255,566 (121)		
255,595 (124)		
255,662 (127)		
255,784 (128)		
255,934 (131)		
256,782 (139)		

3. SYNTHESIS RESULTS AND DISCUSSION

The 14 compounds prepared in the past year ending August 31, 1987 are discussed below.

3.1 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-2-amidoximinoethylene Maleate (SNL-131, WR 255934)

The reaction sequence for the preparation of the title compound is shown in Chart No. 1. 1-(4'-Bromo-4-biphenylyl)-4-chlorobenzophenone (3, p. 48) was treated with acetonitrile in the presence of sodium amide to give the 3-diaryl-3-hydroxypropionitrile 1. This was dehydrated using phosphorus pentoxide to give the corresponding unsaturated nitrile 2. The acrylonitrile 2 was allowed to react with hydroxylamine using the standard procedure to afford the title target amidoxime 3 as a free base which was converted to the target maleate salt 3, SNL-131. A 4.5 g sample of this was shipped to WRAIR on September 12, 1986 as Code No. DJD-07-51, Bottle No. BL24012.

3.2 1,1,2-Tris(4-methoxyphenyl)-3-aminoprop-1-ene Maleate (SNL-133, WR 256123)

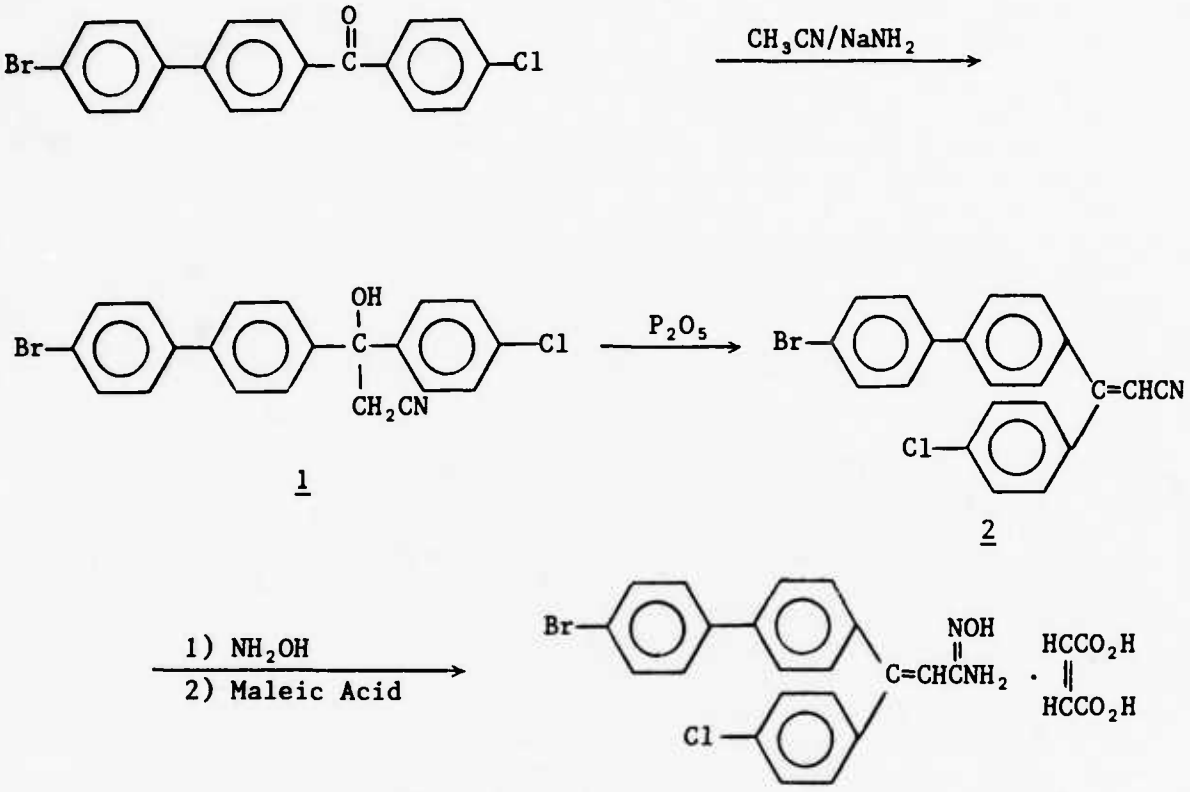
3.3 1,1,2-Tris(4-methoxyphenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-132, WR 256122)

The four-step sequence to the two title compounds is shown in Chart No. 2. 4-Methoxyphenylacetonitrile was treated with isopropyl magnesium chloride followed by 4,4'-dimethoxybenzophenone to give 3-hydroxy-2,3,3-triarylpropionitrile 1 as reported by Kaiser and Hauser for phenylacetonitrile (7). The nitrile group was reduced using a borane-tetrahydrofuran complex to give the 3-hydroxy-2,3,3-triarylpropyl amine 2. Intermediate 2 was dehydrated by heating (steam bath) the compound in an concentrated hydrochloric acid-acetic acid mixture to afford the 2,3,3-triarylallyl amine 3 as a free base. A portion of this free amine was converted to the maleate salt, SNL-133, and a 5.8 g sample was shipped to WRAIR as Code No. DJD-07-66, Bottle No. BL27853, on October 27, 1986.

The balance of the amine 3, free base, was dimethylated using our standard formaldehyde-cyanoborohydride procedure to give the target N,N-dimethylallyl amine 4 as a free base. This was converted to the target maleate salt 4, SNL-132, and a 5 g sample was shipped to WRAIR as Code No. DJD-07-65, Bottle No. BL27862, on October 27, 1986.

CHART NO. 1

1-(4'-BROMO-4-BIPHENYLYL)-1-(4-CHLOROPHENYL)-2-AMIDOXIMINOETHYLENE MALEATE (SNL-131, WR 255934)



1

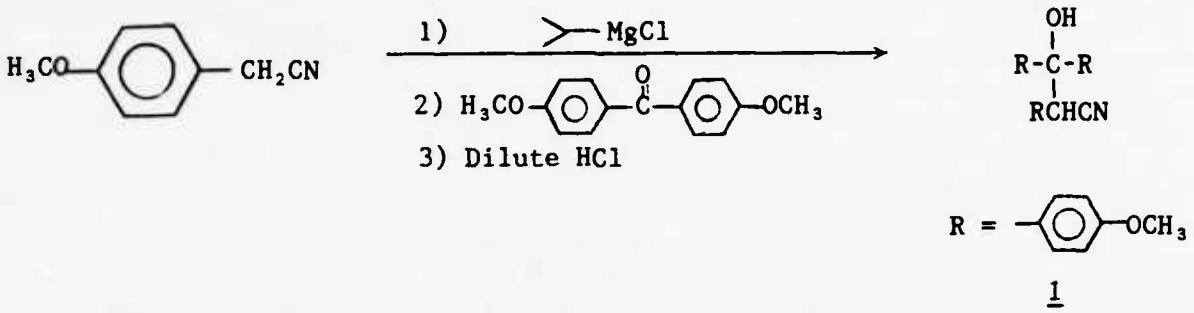
2

3 SNL-131, DJD-07-51, WR 255934

CHART NO. 2

1,1,2-TRIS(4-METHOXYPHENYL)-3-AMINOPROP-1-ENE MALEATE (SNL-133, WR 256123)

1,1,2-TRIS(4-METHOXYPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-132, WR 256122)



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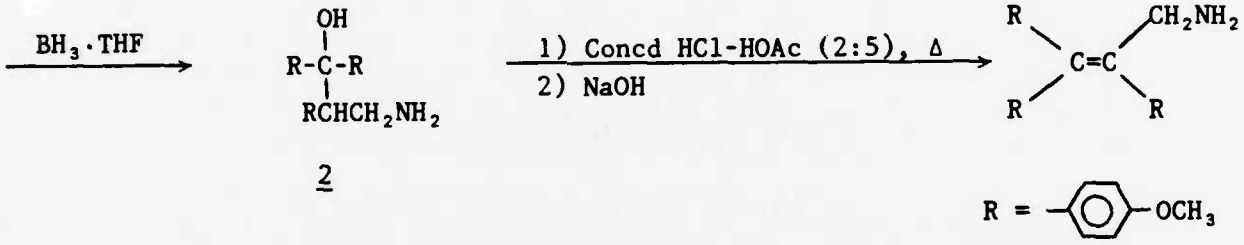
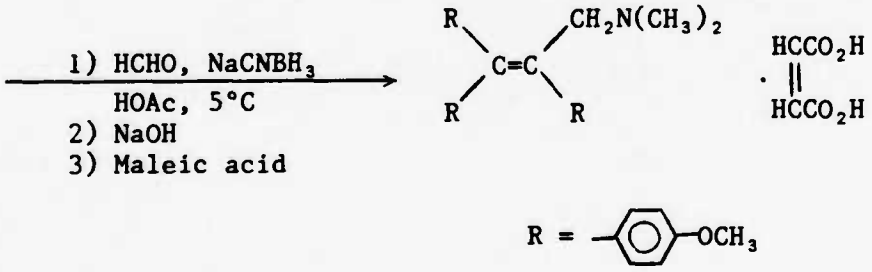


2

3 Free Base

SNL-133, Maleate salt

DJD-07-66, WR 256123



4 Maleate salt

SNL-132, DJD-07-65, WR 256122

3.4 3-Hydroxy-2,3,3-tris(3-trifluoromethylphenyl)propylamine Maleate (SNL-134, WR 256541)

3.5 1,1,2-Tris(3-trifluoromethylphenyl)-3-aminoprop-1-ene Maleate (SNL-136, WR 256540)

3.6 1,1,2-Tris(3-trifluoromethylphenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-135, WR 256539)

The reaction sequence used for the preparation of the above three title compounds is shown in Chart No. 3.

3-Trifluoromethylphenylacetonitrile was treated with isopropyl magnesium chloride followed by the addition of 3,3'-bis(trifluoromethyl)benzophenone to give the 3-hydroxy-2,3,3-triarylpropionitrile 1. The nitrile group was reduced with borane-tetrahydrofuran complex to give the corresponding propyl amine 2 as a free base. A portion of this was treated with maleic acid to afford the target maleate salt SNL-134, and a 3.5 g sample was submitted to WRAIR as Code No. DJD-07-89, Bottle No. BL31768.

The balance of the free base 2 was dehydrated with mixed acids to give the corresponding triarylallyl amine 3 which, after workup, was isolated as the free base. A portion of the free base 3 was converted to the maleate salt, SNL-136. A 4.5 g sample was shipped to WRAIR as Code No. DJD-07-97, Bottle No. BL31759.

The remaining free amine 3 was dimethylated with formaldehyde-cyanoborohydride in the usual manner to afford the target triaryldimethylaminomethyl ethylene 4 as a free base. This was treated with maleic acid to yield the title target maleate salt 4, SNL-135. Of this a 6.5 g sample was submitted to WRAIR as Code NO. DJD-07-94, Bottle No. BL31777.

The above three target compounds, SNL-134, SNL-136 and SNL-135 were shipped to WRAIR on December 29, 1986.

1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl-4-pyridyl]-3-dimethylaminoprop-1-ene Maleate

3.7 SNL-137; Isomer A, WR 256599

3.8 SNL-138; Isomer B, WR 256600

The reaction sequence used for the preparation of both isomers is shown in Chart No. 4.

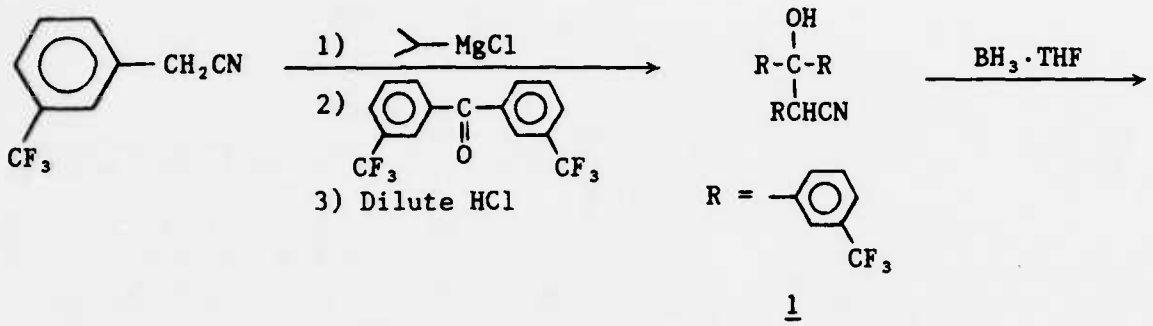
Using the Wittig reaction, 2-pyridyl-4-[6-(trifluoromethylphenyl)-2-trifluoromethyl]pyridyl ketone (available from an earlier antimalarial contract, ref. 8) was condensed with 2-dimethylaminoethyltriphenylphosphonium bromide to give a mixture of the isomers A

CHART NO. 3

3-HYDROXY-2,3,3-TRIS(3-TRIFLUOROMETHYLPHENYL)PROPYLAMINE MALEATE (SNL-134, WR 256541

1,1,2-TRIS(3-TRIFLUOROMETHYLPHENYL)-3-AMINOPROP-1-ENE MALEATE (SNL-136, WR 256540

1,1,2-TRIS(3-TRIFLUOROMETHYLPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-135, WR 256539)



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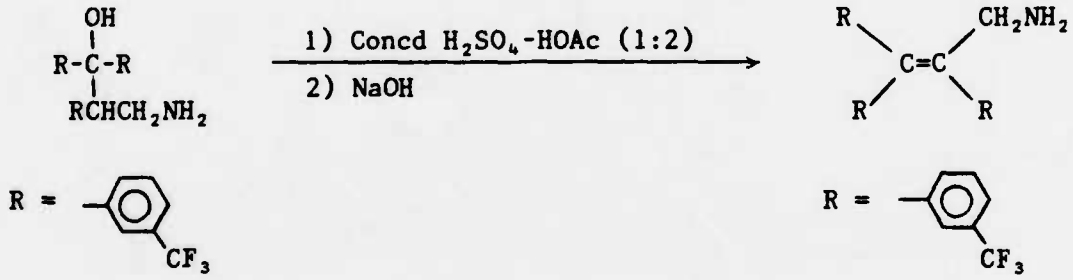
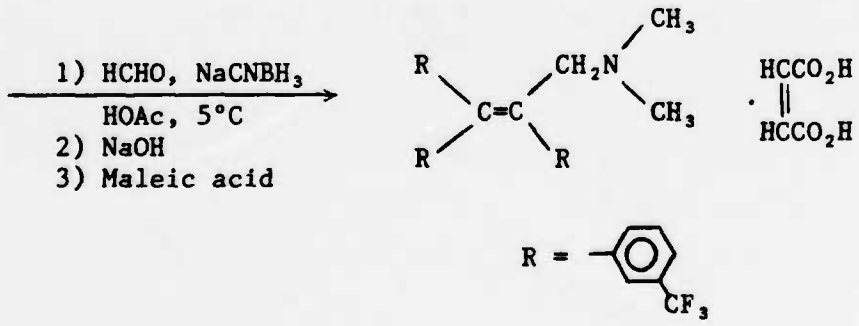


2 Free Base
SNL-134, Maleate salt
DJD-07-89, WR 256541

3 Free Base
SNL-136, Maleate salt
DJD-07-97, WR 256540



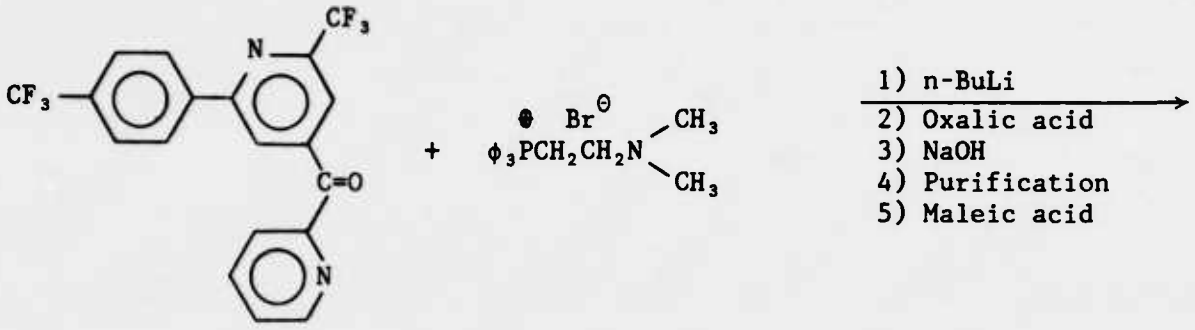
4 SNL-135, DJD-07-94, WR 256539

CHART NO. 4

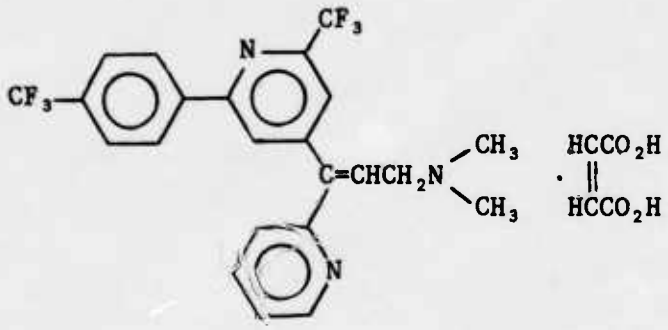
1-(2-PYRIDYL)-1-[6-(4-TRIFLUOROMETHYLPHENYL)-2-TRIFLUOROMETHYL-4-PYRIDYL]-3-DIMETHYLAMINOPROP-1-ENE MALEATE

SNL-137, Isomer A, WR 256599

SNL-138, Isomer B, WR 256600



Ref. 8, p. 57



SNL-137, Isomer A, DJD-07-107, WR 256599

SNL-138, Isomer B, DJD-07-107A, WR 256600

and B, SNL-137 and SNL-138 respectively. After purification (chromatography) the oily mixture in anhyd ether was treated with maleic acid in methanol. Isomer A, being less-soluble, was separated by filtration. A 4.5 g sample of isomer A maleate salt, SNL-137, was shipped to WRAIR on January 20, 1987 as Code No. DJD-07-107, Bottle No. BL33137.

After the separation of isomer A, the mother liquors were evaporated to near dryness. The residue was triturate with ether to afford crystalline isomer B, SNL-138. An 8.5 g sample was shipped to WRAIR on January 20, 1987 as Code No. DJD-07-107A, Bottle No. BL33146.

3.9 1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl-4-pyridyl]-2-amidoximinoethylene Maleate (SNL-139, WR 256782)

The sequence to the title amidoxime is shown in Chart No. 5.

Commercially-available cyanomethyltriphenylphosphonium chloride in dichloromethane was treated with 2 N aq. sodium hydroxide to provide the starting Wittig reagent, triphenylphosphoranylidene-acetonitrile (1). The phosphorane 1 in dichloromethane was allowed to react with the dipyridyl ketone (8, p. 57; purified as described in combined sections 5.7 and 5.8). The resulting acrylonitrile 2 was purified (chromatography) to give an oil which was treated with hydroxylamine hydrochloride and sodium bicarbonate. Workup gave the crude title amidoxime 3 as a free base which was purified *via* the oxalate salt. The free base was regenerated from the oxalate salt and converted to the title target maleate salt 3, SNL-139. A 10 g sample was shipped to WRAIR on March 4, 1987 as Code No. DJD-07-117, Bottle No. BL35828.

3.10 3-Hydroxy-3-[4-(4'-methoxyphenoxy)phenyl]-3-(4-methoxyphenyl)-propylamine Maleate (SNL-140, WR 256780)

3.11 1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-amino-prop-1-ene Maleate (SNL-142, WR 256779)

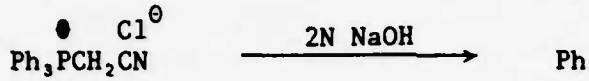
3.12 1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-dimethyl-amino-prop-1-ene Maleate (SNL-141, WR 256781)

The reaction sequence used for the preparation of the above three compounds is shown in Chart No. 6.

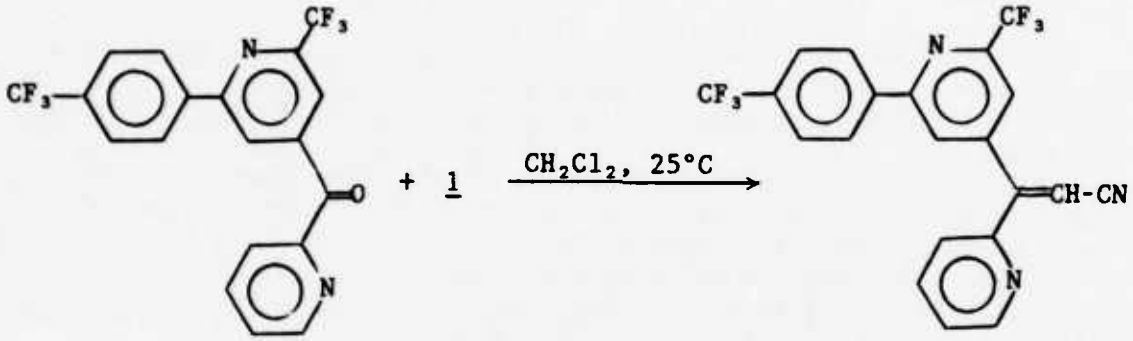
The starting 3,3-diaryl-3-hydroxypropionitrile (ref. 2, p. 44) was reduced with LAH to give the 3,3-diaryl-3-hydroxypropyl amine 1 as the free base. A portion of this intermediate was converted to the title maleate salt, SNL-140, a 3.5 g sample of which was shipped to WRAIR on March 4, 1987 as DJD-07-118, Bottle No. BL35837.

CHART NO. 5

1-(2-PYRIDYL)-1-[6-(4-TRIFLUOROMETHYLPHENYL)-2-TRIFLUOROMETHYL-4-PYRIDYL]-2-AMIDOXIMINOETHYLENE MALEATE (SNL-139, WR 256782)

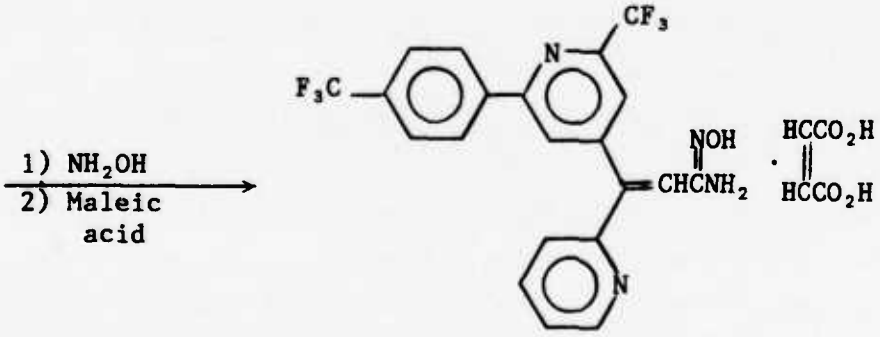


1, Ref. 9



Ref. 8, p. 57

2



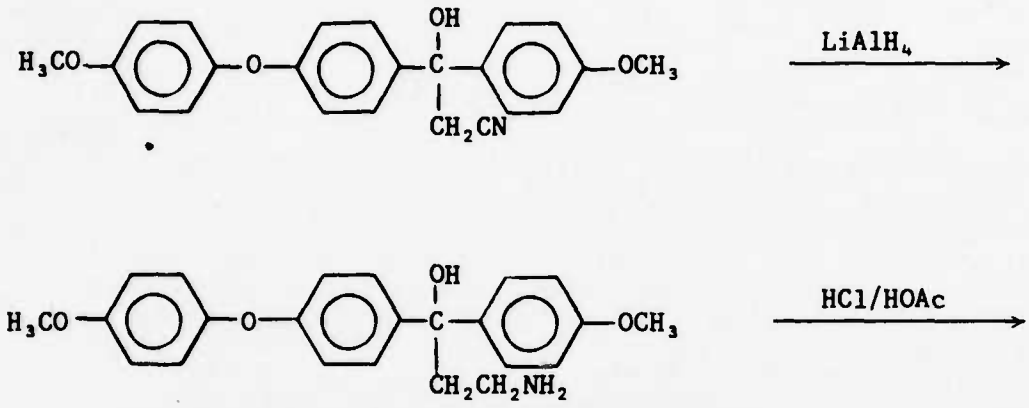
3, SNL-139, DJD-07-117, WR 256782

CHART NO. 6

3-HYDROXY-3-[4-(4'-METHOXYPHENOXY)PHENYL]-3-(4-METHOXYPHENYL) PROPYLAMINE MALEATE 1 (SNL-140, WR 256780)

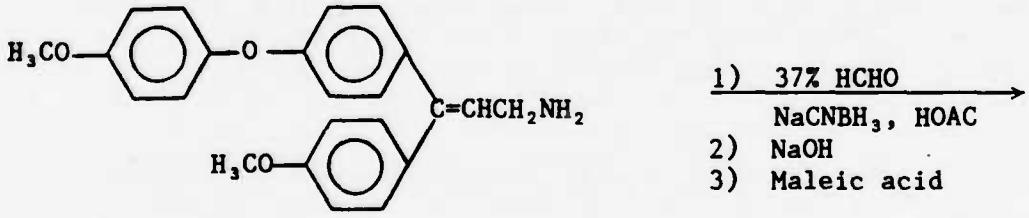
1-[4-(4'-METHOXYPHENOXY)PHENYL]-1-(4-METHOXYPHENYL)-3-AMINOPROP-1-ENE MALEATE 2 (SNL-142, WR 256779)

1-[4-(4'-METHOXYPHENOXY)PHENYL]-1-(4-METHOXYPHENYL)-3-DIMETHYL-AMINOPROP-1-ENE MALEATE 3 (SNL-141, WR 256781)



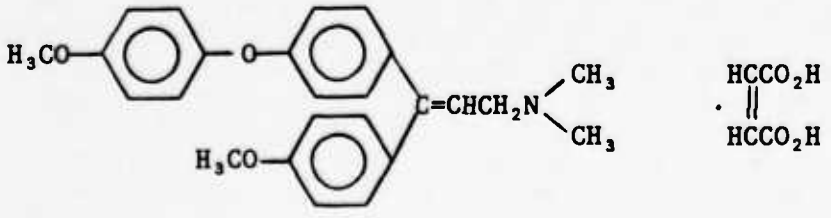
1, Free base

SNL-140, Maleate salt, DJD-07-118, WR 256780



2, Free base

SNL-142, Maleate salt, DJD-07-128, WR 256779



3, SNL-141, Maleate salt, DJD-07-123, WR 256781

The remaining hydroxypropyl amine 1 was dehydrated with mixed acids to give, after workup, the corresponding 3,3-diarylallyl amine 2 as the free base. A portion of this was converted to the maleate salt, SNL-142, and a 5.0 g sample was shipped to WRAIR as Code No. DJD-07-128, Bottle No. BL35855.

The remaining allyl amine 2 free base was dimethylated using the standard formaldehyde-cyanoborohydride method to afford the dimethyl amino derivative 3 as a free base. Treatment with maleic acid afforded the maleate salt 3, SNL-141. A 6.0 g sample of SNL-141 was shipped to WRAIR as Code No. DJD-07-123, Bottle No. BL35846. All three maleate salts, SNL-140, 142 and 141, were shipped on March 4, 1987.

3.13 8-[(4-Amino-1-methylbutyl)amino]-4-methyl-2,5,6-trimethoxyquinoline Hemisuccinate (SNL-143, WR 257305)

The sequence to the title 2,5-dimethoxy-4-methylprimaquine is shown in Chart No. 7.

The starting 8-amino-4-methyl-2,5,6-trimethoxyquinoline in crude form was available from an earlier program (1). This material was purified to give pure product with acceptable analysis and melting point (1, p. 38).

The pure product was condensed with the side-chain reagent 4-iodophthalimidopentane in acetonitrile to give the blocked side-chain 8-aminoquinoline 1 (62%). The phthalimido group was removed with hydrazine to give, after chromatography, pure title free base (82%). Attempts to prepare a monosuccinate salt in pure form was unsuccessful but the hemisuccinate salt was isolated in pure form in 71% yield from the free base or 58% from the precursor 3. A 5.5 g sample was shipped to WRAIR as Code No. DJD-07-153, on May 21, 1987.

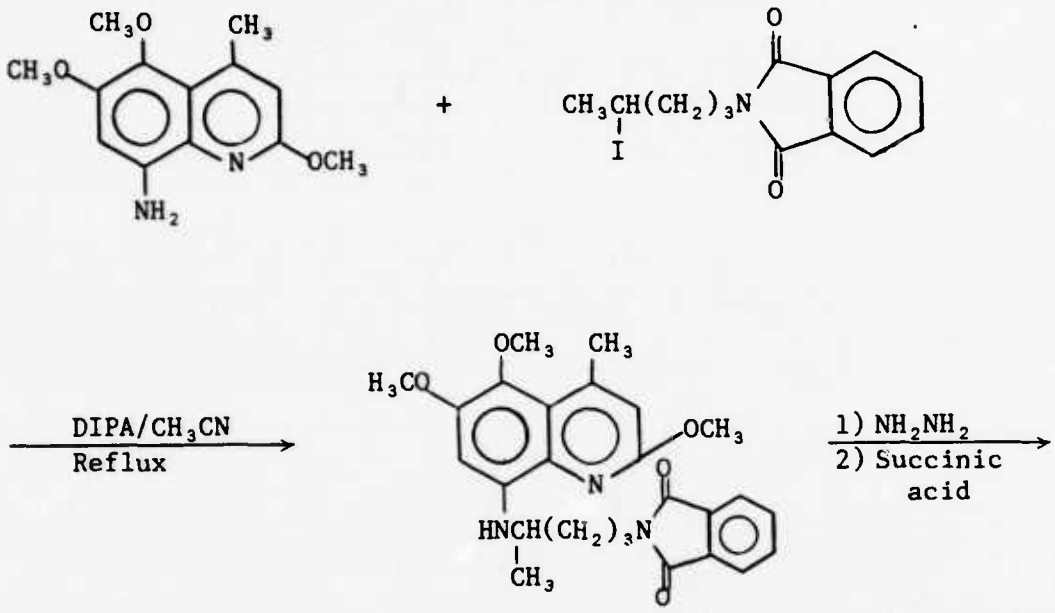
3.14 6-Methoxy-4-methyl-8-[(6-pyrrolidinohexyl)amino]quinoline dihydrochloride (SNL-144, WR 257566)

The sequence to the title compound is shown in Chart No. 8.

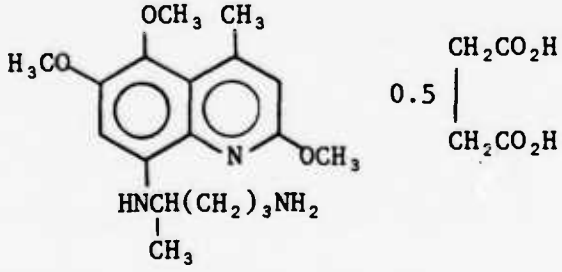
6-Methoxy-4-methyl-8-nitroquinoline was hydrogenated using Raney nickel catalyst to give the corresponding 8-aminoquinoline 1 in 84% yield as described under an earlier contract (10). The 8-aminoquinoline 1 was condensed with 6-bromohexanoyl chloride following a literature procedure (11, Johnson and Werbel, 1983) to give the 8-bromohexanoylaminoquinoline 2 (79%). Intermediate 2 was then condensed with pyrrolidine to give the corresponding 8-(N-pyrrolohexanoylamide 3 (62%). The amide 3 was reduced with LAH to give the title compound free base which was purified and converted to the title dihydrochloride salt 4 (42%). A 5.0 g sample was shipped to WRAIR as Code No. DJD-07-161 on July 14, 1987.

CHART NO. 7

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-4-METHYL-2,5,6-TRIMETHOXY-QUINOLINE HEMISUCCINATE (SNL-143, WR 257305)



1

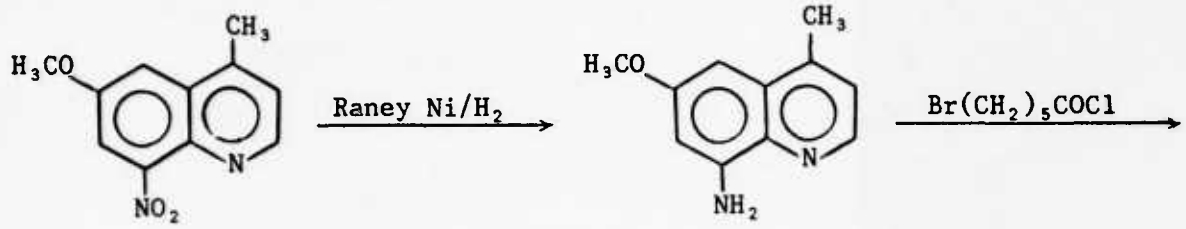


2, Hemisuccinate salt

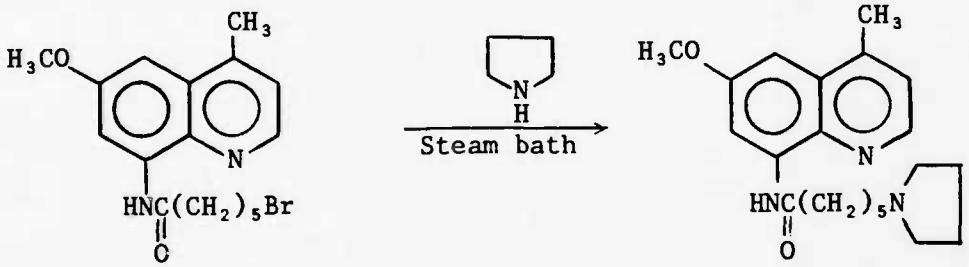
SNL-143, DJD-07-153, WR 257305

CHART NO. 8

6-METHOXY-4-METHYL-8-[(6-PYRROLIDINOHEXYL)AMINO]QUINOLINE DIHYDROCHLORIDE (SNL-144, WR 257566)

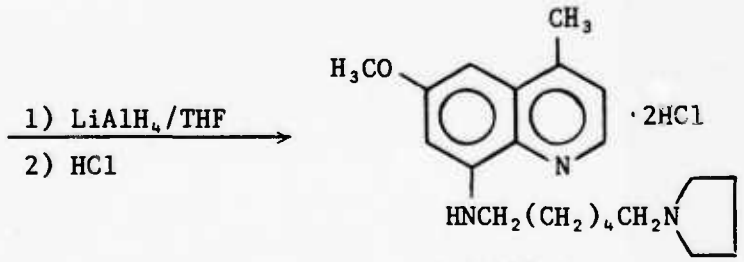


1 (84%)



2 (79%)

3 (62%)



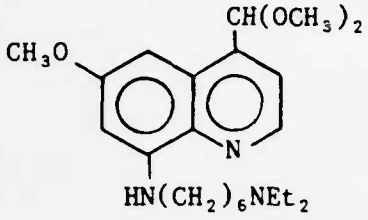
4 (42%)

SNL-144, DJD-07-161, WR 257566

4. WORK IN PROGRESS

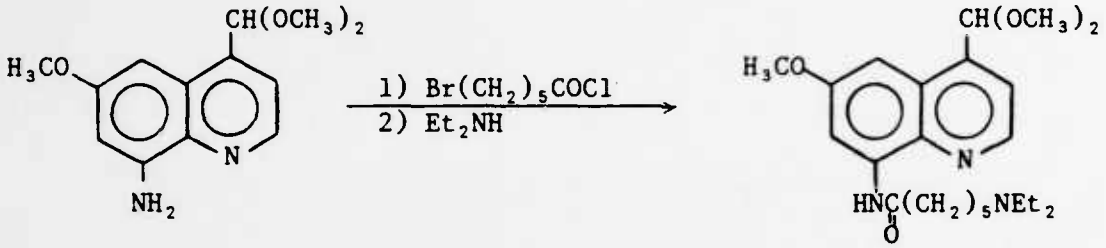
Work in progress or planned is discussed below. The PC numbers refer to our original proposal compound number.

4.1 8-[(6-Diethylaminohexyl)amino]-4-dimethoxymethyl-6-methoxyquinoline



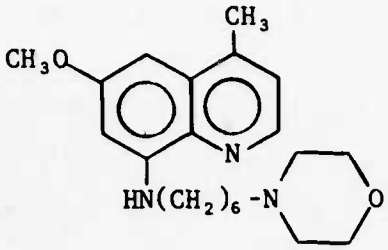
PC-2b

Alkylation of 8-amino-4-dimethoxymethyl-6-methoxyquinoline using standard procedure resulted primarily in decomposition of the starting 8-aminoquinoline. As a result, an alternate procedure was evaluated as follows:



During the reaction, a portion (ca. 40%) of the 4-acetal group is hydrolyzed to aldehyde giving a mixture of 4-acetal and 4-aldehyde (based on NMR data). Studies are underway to avoid this partial hydrolysis side reaction to the precursor 8-aminoquinoline which will be reduced with Lithium aluminum hydride to give the target compound.

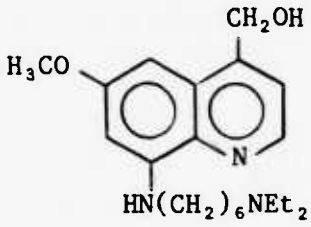
4.2 6-Methoxy-4-methyl-8-[(6-morpholinohexyl)amino]quinoline



PC-6

A probe synthesis has been completed as described for PC-5 above. Scale-up is in progress.

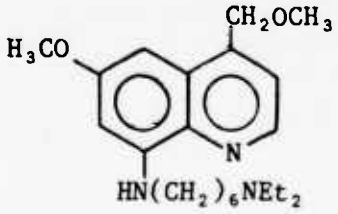
4.3 8-[(6-Diethylaminohexyl)amino]-4-hydroxymethyl-6-methoxyquinoline



PC-2

Probe synthesis has been completed to give the title compound as the dihydrochloride salt. Scale-up is in progress.

4.4 8-[(6-Diethylaminohexyl)amino]-4-methoxymethyl-6-methoxyquinoline



PC-2a

A probe synthesis has been completed to give the title compound as a dihydrochloride monohydrate salt. Scale-up is in progress.

5. EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B Spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Vapor phase chromatography was performed using F and M Model 810 with a flame ionization detector. NMR spectra, when required, were determined on a Varian Model T60 Spectrometer. All thin layer chromatography was carried out using Brinkmann Instruments, Inc., 0.25 mm silica gel plates with a Fluorescent indicator (Polygram Sil G/UV_{254}) unless otherwise stated.

The petroleum ether used was a low boiling grade (bp 35-60°C) unless specified otherwise.

5.1 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-2-amidoximinoethylene Maleate (SNL-131, WR 255934)

The sequence to the title compound is shown in Chart No. 1.

3-Hydroxy-3-(4'-bromo-4-biphenylyl)-3-(4-chlorophenyl)propionitrile (1): - A mixture of sodium amide (6.5 g, 0.17 mol), acetonitrile (10 mL, 7.84 g, 0.19 mol) and dry benzene (1.25 L) was heated at reflux for 10 min and cooled. 1-(4'-Bromo-4-biphenylyl)-4-chlorobenzophenone (30 g, 0.08 mol, ref. 3) and benzene (150 mL) were added and the mixture was heated to reflux for 90 min. Acetonitrile (10 mL) was added to the mixture after 30 min and after 1 h. The brown mixture was cooled to 15°C and poured into cold water (2 L). Ether (1 L) was added and the organic layer was separated and washed with satd brine (500 mL), dried (K_2CO_3) and concd to dryness to give a red syrup, 35 g. The material, 40 g (including product, 5 g, from a trial run), was purified by column chromatography over silica gel (350 g, EM Labs) to give a partially pure fraction, 6 g, and pure title compd, 10 g. The first fraction was rechromatographed over silica gel (60 g, EM Labs) to give additional pure title compd, 5 g. The combined pure material (15 g) was dissolved in dichloromethane (200 mL), charcoaled and filtered (celite). The soln was reduced in volume to ca. 100 mL, diluted with petr ether (150 mL) and stirred for 1 h. The light yellow solid was collected and dried (25°C, 0.3 mmHg, 24 h) to give pure title compd 2, 13.5 g (31%), mp 164-166°C.

Anal. Calcd for $C_{21}H_{15}BrClNO$ (403.56): Halogen, 17.19. Found: Halogen, 17.36.

Product from a trial run was recrystallized from dichloromethane and petr ether to give an analytical sample, mp 165-167°C, which analyzed as follows.

Anal. Calcd for $C_{21}H_{13}BrClNO$ (403.56): C, 61.09; H, 3.67; Halogen, 17.19; N, 3.40. Found: C, 60.96; H, 3.67; Halogen, 17.26; N, 3.61.

1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-2-propenenitrile (2): - Phosphorus pentoxide (30 g) was added to a soln of the hydroxypropionitrile 1 (13.4 g, 0.033 mol) in warm dry benzene (400 mL) and the mixture was refluxed for 10 min. The liquid was decanted and the gummy residue was extracted with hot benzene (100 mL). The combined organic layer was concd to dryness. The residue was triturated with deionized water and the mixture was extracted with dichloromethane (200 mL). The organic layer was separated, washed with satd brine (100 mL), dried (Na_2SO_4) and the volume was reduced to ca. 50 mL. The soln was diluted with petr ether (450 mL) and stirred for 30 min. The solid was collected and dried (25°C, 0.3 mmHg, 2 h) to give pure title compd, 11.0 g (84%), mp 137-140°C. An analytical sample from a trial run had mp 139-141°C and analyzed as follows.

Anal. Calcd for $C_{21}H_{13}BrClN$ (394.47): C, 63.88; H, 3.32; Halogen, 17.98; N, 3.55. Found: C, 63.77; H, 3.23; Halogen, 17.93; N, 3.79.

1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-2-amidoximinoethylene Maleate (3, SNL-131, WR 255934): - A soln of potassium hydroxide (16 g, 0.24 mol) in anhyd alcohol (300 mL) was added over a period of 30 min to a suspension of hydroxylamine hydrochloride (16 g, 0.23 mol) in anhyd alcohol (250 mL). The mixture was stirred for 30 min, filtered and the nitrile 2 (14.5 g, 0.037 mol) was added to the filtrate. The mixture was refluxed (steam bath) for 46 h, cooled to room temp and filtered. The product was washed with petr ether (2 x 150 mL) and dried (25°C, 18 h) to give the title compd free base, 4.4 g (28%), mp 234-236°C dec.

Conversion of the Free Base to the Maleate Salt: - Maleic acid (1.75 g, 0.015 mol) was added to a suspension of the free base (4.4 g, 0.01 mol) in hot methanol (175 mL). The yellow soln was filtered (celite), reduced in volume to ca. 50 mL and filtered. The solid was washed with petr ether (3 x 100 mL) and dried (25°C, 1 h) to give crude title salt, 4.9 g (87%), mp 165°C dec. A total of 6.4 g of the crude salt, prepared in this manner, was dissolved in hot acetonitrile (600 mL) and the soln was filtered. The volume was reduced to ca. 400 mL, and the mixture was stirred for 30 min and filtered. The beige solid was washed with petr ether (3 x 150 mL) and dried (80°C, 0.3 mmHg, 1 h) to give pure title compd 3, 5.15 g (80%), mp 177-179°C

dec. (The yield from nitrile 2 was 20%). A 4.5 g sample was shipped to WRAIR on September 12, 1986 as Code No. DJD-07-51.

Anal. Calcd for $C_{22}H_{20}BrClN_2O_5$ (543.80): C, 55.21; H, 3.71; Halogen, 13.04; N, 5.15. Found: C, 55.32; H, 3.71; Halogen, 13.26; N, 5.21.

5.2 1,1,2-Tris(4-methoxyphenyl)-3-aminoprop-1-ene Maleate (SNL-133, WR 256123)

5.3 1,1,2-Tris(4-methoxyphenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-132, WR 256122)

The sequence to the title compound is shown in Chart No. 2.

3-Hydroxy-2,3,3-tris(4-methoxyphenyl)propionitrile (1): - An ethereal soln of isopropyl magnesium chloride (180 mL, 2 M, 0.36 mol) was added over 15 min to a soln of 4-methoxyphenylacetonitrile (50 g, 0.34 mol) in dry tetrahydrofuran (750 mL) while the temp was maintained between 5-10°C. The yellow soln was stirred (13 min, 0-5°C) and a soln of 4,4'-dimethoxybenzophenone (75 g, 0.31 mol) in dry tetrahydrofuran (1 L) was added over 20 min at 0-5°C. The purple soln was stirred (35 min, 0-5°C), warmed to room temp, stirred for 1 h, and poured into cold hydrochloric acid (6.25 L, concd acid-H_2O, 1:4). The mixture was extracted with ether (3 L) and with dichloromethane (1 L). The combined extract was washed with satd brine (2 x 1 L), dried (Na_2SO_4) with charcoaling, filtered (celite) and concd to dryness. The residue was triturated with hexanes (1 L). The yellow solid was collected and air-dried (25°C, 1 h) to give crude title compd, 110 g, which was dissolved in hot benzene (2 L), charcoaled and filtered (celite). The mixture was stirred for 1 h, filtered and the beige solid was washed with hexanes (4 x 150 mL) and air-dried (25°C, 1 h) to give partially purified compd, 78 g. This material was recrystallized from hot benzene (1.5 L) to give purified material, 63.5 g, mp 124-126°C which was chromatographed over silica gel (630 g, J.T. Baker), eluting with dichloromethane (5 L). The eluate was concd to near dryness, diluted with petr ether (1.5 L) and stirred for 1 h. The off-white solid was collected and dried (80°C, 0.3 mmHg, 2 h) to give pure title hydroxypropionitrile, 53.9 g (44%), mp 129-131°C. An analytical sample, purified by recrystallization from benzene-hexane (1:2), had mp 131-133°C and analyzed as follows.

Anal. Calcd for $C_{24}H_{23}NO_4$ (389.43): C, 74.02; H, 5.95; N, 3.60. Found: C, 74.18; H, 5.83; N, 3.80.

3-Hydroxy-2,3,3-tris(4-methoxyphenyl)propylamine (2): - A soln of borane-tetrahydrofuran complex in tetrahydrofuran (600 mL, 1 M, 0.6 mol) in dry tetrahydrofuran (1 L) over 20 min (5-7°C) and stirred for 30 min. The mixture was heated at reflux (steam bath) for 1 h and the yellow soln was cooled to 5-10°C. Aq 15% sodium hydroxide

(100 mL) was added (cautiously, foaming) and the mixture was concd to dryness. The residue was partitioned between ether (2 L) and 15% aq sodium hydroxide (1 L). The organic layer was separated and the aq layer was reextracted with ether (500 mL). The combined ether extract was washed with satd brine (500 mL), dried (Na_2SO_4) and concd to give crude title compd 2, 42 g, as a light yellow syrup. A soln of oxalic acid (16 g, 0.18 mol) in anhyd ether (500 mL) was added to a clear soln of the yellow syrup 2 in anhyd ether (1.5 L). The mixture was stirred for 20 min and filtered, and the solid was reslurried with anhyd ether (750 mL). The slurry was stirred for 16 h, filtered and the off-white solid was washed with petr ether (2 x 300 mL) and dried (25°C, 1 h) to give the title compd oxalate salt, 36 g (67%), mp 160-165°C (eff). The oxalate salt (36 g) was partitioned between dichloromethane (1.5 L) and 2 N NaOH (1.5 L). The organic layer was separated and the aqueous layer was reextracted with dichloromethane (500 mL). The combined organic layer was washed with aq 2 N NaOH (500 mL) and with satd brine (500 mL), dried (Na_2SO_4) and concd The residue was dissolved in anhyd ether (1 L), the soln was filtered (celite) and concd to give purified title compd, 22 g (51%), as a white foam. An analytical sample, prepared by column chromatography, had mp 120-125°C with shrinkage between 50-60°C.

Anal. Calcd for $C_{24}H_{27}NO_4$ (393.47): C, 73.26; H, 6.92; N, 3.56. Found: C, 72.85; H, 7.14; N, 3.80.

1,1,2-Tris(4-methoxyphenyl)-3-aminoprop-1-ene Maleate (3, SNL-133, WR 256123)

Preparation of the Free Base: - Concd hydrochloric acid (80 mL) was added to a warm (ca. 50°C) soln of the hydroxypropylamine 2 (22 g, 55.9 mol) in acetic acid (200 mL) and heated (steam bath) for 30 min. The soln was concd (steam bath, aspirator) to dryness and the residue was dissolved in warm (50°C) deionized water (1 L). The light-yellow soln was cooled (10°C) and the pH was adjusted to 14 with 15% NaOH (200 mL). The mixture was extracted with ether (1 L). The organic layer was separated and the aq layer was reextracted with ether (500 mL). The combined organic layer was washed with satd brine, dried (k_2CO_3) with charcoaling and filtered (celite). The soln was reduced to ca. 200 mL in volume and filtered. The off-white solid was washed with petr ether (2 x 75 mL) and air-dried (25°C, 2 h) to give purified title compd free base, 8.4 g, mp 117-119°C. The filtrate was concd to dryness to give crude free base, 11.8 g, which was purified by column chromatography over silica gel (150 g, J.T. Baker) eluting with dichloromethane (1.5 L) to remove impurities. The column was eluted with 1% MeOH-CH_2Cl_2 (1 L) and 2% MeOH-CH_2Cl_2 (500 mL) to give slightly-impure compd, 1.7 g, followed by 3% MeOH-CH_2Cl_2 (1 L) and 5% MeOH-CH_2Cl_2 (1 L) to give purified free base, 7.0 g, mp 119-121°C. The combined yield of pure free base, 15.4 g (89%).

Conversion to the Maleate Salt: - The purified title compd free base (8.4 g) was purified further by column chromatography (silica gel, 80 g, J.T. Baker) in the same manner as described above to give purified free base in two fractions: 1.10 g, mp 119-121°C (light yellow) and 5.56 g, mp 120-122°C, off-white.

Maleic acid (1.57 g, 0.013 mol) was added to a warm (50°C) soln of the pure free base 3 (5.56 g, 0.015 mol, mp 120-122°C) in methanol (20 mL). The mixture was diluted with anhyd ether (200 mL) and stirred for 15 min. The beige solid was collected by filtration and slurried with anhyd ether (700 mL) for 30 min. The solid was collected, washed with petr ether (2 x 100 mL) and dried (25°C, 0.3 mmHg, 18 h) to give pure title maleate salt 3, 6.4 g (96%), mp 194-196°C. A 5.8 g sample was shipped to WRAIR on October 27, 1986 as Code No. DJD-07-66.

Anal. Calcd for $C_{28}H_{29}NO_7$ (491.52): C, 68.41; H, 5.95; N, 2.85. Found: C, 68.25; H, 5.78; N, 3.07.

1,1,2-Tris(4-methoxyphenyl)-3-dimethylaminoprop-1-ene Maleate (4, SNL-132, WR 256122): - Aq formaldehyde (37%, 17 mL, 0.21 mol), sodium cyanoborohydride (7.8 g, 0.12 mol) and acetic acid (5.8 mL) were added to a cold (0°C) soln of the purified free base 3 (3.5 g, 9.3 mmol) in HPLC-grade acetonitrile (200 mL). The mixture, which exothermed to 12°C, was stirred for 10 min and cold sodium hydroxide (2 N NaOH-water, 3:7; 550 mL) was added. The soln was extracted with ether (2 x 500 mL). The extract (combined with that from an identical run) was concd to dryness and the residue was dissolved in ether (500 mL). The soln was washed with satd brine (4 x 250 mL), dried (K_2CO_3) and concd to a yellow oil which was dissolved in anhyd ether (500 mL). A soln of maleic acid (3.5 g, 0.03 mol) in methanol was added and the mixture was stirred for 1 h. The off-white solid was collected, washed with anhyd ether (2 x 150 mL) and dried (25°C, 18 h) to give crude title salt, 8 g.

This material (8 g) was partitioned between dichloromethane (700 mL) and 2 N aq NaOH (1 L). The organic layer was separated and the aq layer was reextracted with dichloromethane (300 mL). The combined organic layer was washed with deionized water (500 mL), dried (K_2CO_3) and concd to give crude free base, 8 g. The free base was chromatographed over silica gel (65 g, J.T. Baker) eluting with dichloromethane (250 mL) to give impure compound (0.6 g, discarded). The column was then eluted with 2% MeOH-CH_2Cl_2 (500 mL) to give partially purified free base which was codistilled with hexanes (2 x 100 mL) and dissolved in anhyd ether (250 mL). Charcoal was added and the ethereal soln was filtered (celite, x 2) and concd to give pure free base as clear light-yellow oil, 5.02 g (67%). A soln of maleic acid (1.31 g, 0.011 mol) in methanol (8 mL) was added to a soln of the free base (5.02 g, 0.012 mol) in anhyd ether (200 mL).

The mixture was stirred (30 min) and filtered. The solid was washed with anhyd ether (4 x 150 mL) and with petr ether (2 x 150 mL) and dried (45°C, 0.3 mmHg, 4 h) to give pure title maleate salt 4, 5.6 g (95%), mp 169-171°C. A 5.0 g sample was shipped to WRAIR on October 27, 1986 as Code No. DJD-07-65.

Anal. Calcd for $C_{30}H_{33}NO_7$ (519.67): C, 69.33; H, 6.40; N, 2.69. Found: C, 69.39; H, 6.30; N, 2.79.

5.4 3-Hydroxy-2,3,3-tris(3-trifluoromethylphenyl)propylamine Maleate (SNL-134, WR 256541)

5.5 1,1,2-Tris(3-trifluoromethylphenyl)-3-aminoprop-1-ene Maleate (SNL-136, WR 256540)

5.6 1,1,2-Tris(3-trifluoromethylphenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-135, WR 256539)

The sequence to the three title compounds is shown in Chart No. 3.

3-Hydroxy-2,3,3-tris(3-trifluoromethylphenyl)propionitrile (1): An ethereal soln of isopropyl magnesium chloride (90 mL, 2 M, 0.18 mol) was added to a soln of 3-trifluoromethylphenylacetonitrile (30 g, 0.16 mol) in dry tetrahydrofuran (450 mL) over 12 min, 0-5°C. The red soln was stirred (18 min, 0-5°C) and a soln of 3,3'-bis(trifluoromethyl)benzophenone (48 g, 0.15 mol) in dry tetrahydrofuran (300 mL) was added over 18 min (5°C) with continued stirring for 90 min. The mixture was poured into aq hydrochloric acid (1.5 L, concd acid-water, 1:19) and extracted with ether (1 L). the organic layer was separated, and the aq layer was extracted again with ether (500 mL). The combined ether extract was washed with cold water (2 x 500 mL) and with satd brine (500 mL) and dried (Na_2SO_4). The extract was concd to a thick orange oil, 83 g, which was purified by column chromatography over silica gel (800 g, J.T. Baker). The column was first eluted hexanes (1.5 L) and with CH_2Cl_2-hexanes (1:2, 1.5 L) to remove starting ketone, 6 g, and impure title compd, 8 g. The column was then eluted with CH_2Cl_2-hexanes (1:1, 2.5 L) and with CH_2Cl_2-hexanes (3:1, 1 L) to give purified title compd, 38.8 g (59%), mp 115-117°C.

An analytical sample, prepared from a trial run (10 g) had mp 116-118°C and gave the following results.

Anal. Calcd for $C_{24}H_{14}F_9NO$ (503.36): C, 57.26; H, 2.80; F, 33.97; N, 2.78. Found: C, 57.29; H, 2.68; F, 33.73; N, 2.71.

3-Hydroxy-2,3,3-tris(3-trifluoromethylphenyl)propylamine Maleate (2, SNL-134, WR 256541): - A soln of borane-tetrahydrofuran complex in tetrahydrofuran (600 mL, 1 M, 0.6 mol) was added under a nitrogen atmosphere to a soln of the hydroxypropionitrile 1 (38.8 g, 0.077 mol) in dry tetrahydrofuran (400 mL). The mixture was heated at reflux (steam bath) for 2.5 h, cooled to 5°C and treated with methanol (50 mL) to destroy excess borane. The mixture was heated to 50-60°C for 15 min and cond to dryness (aspirator). The residue was codistilled with hexanes (400 mL), then dissolved in ether (1 l). The soln was washed with aq 2 N NaOH (500 mL) and with cold water (500 mL), dried (Na_2SO_4) and concd to give the 3-hydroxypropylamine free base as an off-white syrup, 42 g.

Purification of the Free Base: - The free base, 42 g, was redissolved in anhyd ether (600 mL). The soln was filtered (celite) and the filtrate was stirred with a soln of maleic acid (13.5 g, 0.12 mol) in methanol (50 mL) for 15 min and concd to dryness. The residue was codistilled with hexanes (250 mL) and triturated with anhyd ether (600 mL). The white solid was collected, washed with anhyd ether (100 mL) and with petr ether (2 x 100 mL) and dried (25°C, 18 h) to give crude title salt, 31.5 g, mp 184-186°C.

This material, 42.6 g (31.5 g plus 11.1 g from a trial run), was partitioned between dichloromethane (1.5 L) and aq NaOH (2 L, 50% NaOH-water, 1:3) to regenerate the free base. The organic layer was separated and the aq layer was reextracted with dichloromethane (500 mL). The combined organic layer was washed with cold water (500 mL) and with satd brine (500 mL) and dried (K_2CO_3). The soln was filtered (celite), concd to dryness and triturated with hexanes (250 mL). The off-white solid was collected and dried (25°C, 0.3 mmHg, 18 h) to give the 3-hydroxypropylamine as a relatively pure free base, 30.8 g (89% recovery, 58% yield), mp 115-118°C.

Conversion to the Maleate Salt 2: - A portion of the free base (5.3 g) was purified further by chromatography over silica gel (50 g, J.T. Baker) eluting with hexanes (150 mL), CH_2Cl_2-hexane (3:7, 100 mL, 1:1, 100 mL; 7:3, 100 mL; 9:1, 100 mL) to remove impurities (discarded). Elution with dichloromethane (300 mL) gave pure title compd free base, 3.85 g (73% recovery), mp 117-119°C. A soln of maleic acid (0.82 g, 7.1 mmol) in methanol (3 mL) was added to a soln of the free base (3.85 g, 7.5 mmol) in anhyd ether (100 mL). The soln was stirred and concd to dryness. The residue was triturated with anhyd ether (150 mL) and the resulting white solid was washed with petr ether (50 mL) and dried (75°C, 0.3 mmHg, 2 h) to give pure title compd, 4.1 g (93%), mp 207-209°C (eff). A 3.5 g sample was shipped to WRAIR on December 29, 1986 ad Code No. DJD-07-89.

Anal. Calcd for $C_{20}H_{22}F_9NO_5$ (623.48): C, 53.93; H, 3.55; F, 27.42; N, 2.24. Found: C, 53.83; H, 3.79; F, 27.04; N, 2.09.

1,1,2-Tris(3-trifluoromethylphenyl)-3-aminoprop-1-ene Maleate (3, SNL-136, WR 256540): - Concd sulfuric acid (38.5 mL) was added to a hot (75°C) soln of the hydroxypropylamine free base 2 (25.5 g, 0.05 mol) in glacial acetic acid (77 mL). The mixture was heated (steam bath, 30 min), cooled and poured onto crushed ice (2.5 L). The pH of the mixture was adjusted to ca. 14 with 50% aq NaOH (200 mL) while maintaining the temp between 0-2°C. The product was extracted with ether (1 L). The organic layer was separated and aq layer was reextracted with ether (500 mL). The combined ether layer was washed with satd brine (500 mL), dried (K_2CO_3) and concd to dryness to give the title compd free base, 25 g, as a yellow oil. This material was purified by column chromatography over silica gel (250 g, J.T. Baker) eluting first with CH_2Cl_2-hexanes (3:7, 1 L; 6:4, 1 L; 9:1, 1 L) to remove impurities. Elution with 2% MeOH-CH_2Cl_2 (1 L) and 5% MeOH-CH_2Cl_2 (500 mL) gave partially purified free base as a yellow oil, 23.8 g. The oil was treated with cold petr ether with scratching and stirring to give pure title compd free base, 18 g (76%), mp 75-76°C, which was set aside for conversion to compd 4.

The filtrate was evaporated to dryness and the residue (ca. 5 g) was chromatographed over silica gel (50 g, J.T. Baker) eluting with CH_2Cl_2-hexanes (1:1, 300 mL; 3:1, 200 mL) to remove impurities. The column was then eluted with dichloromethane (1.3 L) to give additional partially purified free base, 4.4 g, as a yellow oil. This material was used for conversion to the maleate salt 3.

Conversion to the Maleate Salt 3: - A soln of maleic acid (0.94 g, 8.1 mmol) in methanol (4 mL) was added to a clear soln of the free base 3 (4.4 g, 9.0 mmol) in anhyd ether (200 mL). The mixture was stirred for 30 min and filtered. The solid was washed with anhyd ether (4 x 50 mL) and the petr ether (2 x 50 mL) and dried (25°C, 18 h) to give the purified title salt 3, 4.8 g (98%), mp 195-197°C. This material, combined with additional salt (1.7 g, from a pilot run) was dissolved in hot ethanol (110 mL). The soln was filtered hot (gravity), stirred (30 min at 10°C) and filtered. The white solid was washed with anhyd ether (2 x 50 mL) and with petr ether (100 mL) and dried (60°C, 0.3 mmHg, 16 h) to give pure title salt 3, SNL-136, 5.3 g (81%), mp 198-199°C. A 4.5 g sample was shipped to WRAIR on December 29, 1986 as Code No. DJD-07-97.

Anal. Calcd for $C_{28}H_{20}F_9NO_4$ (605.45): C, 55.54; H, 3.33; F, 28.24; N, 2.31. Found: C, 55.60; H, 3.23; F, 28.11; N, 2.16.

1,1,2-Tris(3-trifluoromethylphenyl)-3-dimethylaminoprop-1-ene Maleate (4, SNL-135, WR 256539): - Aq formaldehyde (37%, 13.2 mL, 0.16 mol), sodium cyanoborohydride (7.1 g, 0.11 mol) and acetic acid (6.3 mL) were added rapidly to a cold (3°C) soln of the free base 3 (5.25 g, 10.7 mmol) in HPLC-grade acetonitrile (250 mL, exothermed to

9°C). The mixture was stirred for 11 min (3°C) and cold dil NaOH (2 N NaOH-water, 1:3, 500 mL) was added. The mixture was extracted twice with ether (300 mL and 200 mL) and the combined extract was concd to dryness. The residue, combined with the product from an identical run, was redissolved in ether (500 mL). The soln was washed with satd brine (3 x 250 mL), dried (K_2CO_3) and concd to dryness. This residue was dissolved in methanol (25 mL) and maleic acid (4.5 g, 0.039 mol) was added with stirring. The soln was concd to dryness and the residue was codistilled with hexanes (200 mL) and triturated with anhyd ether (250 mL). The off-white solid was washed with anhyd ether (15 mL) and with petr ether (2 x 50 mL) and dried (25°C, 18 h) to give crude title salt, 7.2 g, mp 138-140°C. This material, combined with product from another run (2.75 g from 6 g of the free base 3) was dissolved in dichloromethane (400 mL). The soln was washed with 2 N NaOH (3 x 200 mL) and with satd brine (200 mL), dried (K_2CO_2) and concd to give the free base as an oil which was chromatographed over silica gel (80 g, J.T. Baker) eluting with CH_2Cl_2-hexanes (1:2, 450 mL) to remove impurities. Elution with CH_2Cl_2-hexanes (1:1, 500 mL, 8:2, 500 mL) to give pure title compd free base, 7.22 g (41%), as a light yellow oil.

Conversion to the Maleate Salt: - Maleic acid (1.46 g, 12.6 mmol) was added to a soln of the free base 4 (7.22 g, 13.9 mmol) in methanol (30 mL). The soln was stirred, filtered (celite) and concd to dryness. The residue was codistilled with hexanes (100 mL) and triturated with anhyd ether (175 mL). The white solid was washed with anhyd ether (2 x 50 mL) and with petr ether (2 x 50 mL) and dried (25°C, 0.3 mmHg, 18 h) to give pure title salt 4, 7.3 g (82%), mp 142-144°C. A 6.5 g sample was shipped to WRAIR on December 29, 1986 as DJD-07-94.

Anal. Calcd for $C_{30}H_{24}F_9NO_4$ (633.50): C, 56.87; H, 3.82; F, 26.99; N, 2.21. Found: C, 56.86; H, 3.60; F, 26.73; N, 2.37.

1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl-4-pyridyl]-3-dimethylaminoprop-1-ene Maleate

5.7 SNL-137, Isomer A, WR 256599

5.8 SNL-138, Isomer B, WR 256600

The sequence to the two isomers is shown in Chart No. 4.

2-Pyridyl-4-[6-(trifluoromethylphenyl)-2-trifluoromethyl]-pyridyl ketone: - The title ketone was prepared under an earlier contract as the precursor to the clinical antimalarial drug, WR 180,409. This material, Code Nos. AP-VIII-65, 73 and 75 (ref. 7) was purified as described below.

The ketone (108 g) was dissolved in hot, high-boiling petr ether (50-110°C, 800 mL). The soln was charcoaled, filtered (celite) and cooled to room temp for 1 h. The beige solid was collected and air-dried (25°C, 16 h) to give partially-purified title compd, 92 g, mp 84-86°C. This material (92 g) was redissolved in hot 2-propanol (400 mL), charcoaled, filtered (celite), refiltered (gravity) and held at room temp for 1 h. The cream-colored solid was collected and washed with petr ether (2 x 250 mL) and dried (55°C, 0.3 mmHg, 3 h) to give pure title compd, 68 g (63% recovery), mp 85-87°C.

Anal. Calcd for $C_{19}H_{10}F_6N_2O$ (396.29): C, 57.58; H, 2.54; F, 28.77; N, 7.07. Found: C, 57.49; H, 2.34; F, 28.50; N, 7.29.

1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl-4-pyridyl]-3-dimethylaminoprop-1-ene Maleate (Isomer A, SNL-137, WR 256599 and Isomer B, SNL-138, WR 256600: - n-Butyllithium (1.6 M in hexanes, 55 mL, 0.088 mol) was added dropwise to a suspension of 2-dimethylaminoethyltriphenylphosphonium bromide (32.5 g, 0.078 mol) in dry tetrahydrofuran (THF, 450 mL) maintained at 0-3°C (exothermed to 9°C) with stirring. The mixture was stirred for 12 min and a soln of the above pure dipyridyl ketone (25 g, 0.063 mol) in dry THF (200 mL) was added dropwise over 20 min. The mixture was stirred for 30 min, warmed to room temp, then stirred for 90 min. Deionized water (50 mL) was added and the mixture was concd to dryness. The residue was codistilled with hexanes (2 x 200 mL), then partitioned between ether (500 mL) and 2 N NaOH (400 mL). The organic layer was separated, washed with aq 2 N NaOH (400 mL) and with satd brine (200 mL), dried (K_2CO_3) and filtered. A soln of anhyd oxalic acid (8.5 g, 0.094 mol) in anhyd ether (400 mL) was added to the filtrate. The mixture was stirred for 30 min and filtered. The solid was washed with anhyd ether (2 x 250 mL) and with petr ether (250 mL) and dried (25°C, 18 h) to give the oxalate salt of the title free base, 33.5 g. This solid, together with additional salt (6 g) from a trial run, was partitioned between dichloromethane (500 mL) and aq 2 N NaOH (400 mL). The organic layer was separated, washed with aq 2 N NaOH (400 mL) and satd brine (200 mL) and dried (K_2CO_3). The soln was filtered and concd to dryness. The residue (ca. 30 g) was chromatographed over silica gel (300 g, J.T. Baker), eluting with dichloromethane (2 L) to remove impurities. The column was then eluted with 2.5% MeOH-CH_2Cl_2 (2 L) and 5% MeOH-CH_2Cl_2 (1 L) to give partially-purified product, 21 g. This material was rechromatographed over silica gel (210 g, J.T. Baker), again eluting with dichloromethane (1.5 L) to remove impurities. Elution with 1% MeOH-CH_2Cl_2 (1 L) gave slightly impure free base, 4.3 g, followed by 3% MeOH-CH_2Cl_2 (1 L) and 5% MeOH-CH_2Cl_2 (1.5 L) to give pure title free base as a reddish-brown oil. The oil was dissolved in hexanes (200 mL) and charcoaled. The soln was filtered (celite, x 2) and concd to give pure title free base, 14.87 g (44%).

Conversion to the Maleate Salt, Isomer A (SNL-137, WR 256599): A soln of maleic acid (3.37 g, 0.029 mol) in warm (45°C) methanol (10 mL) was added to a soln of the above pure free base (14.87 g, 0.033 mol) in anhyd ether (250 mL). The mixture was stirred for 30 min at room temp and filtered. The off-white solid was washed with anhyd ether (4 x 50 mL) and with petr ether (2 x 50 mL) and dried (80°C, 0.3 mmHg, 2 h) to give the title maleate salt, 5.35 g (32%), mp 153-155°C, designated as Isomer A.

Anal. Calcd for $C_{27}H_{23}F_6N_3O_4$ (567.74): C, 57.14; H, 4.08; F, 20.09; N, 7.40. Found: C, 57.17; H, 4.06; F, 20.26; N, 7.54.

Isomer B (SNL-138, WR 256600): - The filtrate from the isolation of Isomer A was concd to dryness. The residue was codistilled with hexanes (100 mL) and triturated extensively with anhyd ether (300 mL). The off-white solid was collected, washed with anhyd ether (2 x 50 mL) and with petr ether (2 x 100 mL) and dried (80°C, 0.3 mmHg, 2 h) to give the title maleate salt, 9.15 g (55%), mp 138-140°C, designated Isomer B.

Anal. Calcd for $C_{27}H_{23}F_6N_3O_4$ (567.74): C, 57.14; H, 4.08; F, 20.09; N, 7.40. Found: C, 57.23; H, 4.18; F, 20.24; N, 7.54.

A 4.5 g sample of isomer A as Code No. DJD-07-107 and 8.5 g sample of isomer B as Code No. DJD-07-107A were shipped to WRAIR on January 20, 1987.

5.9 1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl-4-pyridyl]-2-amidoximinoethylene Maleate (SNL-139, WR 256782)

The three step sequence to the title compound is shown in Chart No. 5.

Triphenylphosphoranylideneacetonitrile (1): - Aq 2 N sodium hydroxide (75 mL, 0.15 mol) was added to a soln of cyanomethyltriphenylphosphonium chloride (50 g, 0.15 mol) in dichloromethane (600 mL). The mixture was stirred vigorously for 2 h. The organic layer was separated, washed with deionized water (3 x 250 mL), dried (K_2CO_3) and filtered. The volume was reduced to ca. 150 mL and diluted with anhyd ether (400 mL). The mixture was stirred for 1 h and filtered. The solid was washed with anhyd ether (3 x 150 mL) and dried (50°C, 0.3 mmHg, 16 h) to give the title intermediate 1, 31.5 g (71%), mp 183-187°C; lit. mp 190-192°C (9).

1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl)-4-pyridyl]-2-amidoximinoethylene Maleate (3, SNL-139, WR 256782)

Preparation of the Intermediate Dipyridylacrylonitrile 2: - The dipyridyl ketone (30 g, 0.076 mol), purified as described above in sections 5.7 and 5.8, was added to a soln of phosphorane 1 (28.5 g, 0.095 mol) in dichloromethane (300 mL). The yellow soln was stirred for 3 h, and concd to dryness. The residue was codistilled with hexanes (2 x 150 mL) and chromatographed over silica gel (800 g, J.T. Baker) eluting with benzene (5 L). The benzene eluate was concd to dryness and dried (25°C, 0.3 mmHg, 16 h) to give pure dipyridylacrylonitrile 2, 31.2 g (98%), as a thick yellow syrup. Two isomers were present by TLC (Polygram 1% MeOH-$CHCl_3$) and the IR spectrogram showed a strong nitrile peak at 2250 cm^{-1}. This material was used as such in the next step.

Conversion of the Nitrile 2 to the amidoxime Free Base 3; Purification via the Oxalate Salt: - Hydroxylamine hydrochloride (15.7 g, 0.22 mol) was added to a soln of the nitrile 2 (31.2 g, 0.074 mol) in methanol (300 mL) maintained under nitrogen. Sodium bicarbonate (19 g, 0.23 mol) was added. The mixture was heated at reflux (steam bath) for 2 h, concd to dryness (aspirator) and the green residue was stirred with deionized water (500 mL). The mixture was filtered and the solid was dissolved in ether (1 L). The soln was washed with deionized water (2 x 250 mL) and dried ($MgSO_4$), charcoaled and filtered (celite). Anhyd oxalic acid (30 g, 0.33 mol) was added to the filtrate. The soln was reduced to 400 mL in volume, stirred for 30 min and filtered. The solid was washed with anhyd ether (2 x 100 mL) and with petr ether (100 mL) and air-dried (25°C, 16 h) to give the crude oxalate salt of the title free base, 25.5 g (63%), mp 145°C. The oxalate salt was dissolved in hot acetonitrile (400 mL), charcoaled, filtered (celite) and the volume was reduced to ca. 50%. The suspension was stirred for 30 min and filtered. The solid was washed with anhyd ether (3 x 50 mL) and with petr ether (50 mL) and dried (50°C, 0.3 mmHg, 1 h) to give pure oxalate salt, 19.2 g (75%), mp 165-170°C.

The oxalate salt was stirred with 1 N NaOH (500 mL) to liberate the free base which was extracted with ether (2 x 300 mL). The ether extract was washed with deionized water (3 x 150 mL), dried (K_2CO_3), charcoaled, filtered (celite) and concd to dryness. The residual solid was triturated with hexanes (150 mL), collected and air-dried (25°C, 16 h) to give purified title free base, 14.4 g. The free base, a yellow solid, was purified further by column chromatography over silica gel (250 g, J.T. Baker) eluting with dichloromethane (2 L, discarded). The column was eluted with 1% MeOH-CH_2Cl_2 (3 L). The eluate was concd and the residue was triturated with hexanes (150 mL) to give pure free base, 10.45 g (65%), mp 174-176°C.

Conversion of the Free Base to the Maleate Salt 3: - A soln of maleic acid (2.42 g, 0.021 mol) in methanol (15 mL) was added to a soln of pure free base (10.45 g, 0.023 mol) in anhyd ether (150 mL). The soln was stirred, concd to dryness and the residue was codistilled with hexanes (100 mL). The yellow gummy residue was triturated with anhyd ether (50 mL) and stirred for 30 min at ca. 10°C. The solid was collected, washed with anhyd ether (2 x 15 mL) and with petr ether (3 x 25 mL) and dried (70°C, 0.3 mmHg, 1 h) to give pure title maleate salt 3, 11.4 g (96%), mp 168-170°C. A 10 g sample was shipped to WRAIR on March 4, 1987 as Code No. DJD-07-117.

Anal. Calcd for $C_{25}H_{18}F_6N_4O_5$ (568.42): C, 52.82; H, 3.19; F, 20.06; N, 9.86. Found: C, 52.87; H, 3.21; F, 19.77; N, 10.06.

5.10 3-Hydroxy-3-[4-(4'-methoxyphenoxy)phenyl]-3-(4-methoxyphenyl)-propylamine Maleate 1 (SNL-140, WR 256780)

5.11 1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-amino-prop-1-ene Maleate 2 (SNL-142, WR 256779)

5.12 1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-dimethylaminoprop-1-ene Maleate 3 (SNL-141, WR 256781)

The synthesis sequence for the above three compounds is shown in Chart No. 6.

3-Hydroxy-3-[4-(4'-methoxyphenoxy)phenyl]-3-(4-methoxyphenyl) propylamine Maleate (1, SNL-140, WR 256780): - A soln of the 3-hydroxypropionitrile (45.5 g, 0.12 mol, ref. 2) in dry tetrahydrofuran (THF, 500 mL) was added over 40 min to a suspension of lithium aluminum hydride (18.3 g, 0.48 mol) in dry anhyd ether (150 mL) held between 5-10°C (ice bath). The mixture was warmed and stirred for 1 h at room temp, then cooled to -20°C. Aq THF (H_2O-THF, 1:4; 30 mL), water (30 mL), 15% aq sodium hydroxide (43.5 mL) and water (72.5 mL) were added. The mixture was stirred for 30 min and filtered (celite). The inorganic residue was slurried with THF (250 mL) and dichloromethane (250 mL). The mixture was filtered (celite) and the filtrate was concd to dryness. The residue was dissolved in ethyl acetate (500 mL). The organic layer was separated, dried (Na_2SO_4), concd and the syrup was triturated extensively with anhyd ether (200 mL). The pale yellow solid was washed with cold anhyd ether (3 x 50 mL) and dried (25°C, 0.3 mmHg, 2 h) to give the title compd 1 as a free base, 32.9 g (71%), mp 116-119°C. Additional free base was obtained from the filtrate, 2.8 g (6%), mp 115-118°C.

Conversion to the Maleate Salt 1: - A portion of the free base 2 (6 g) was purified further by chromatography over silica gel (60 g, J.T. Baker) eluting first with dichloromethane (250 mL) to remove impurities. The column was eluted successively with 1% MeOH-CH_2Cl_2 (500 mL) and with 2% MeOH-CH_2Cl_2 (500 mL). The appropriate fractions were combined, concd and the residue was triturated with hexanes (50 mL) and dried (60°C, 0.3 mmHg, 1 h) to give pure free base 1, 3.6 g (60%), mp 120-122°C.

Maleic acid (1.03 g, 8.9 mmol) was added to a soln of the free base (3.6 g, 9.5 mmol) in warm (40°C) methanol (30 mL) with stirring. The soln was filtered (gravity) and concentrated to dryness. The residue was codistilled with hexanes (50 mL) and stirred with anhyd ether (100 mL) for 16 h. The white solid was washed with anhyd ether (2 x 25 mL) and with petr ether (50 mL) and dried (70°C, 0.3 mmHg, 2 h) to give pure title maleate salt 1, SNL-140, 4.1 g (93%), mp 164-166°C. A 3.5 g sample was shipped to WRAIR on March 4, 1987 as Code No. DJD-07-118.

Anal. Calcd for $C_{27}H_{29}NO_8$ (495.50): C, 65.44; H, 5.90; N, 2.83. Found: C, 65.61; H, 6.06; N, 3.01.

1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-amino-prop-1-ene Maleate (2, SNL-142, WR 256779): - Concd hydrochloric acid (120 mL) was added to a warm (60°C) soln of the free base 1 (29.5 g, 0.078 mol) in acetic acid (295 mL). The mixture was heated (steam bath) for 35 min and concd to dryness (aspirator, steam bath). The residue was dissolved in warm (50°C) deionized water (325 mL). The soln was cooled to 10°C and the pH was adjusted to ca. 14 with aq 2 N NaOH (200 mL). The soln was extracted with ether (750 mL) and the extract was washed with deionized water (2 x 250 mL) and dried (K_2CO_3) with charcoaling. The soln was filtered (celite) and concd to give crude title compd 2 free base, 26 g, as a thick orange oil. The oil was purified by column chromatography over silica gel (260 g, J.T. Baker), eluting with dichlomethane (1.5 L) and with 1% MeOH-CH_2Cl_2 (1 L) to remove impurities. The column was then eluted with 2% MeOH-CH_2Cl_2 (1 L) to give slightly impure free base 2, 9.94 g. Elution with 3% MeOH-CH_2Cl_2 (1 L) and with 4% MeOH-CH_2Cl_2 (1 L) gave pure title free base 2, 13.9 g. The combined yield of free base 2 in this step was 23.8 g (85%) from free base 1.

Conversion to the Maleate Salt 2: - A soln of maleic acid (2.9 g, 0.025 mol) in methanol (25 mL) was added to a soln of the above slightly impure free base (9.94 g) in anhyd ether (200 mL) gave crude title salt, 11.3 g, which after crystallization from acetonitrile (400 mL) gave partially purified salt, 8.5 g (71%). This salt was partitioned between dichloromethane (500 mL) and aq 2 N NaOH (500 mL). The organic layer was separated, washed with satd aq sodium chloride (2 x 200 mL), dried (K_2CO_3) and concd to give crude free base 2, 6.5 g. This was purified by column chromatography over silica gel (65 g, J.T. Baker) eluting with dichloromethane (500 mL) and with 1% MeOH-CH_2Cl_2 (500 mL) to remove impurities. The column was then eluted successively with 2% MeOH-CH_2Cl_2 (500 mL), 4% MeOH-CH_2Cl_2 (500 mL) and 6% MeOH-CH_2Cl_2 (500 mL) to give purified free base 3, 6.22 g (96%).

This material was converted, as described above, to the title maleate salt (7.5 g). The salt crystallized from acetonitrile (6.6 g), but the product did not give acceptable elemental analysis. Accordingly, as described above also,the salt was converted back to the free base 2 which was extracted with warm hexanes-anhyd ether (2:1, 150 mL). The extract was filtered (celite) and concd to give purified free base 2 as clear yellow oil, 4.99 g (quantitative). A soln of maleic acid (1.45 g, 0.012 mol) in methanol (10 mL) was added to the soln of the pure free base 2 (4.99 g, 0.014 mol) in anhyd ether (200 mL). The soln was stirred for 1 h and filtered. The light yellow solid washed with ether (2 x 100 mL) and with petr ether (100 mL) and dried (25°C, 0.3 mmHg, 18 h) to give pure title maleate salt 2, SNL-142, 5.9 g (99%), mp 150-152°C with effervescence at 165°C. A 5.0 g sample was shipped to WRAIR on March 4, 1987 as Code No. DJD-07-128.

Anal. Calcd for $C_{27}H_{27}NO_7$ (477.50): C, 67.91; H, 5.70; N, 2.93. Found: C, 67.87; H, 5.52; N, 3.13.

1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-dimethylaminoprop-1-ene Maleate (3, SNL-141, WR 256781): - Aq formaldehyde (37%, 35 mL, 0.44 mol), sodium cyanoborohydride (13 g, 0.20 mol) and acetic acid (10 mL) were added rapidly to a cold soln of free base 2 (5.66 g, 0.016 mol) in HPLC-grade acetonitrile (300 mL, exothermed to + 11°C). The mixture was stirred for 10 min (10°C) and cold aq NaOH (2 N NaOH-water, 4:6, 500 mL) was added. The mixture was extracted with ether (500 mL) and the layers were separated. The aqueous layer was reextracted with ether (300 mL). The combined ether extracts were combined further with free base (2.45 g) from a prior run. The soln was concd to dryness and the residue redissolved in ether (500 mL). The ether soln was washed with satd brine (3 x 200 mL), dried (K_2CO_3) and filtered (celite).

A soln of maleic acid (4 g, 0.034 mol) in methanol (20 mL) was added to the filtrate. The mixture was stirred for 5 min, concd to dryness and codistilled with hexanes (100 mL). The gummy residue was triturated extensively with anhyd ether (300 mL) with scratching. The

resulting solid was collected and air-dried for 16 h to give crude title maleate salt 3, 4.1 g (36%). Using this procedure, the free base 2 (13.85 g total) was processed to give crude title salt 3 (6.45 g). The filtrates from all the runs were concd to dryness and the residue was partitioned between dichloromethane (250 mL) and 15% aq NaOH (300 mL). The organic layer was separated, washed with satd brine (100 mL), dried (K_2CO_3) and concd to a residue, 12 g. This material (12 g) was chromatographed over silica gel (80 g, J.T. Baker) eluting with dichloromethane (1 L) to remove impurities. Elution with 2% MeOH-CH_2Cl_2 (500 mL) gave partially purified title free base, ca. 7 g.

Purification of the Partially-Purified Free Base 3: - A soln of maleic acid (2.7 g, 0.023 mol) in methanol (10 mL) was added to a soln of the partially purified free base (7 g, 0.018 mol) in anhyd ether (150 mL). The mixture was stirred for 5 min and concd to dryness. The mixture was codistilled with hexanes (100 mL) and triturated with ethanol-anhyd ether (1:15, 160 mL). The white solid was slurried with anhyd ether (200 mL) and air-dried (25°C, 16 h) to give additional purified title salt 3, 9 g, total 15.45 g. This material (15.45 g) was dissolved in dichloromethane (600 mL). The soln was washed with 2 N aq NaOH (4 x 250 mL), satd brine (2 x 150 mL), dried (K_2CO_3), filtered and concd to dryness (10 g). The residue was chromatographed over silica gel (80 g, J.T. Baker) eluting with dichloromethane (500 mL) to remove impurities. Elution with 1% MeOH-CH_2Cl_2 (500 mL) and with 2% MeOH-CH_2Cl_2 (500 mL) gave purified title free base, 9 g. This material was extracted with warm (60°C) hexanes (3 x 75 mL). The extract was filtered (celite) and concentrated to give pure title free base 3, 8.2 g (55%).

Preparation of the Maleate Salt 3 (SNL-141): - A soln of maleic acid (2.2 g, 0.019 mol) in methanol was added to the a soln of pure free base 3 (8.2 g, 0.021 mol) in anhyd ether (200 mL). The soln was stirred, filtered and the white solid was slurried with additional anhyd ether (150 mL). The slurry was filtered and the solid was washed with anhyd ether (50 mL) and with petr ether (50 mL) and dried (25°C, 0.3 mmHg, 16 h) to give pure title maleate salt 3, SNL-141, 7.1 g (74%), mp 122-125°C. A 6.0 g sample was shipped to WRAIR on March 4, 1987 as Code No. DJD-07-123.

Anal. Calcd for $C_{29}H_{31}NO_7$ (505.55): C, 68.89; H, 6.18; N, 2.77. Found: C, 68.88; H, 6.20; N, 2.84.

5.13 8-[(4-Amino-1-methylbutyl)amino]-4-methyl-2,5,6-trimethoxyquinoline Hemisuccinate (SNL-143, WR 257305)

The route to the title 2,5-dimethoxy-4-methylprimaquine is shown in Chart No. 7.

8-Amino-4-methyl-2,5,6-trimethoxyquinoline: - Recovered 8-amino-4-methyl-2,5,6-trimethoxyquinoline from an earlier program (1) was purified prior to use as starting material. The impure material (15.3 g) was dissolved in anhyd ether (750 mL). The soln was charcoaled and filtered (celite) and the volume of the filtrate was reduced to ca. 100 mL. The light yellow-green solid was collected and dried (25°C, 1 1/2 h, 0.3 mmHg) to give pure title compd, 9.7 g (63% recovery), mp 115-117°C; lit. mp 114-115°C (1, p. 38).

Anal. Calcd for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.88; H, 6.50; N, 11.29. Found: C, 63.03; H, 6.70; N, 11.40.

From the mother liquor, additional title compd, 1 g (6%), with the same mp was obtained.

8-[(4-Phthalimido-1-methylbutyl)amino]-4-methyl-2,5,6-trimethoxyquinoline (1): - A soln of the above 8-aminoquinoline 1 (9.6 g, 38.7 mmol), 4-iodo-1-phthalimidopentane (13.9 g, 40.5 mmol) and diisopropylamine (4.2 g, 41.5 mmol) in acetonitrile (80 mL) was heated at reflux (steam bath) for 48 h. Additional 4-iodo-1-phthalimidopentane (6.9 g, 20 mmol) and diisopropylamine (2.1 g, 20.7 mmol) were added after 21 h and 28 h. The soln was allowed to cool to room temp, saturated brine (200 mL) was added and the soln was extracted with ether (300 mL). The extract was washed with saturated brine (3 x 50 mL), dried (K_2CO_3) with charcoaling and filtered (celite). The filtrate was concd to dryness and codistilled with hexanes (2 x 100 mL). The residue was dissolved in warm (ca. 40°C) hexanes-ethanol (10:1, 220 mL). Seed crystals from a trial run were added and the soln was stirred at room temp for 18 h. The bright orange solid was collected, washed with hexanes (3 x 100 mL) and dried (25°C, 2 h, 0.3 mmHg) to give pure title compd, 11.2 g (62%), mp 92-94°C.

Anal. Calcd for $C_{26}H_{29}N_3O_5$ (463.51): C, 67.37; H, 6.31; N, 9.07. Found: C, 67.43; H, 6.11; N, 9.21.

Additional title compd, 1.4 g (8%) was obtained from the mother liquor.

8-[(4-Amino-1-methylbutyl)amino]-4-methyl-2,5,6-trimethoxyquinoline Hemisuccinate (2, SNL-143, WR 257305): - Anhyd hydrazine (3.8 g, 0.12 mol) was added to a warm (40-50°C) soln of intermediate 1 (12.4 g, 26.8 mmol) in ethanol (500 mL). The mixture was heated at reflux (steam bath) for 1 h, additional anhyd hydrazine (0.75 g, 23.4 mmol) was added, and the reflux was continued for 30 min. The mixture was cooled to room temp, filtered and the solid was washed with ethanol (100 mL). The filtrate was concd to dryness, codistilled with hexanes (2 x 100 mL), then treated with dichloromethane (200 mL) and 25% aq NaOH (100 mL). The organic layer was separated, washed with additional 25% aq NaOH (50 mL) and with saturated brine (2 x 100 mL) and dried (K_2CO_3) with charcoaling. The soln was filtered (celite), concd to dryness to give crude title compd free base, 9 g, as a green oil. The oil was chromatographed over silica gel (65 g, Baker) eluting with dichloromethane (500 mL, discarded). The column was eluted with 2% MeOH-CH_2Cl_2 (250 mL) to give slightly impure free base, 0.6 g. Elution with 4%, 6%, 8%, 10% MeOH-CH_2Cl_2 (250 mL each) gave pure free base, 7.34 g (82%).

Attempted Preparation of the Succinate Salt: - A warm (ca. 40°C) soln of succinic acid (2.61 g, 22.1 mmol) in ethanol (30 mL) was added to a soln of the pure title compd free base (7.34 g, 22 mmol) in anhyd ether (750 mL). The mixture was stirred for 30 min and filtered. The solid was washed with anhyd ether (2 x 200 mL) and dried (25°C, 16 h, 0.3 mmHg) to give the monosuccinate salt, 9 g, mp 158-160°C. The elemental analysis was not acceptable and so the salt was converted back to the free base as follows.

The monosuccinate salt (9 g from above, plus 0.7 g from probe runs) was suspended between dichloromethane (750 mL) and 10% aq NaOH (750 mL). The organic layer was separated, washed successively with 10% aq NaOH (300 mL) and brine (3 x 250 mL) and deionized water (2 x 250 mL) and dried (K_2CO_3). The soln was filtered and concd to dryness. The residue was codistilled with hexanes (100 mL), dissolved in warm hexanes (150 mL), charcoaled, filtered (celite), refiltered (gravity) and concd to dryness. The yellow oil was dried (50°C, 0.1 mmHg, 1 h) to give pure free base, 7.13 g.

Conversion to the Hemisuccinate Salt (2, SNL-143): - A soln of succinic acid (2.66 g, 22.5 mmol) in hot ethanol (30 mL) was added to a soln of the pure free base of the title compd (7.13 g, 21.4 mmol) in ethanol (15 mL). The mixture was stirred at room temp for 18 h and filtered. The solid was washed with cold ethanol (20 mL) and with anhyd ether (3 x 50 mL) and dried (80°C, 2 h, 0.3 mmHg) to give the pure title primaquine, 6 g (71%), mp 163-165°C. A 5.5 g sample was shipped to WRAIR on May 21, 1987 as Code No. DJD-07-153.

Anal. Calcd for $C_{20}H_{30}N_3O_5$ (392.46): C, 61.20; H, 7.70; N, 10.71; O, 20.38. Found: C 61.36; H, 7.80; N, 11.24; O, 20.17.

From the mother liquor additional pure title compd, 1.7 g (20%) with same mp was obtained and placed in storage.

5.14 6-Methoxy-4-methyl-8-[(6-pyrrolidinohexyl)amino]quinoline dihydrochloride (4, SNL-144, WR 257566)

The route to the title compd is shown in Chart No. 8.

8-Amino-6-methoxy-4-methylquinoline (1): - The title compd was prepared by the reduction of 6-methoxy-4-methyl-8-nitroquinoline (16 g) with Raney nickel catalyst using a procedure (slightly modified) developed under a prior contract (10). The crude product was chromatographed over silica gel followed by crystallization from cyclohexane (75 mL) to give the title intermediate 1, 11.6 g (84%), mp 84-86°C; lit. mp 86.5-87.5°C (10).

6-Bromo-N-(6-methoxy-4-methyl-8-quinolinyl)hexanamide (2): - A soln of 6-bromohexanoyl chloride (16.8 g, 0.08 mol) in reagent acetone (50 mL) was added with stirring at room temp over 20 min (small exotherm) to a mixture of intermediate 1 (11.6 g, + 3 g from an earlier run, 0.08 mol) and sodium carbonate (13.6 g, 0.13 mol) in reagent acetone (180 mL). The mixture was refluxed (steam bath) for 2 1/2 h and allowed to cool to room temp. Triethylamine (11 mL) was added to the stirred mixture until the gold yellow color disappeared. The solid was collected, washed with dichloromethane (2 x 100 mL). The filtrate was concd to dryness and the residue was dissolved in dichloromethane (500 mL). The organic layer was washed with deionized water (250 mL) and with saturated brine (250 mL) and dried (Na_2SO_4). The organic soln was filtered and concd to dryness. The residue was stirred with hexanes (250 mL) for 10 min. The solid was collected and air-dried (1 h) to give crude title compd, 25.5 g. This solid was recryst from ethanol (250 mL) to give pure title compd, 22.3 g (79%), mp 115-118°C; lit. mp 114-116°C (11).

6-Pyrrolidino-N-(6-methoxy-4-methyl-8-quinolinyl)hexanamide (3): - A soln of intermediate 2 (18.3 g, 0.05 mol) in pyrrolidine (90 mL) was heated (steam bath) for 1 1/2 h (internal temp 83-85°C). The soln was concd to dryness and the residue was treated with cold water (400 mL). The solid was collected and dissolved in dichloromethane (300 mL). The soln was washed with deionized water (150 mL) and with saturated brine (300 mL) and dried (Na_2SO_4) with charcoaling. The soln was filtered (celite), concd to dryness and codistilled with hexanes (100 mL). The residue was dissolved in hot hexanes (300 mL). The soln was charcoaled, filtered (celite), refiltered (gravity) and the volume was reduced to ca. 100 mL. The off-white solid was collected and dried (25°C, 20 h) to give pure title compd, 11 g (62%), mp 73-76°C. An analytical sample, prepared as described above, had mp 75-76°C.

Anal. Calcd for $C_{21}H_{29}N_3O_2$ (355.46): C, 70.95; H, 8.22; N, 11.82. Found: C, 70.78; H, 8.50; N, 11.61.

8-[(6-Pyrrolidinohexyl)amino]-6-methoxy-4-methylquinoline Dihydrochloride (4, SNL-144, WR 257566): - A soln of the amide 3 (5.5 g, 15.5 mmol) in dry tetrahydrofuran (150 mL) was added at room temp (slight exotherm) over a 30 min period to a suspension of lithium aluminum hydride (5.5 g, 0.14 mol) in dry tetrahydrofuran (250 mL). The mixture was stirred at room temp for 21 h, cooled to ca. 10°C (ice bath) and 2 N aq NaOH (25 mL) was added over 30 min while maintaining the temp between 15-22°C. The mixture was stirred for 10 min and filtered (celite) to remove salts. The salts were slurried with tetrahydrofuran (200 mL) for 10 min and filtered (celite). An identical run was carried out and the filtrates were combined with those from the first run. The combined filtrates were concd to dryness and codistilled with hexanes (2 x 100 mL) to give a dark orange residue. This residue was dissolved in dichloromethane (400 mL). The soln was dried (K_2CO_3), filtered and concd to dryness. The residue was codistilled with hexanes (100 mL) to give crude title compd as a free base, 10.7 g, oil.

This oil was chromatographed over silica gel (110 g, J.T. Baker), eluting with dichloromethane (1 l) to remove faster impurities (discarded). The column was then eluted with 1% MeOH-CH_2Cl_2 (500 mL) to give slightly impure free base, 1 g. Further elution successively with 2%, 3%, 4% and 5% MeOH-CH_2Cl_2 (500 mL each) gave pure title free base, 6 g (57%).

Conversion to the Hydrochloride Salt: - Hydrogen chloride-2-propanol soln (7.6 mL of 4.6 molar soln, 35 mmol) was added with stirring to a warm (ca 40°C) soln of pure free base (6 g, 17.6 mmol) in 2-propanol (60 mL). The mixture was stirred at room temp for 1 h and filtered. The bright yellow-orange solid was washed with anhyd ether (2 x 100 mL) to give purified title compd, 5.2 g. Similarly slightly impure free base was converted to purified salt, 0.7 g.

Both salts (5.9 g) were redissolved in hot 2-propanol (120 ml). The hot soln was filtered (gravity) and the filtrate was stirred at room temp for 18 h. The bright yellow solid was collected, washed with cold 2-propanol (2 x 10 mL) and with anhyd ether (2 x 100 mL) and dried (80°C, 2 h, 0.3 mmHg) to give pure title compd, 5.45 g (42%), mp 202-204°C. A 5.0 g sample was shipped to WRAIR on July 14, 1987 as Code No. DJD-07-161.

Anal. Calcd for $C_{21}H_{33}Cl_2N_3O$ (414.41): C, 60.86; H, 8.03; Cl, 17.11; N, 10.14. Found: C, 60.81; H, 8.00; Cl, 17.31; N, 10.41.

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