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NAPHTHYRIDINE ANTIMALARIAL AGENTS

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NAPHTHYRIDINE
ANTIMALARIAL
AGENTS

FINAL TECHNICAL REPORT

for

April 1, 1973 - June 30, 1975

by

JOHN F. PILOT
EUGENE L. STOGRYN
(201-474-2015)

JUNE, 1975

Sponsored By

UNITED STATES ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
WASHINGTON, D.C. 20314

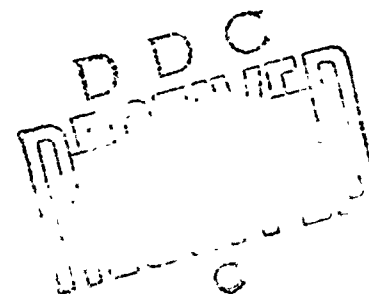
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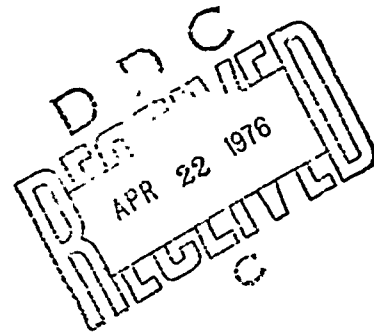
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naphthyridine target and 145 naphthyridine intermediates and miscellaneous precursors have been prepared and submitted for biological testing.

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The brunt of the second years program was the formation of 2-methoxy-4-amino-1,5-naphthyridine derivatives, isosteric to primaquine, pentaquine, and pamaquin. In addition, both the 6-methyl (alkoxy) and the 8-methyl functionalities were desired because of their known activity enhancement in the related 8-amino quinolines. Accordingly, the requisite 6- and 8-substituted-2,4-dichloro-1,5-naphthyridines were synthesized.

The terminal phase of the naphthyridine program yielded authentic 4-amino-1-methyl-naphthyridin-2-one derivatives and a 2,6-dialkoxy-4-amino-1,5-naphthyridine.

While antimalarial testing has not yet been completed, results obtained for most of the target drugs submitted to WRAIR have disclosed no significant prophylactic activity in the lower dosage range (1.0 and 3.0 mg/kg). However, one of the target structures, 2-hydroxy-4-(5-isopropyl-aminopentylamino)-1,5-naphthyridine, has now proven to be curative in the Rhesus monkey infected with sporozoites of the R strain of P.cynomolgi at a dosage level of 10.0 mg/kg. In the P.berghei/mouse, curative screen to date, the targets showed only marginal activity and the sixty-four variously substituted intermediates or precursors, no activity.

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I. SUMMARY

Interest in the 4-amino-1,5-naphthyridines as potential prophylactic antimalarial agents has been generated by the structural similarity of this ring system to both the 4- and 8-aminoquinolines. In our synthetic studies during this program, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine which are currently available in an effort to secure an optimal prophylactic antimalarial drug. Accordingly, as a result of our synthetic efforts, a total of 26 naphthyridine target and 145 naphthyridine intermediates and miscellaneous precursors have been prepared and submitted for biological testing.

The synthetic studies during the first year of our program was concerned mainly with the formation of three classes of target structures: 2-alkoxy, 6-alkoxy, and 2,6-dialkoxy-4-amino-1,5-naphthyridine. Significant accomplishments included: new synthetic techniques for the preparation of 6-alkoxy-4-amino-1,5-naphthyridines and for the introduction of the pentaquine sidechain into alkoxy-1,5-naphthyridines.

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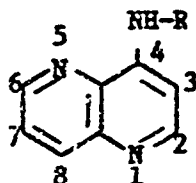
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While antimalarial testing has not yet been completed, results obtained for most of the target drugs submitted to WRAIR have disclosed no significant prophylactic activity in the lower dosage range (1.0 and 3.0 mg/kg). However, one of the target structures, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine, has now proven to be curative in the Rhesus monkey infected with sporozoites of the B strain of P.cynomolgi at a dosage level of 10.0 mg/kg. In the P.berghei/mouse, curative screen to date, the targets showed only marginal activity and the sixty-four variously substituted intermediates or precursors, no activity.

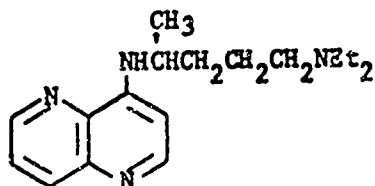
2. INTRODUCTION

The drugs presently available for the treatment of malaria suffer from two serious deficiencies. First, no single agent is suitable for all purposes. Secondly, drug resistant strains of the parasite have evolved in the early 1960's. Clearly, further developments in drug design must lead to agents which possess pharmacologic and chemotherapeutic properties which are superior to those presently available. The goals of new synthetic efforts must be directed toward the development of agents which exhibit broad activity against all life cycles of the parasite. In addition, they should possess high potency, low toxicity, and a long duration of activity. Ideally, a prophylactic drug is sought for the recently encountered drug resistant strains of the malaria parasite.

With all of the above in mind, it is our contention that certain 4-amino-1,5-naphthyridines,



should possess the desired prophylactic characteristics. Quinine, a classic example of a specific chemotherapeutic agent, incorporates a quinoline ring as a basic structural fragment. The quinoline nucleus has, therefore, served as a template for biochemists in the design of a wide array of candidate antimalarial drugs. Of the many substituent variations effected upon the quinoline nucleus, the 4-amino and 8-amino substituted analogs have exhibited the greatest activity (1). In general, the 4-aminoquinolines, e.g., chloroquine, are schizontocidal agents which act at the asexual erythrocytic life cycle of the malaria parasite. By contrast, the 8-aminoquinolines, as typified by pamaquine, are gametocytocidal drugs which act against the secondary exoerythrocytic stages and thereby destroy the sexual forms of the human malaria parasite (2). Derivatives of the 4-amino-1,5-naphthyridines should, therefore, exhibit an enhanced antimalarial activity, since they are isosteres of both the 4- and 8-aminoquinolines. This supposition has been confirmed by an early report in the literature that 4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine,



was found to exhibit an antimalarial activity comparable to quinine itself (3,4). Moreover, recent reports in the literature have disclosed significant antimalarial activity for the 4-amino-1,5-naphthyridines which are substituted with alkoxy groups in both the 2- and 6-positions (2,5). In our research, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine currently available in an effort to produce an optimum drug. The results of our synthetic studies for this year are fully discussed in the text of this report.

The results of our previous synthetic studies are described in two annual reports (6,7). The compounds are designated and reported therein as follows:

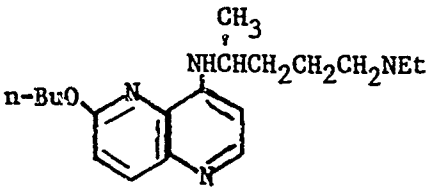
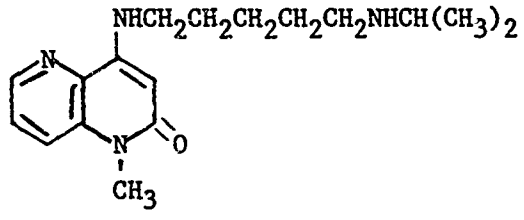
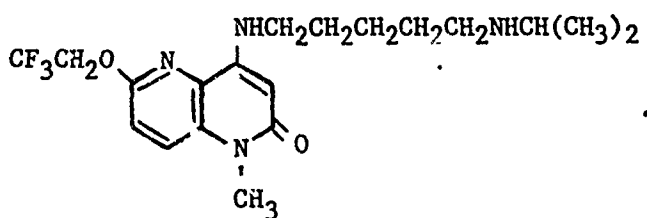
<u>NT</u>	<u>NI</u>	<u>NP</u>	<u>Report Reference</u>
1-19	1-41	1-43	6
20-23	42-72	44-69	7

The structure of those compounds is shown within this report in pages 4 to 8 for the NT series; pages 19 to 23, NI series; and pages 32-43, NP series.

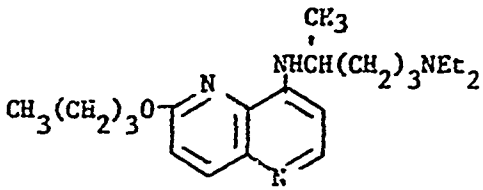
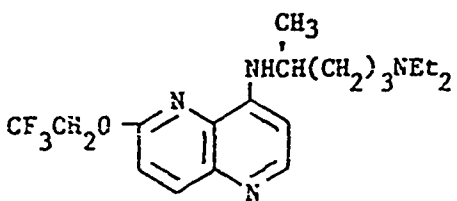
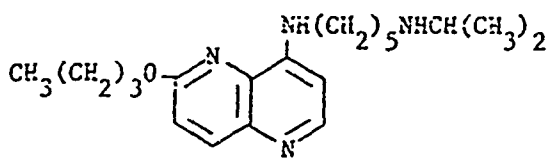
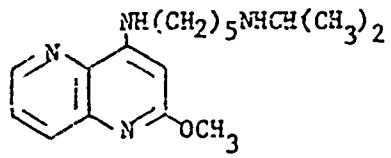
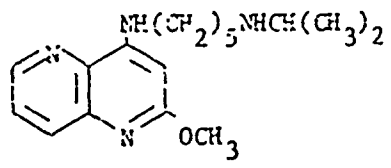
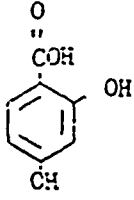
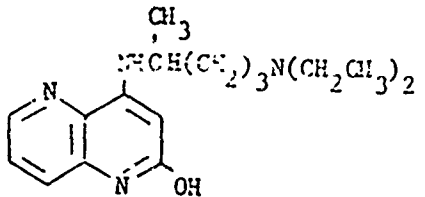
3. NAPHTHYRIDINE TARGETS SUBMITTED 4/1/73 - 6/30/75

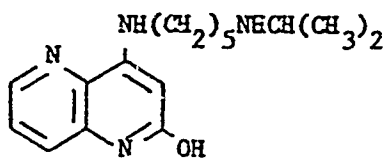
The chemical structures and our code designation for compounds prepared and submitted to WRAIR for biological testing are shown below. Where available, the Walter Reed bottle numbers appear in parentheses below our code. Structures not detailed in this report have been referenced.

Naphthyridine Targets (NT-24-26)

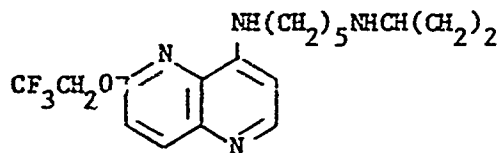
<u>Structure</u>		<u>Code No.</u>
	• 2	NT-24 (BE 83502)
	•	NT-25
	•	NT-26

Naphthyridine Targets (NT-1 through NT-19)⁶

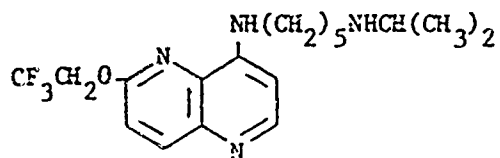
<u>Structure</u>	<u>Code No.</u>	
	NT-1 (BD 26404)	
	NT-2 (BD 26413)	
	NT-3 (BD 26422)	
	NT-4 (BD 54711)	
		NT-5 (BD 54720)
	NT-6 (BD 54739)	



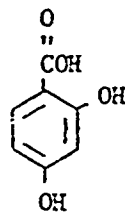
NT-7
(BD 54748)



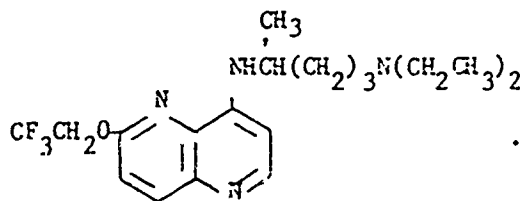
NT-8
(BD 54757)



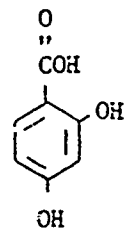
• 2



NT-9
(BD 54766)

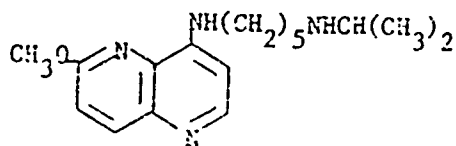


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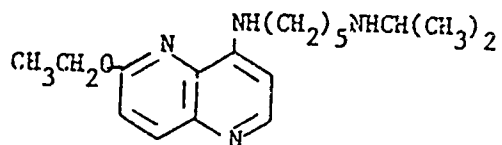


• H₂O

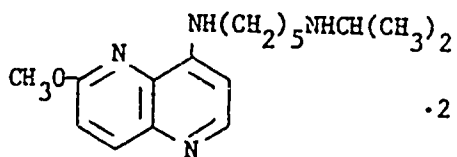
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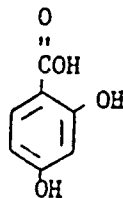
NT-11
(BE 10965)



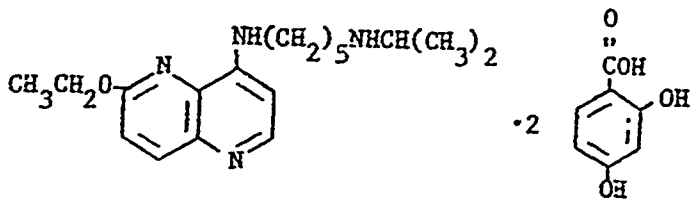
NT-12
(BE 10974)



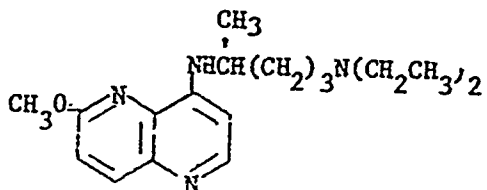
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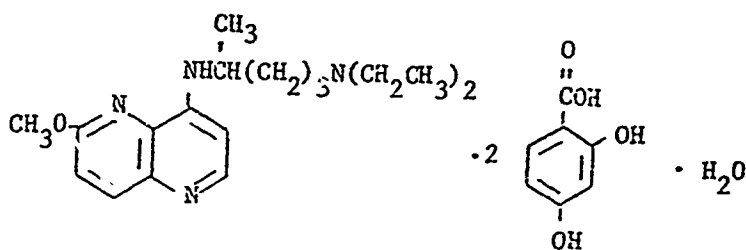
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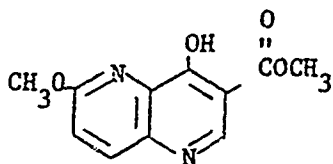
NT-14
(BE 10992)



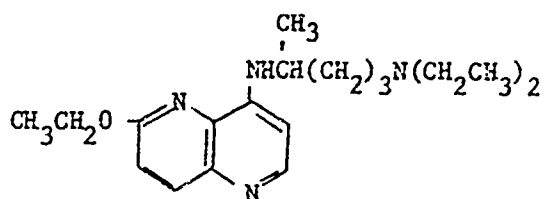
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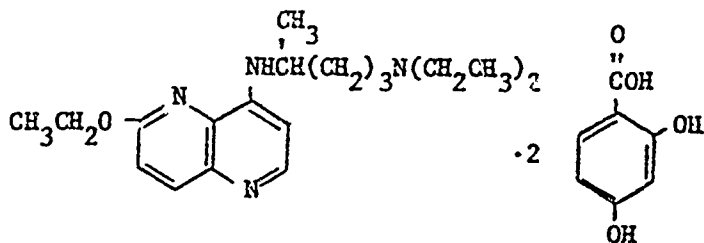
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NT-17
(BE 11024)

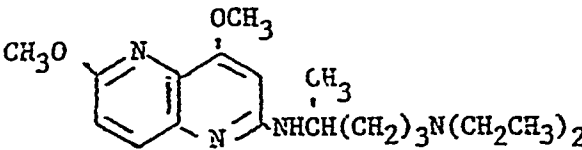
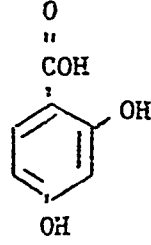
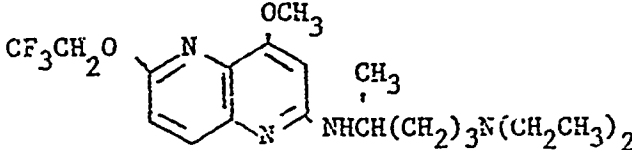
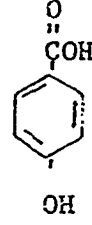
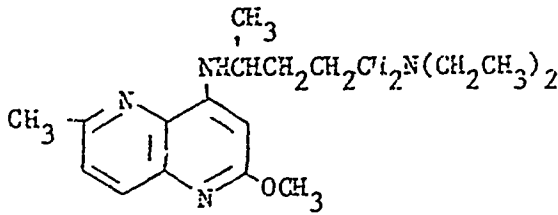
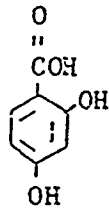
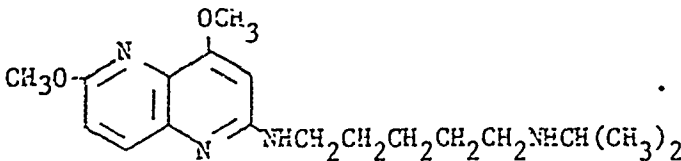
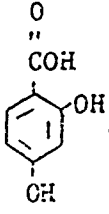


NT-18
(BE 13493)



NT-19
(BE 13500)

Naphthyridine Targets (NT-20 through NT-23)

<u>Structure</u>		<u>Code Number</u>	
	$\cdot 2$	 $\cdot 1/2 \text{H}_2\text{O}$	NT-20 (BE 17286)
	$\cdot 2$	 OH	NT-21 (BE 17295)
	$\cdot 2$	 OH	NT-22 (BE 67286)
	$\cdot 2$	 $\cdot 1/2 \text{H}_2\text{O}$	NT-23 (BE 67295)

4. SYNTHESIS

The synthetic efforts in the 4-amino-1,5-naphthyridine class of antimalarials during the 3-month extension period have been directed toward,

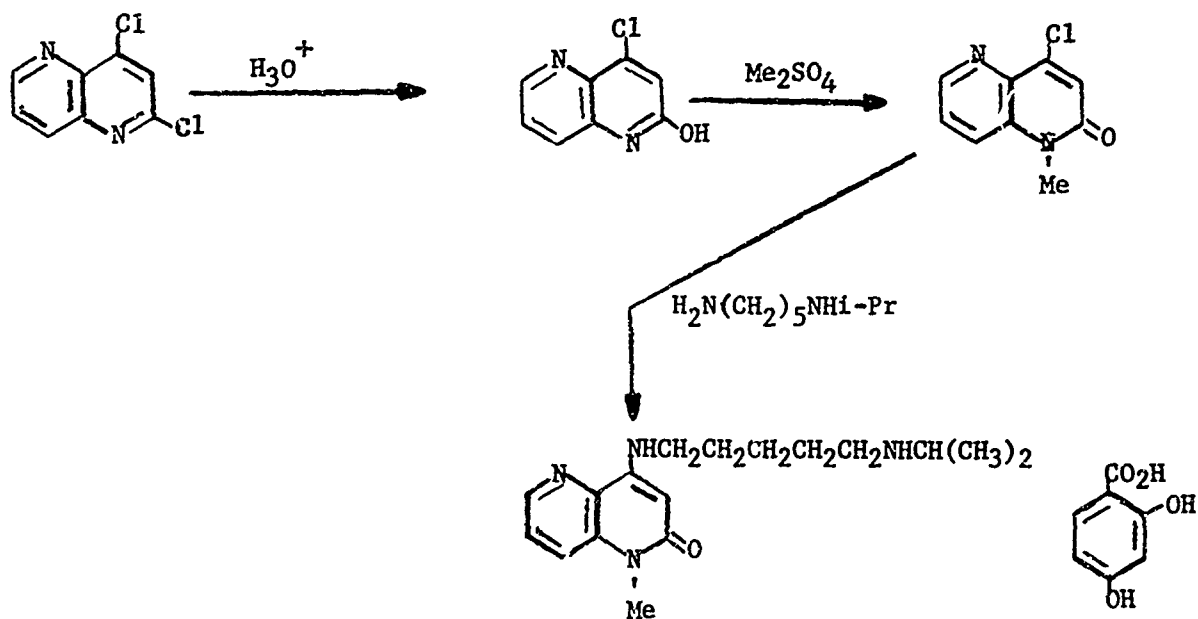
- a 4-amino-1-methyl-naphthyridin-2-one
- a 2,6-diaxoxy-4-amino-1,5-naphthyridine
- a 4,5-naphthyridine with the primaquine sidechain

Biological rationale for these target derivatives are adequately described and referenced in our previous Annual Reports.^{6,7}

4.1 4-Amino-1-methyl-naphthyridin-2-ones

The synthetic entry into this class of potential antimalarials has been realized according to the sequence depicted in Scheme 1. The infrared spectrum of NT-25, as the β -resorcyate, is shown in Figure 1.

Scheme 1



NT-25

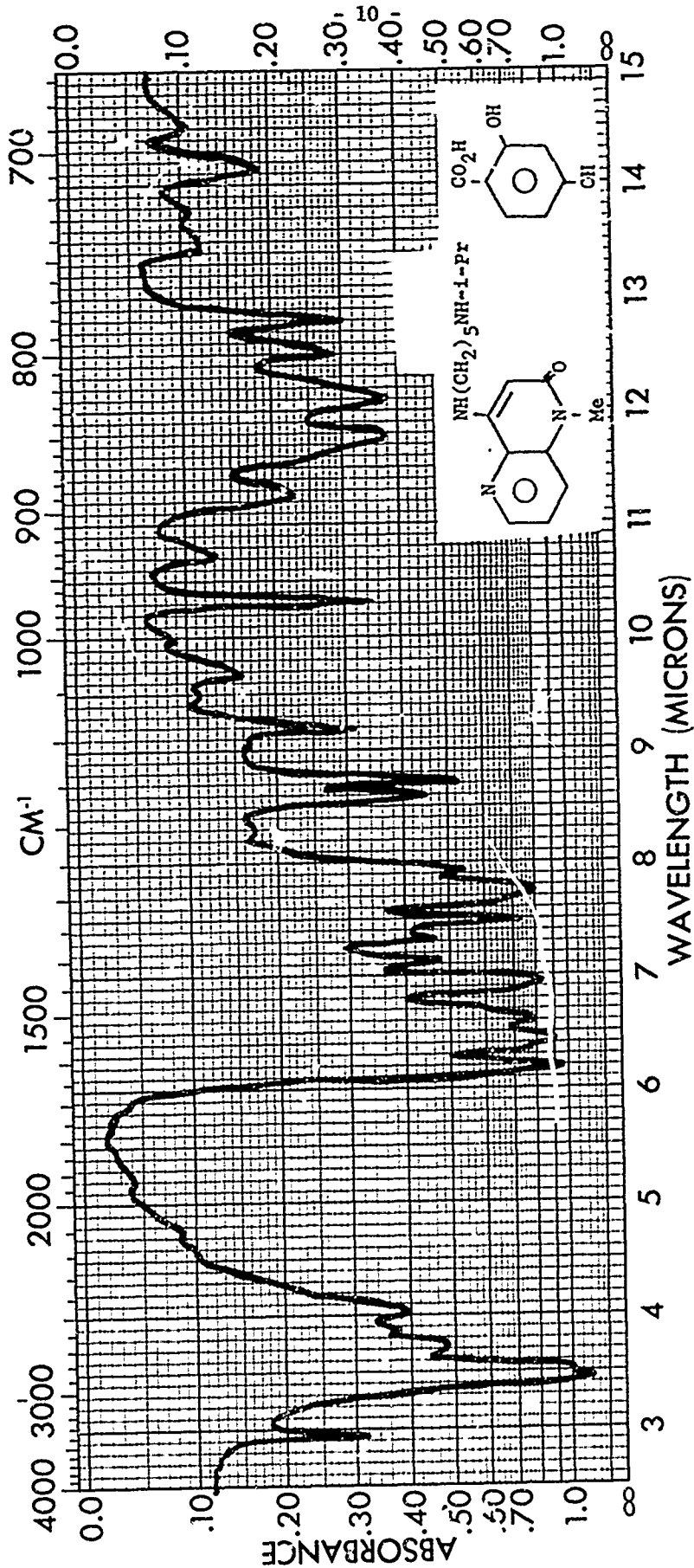
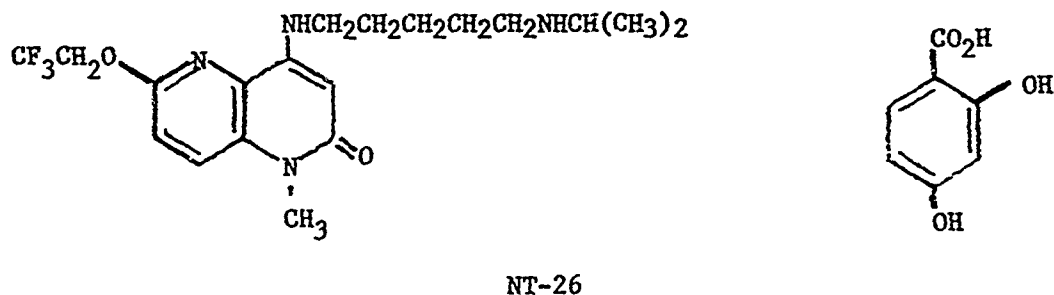
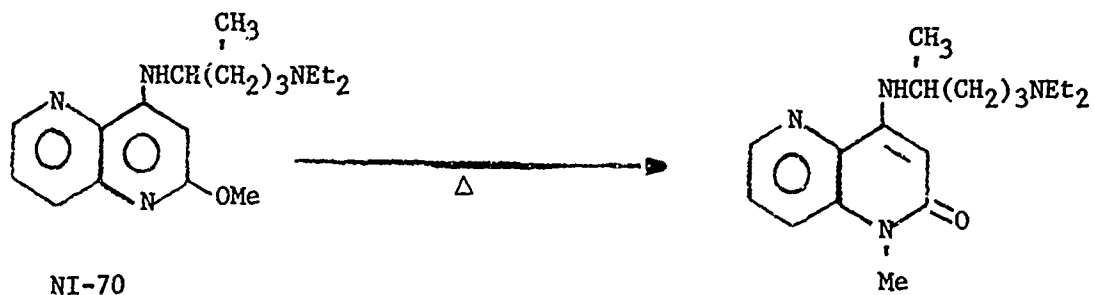


Figure 1 4-(5-Isopropylaminopentylamino)-1-methyl-1,5-naphthyridin-2-one
 β-resorcylate [NT-25]

The above sequence of reactions was noted to be also applicable to the synthesis of more complex naphthyridinones. The structure of this target naphthyridinone, NT-26, is given below. The spectrum of NT-26 is shown in Figure 2.



Concomitant with this mode of naphthyridinone synthesis attempts were made to effect an N → O methyl migration of NI-70. This approach was based on Cheng's² report that methyl migration may have occurred during the preparation of NI-70 in acid media.



Although N → O migrations in nitrogen heterocycles, including naphthyridines systems, are well documented thermolysis of NI-70, neat, in the presence of p-toluenesulfonic acid, or novaldiamine hydrochloride at temperatures up to 230°C were unrewarding.

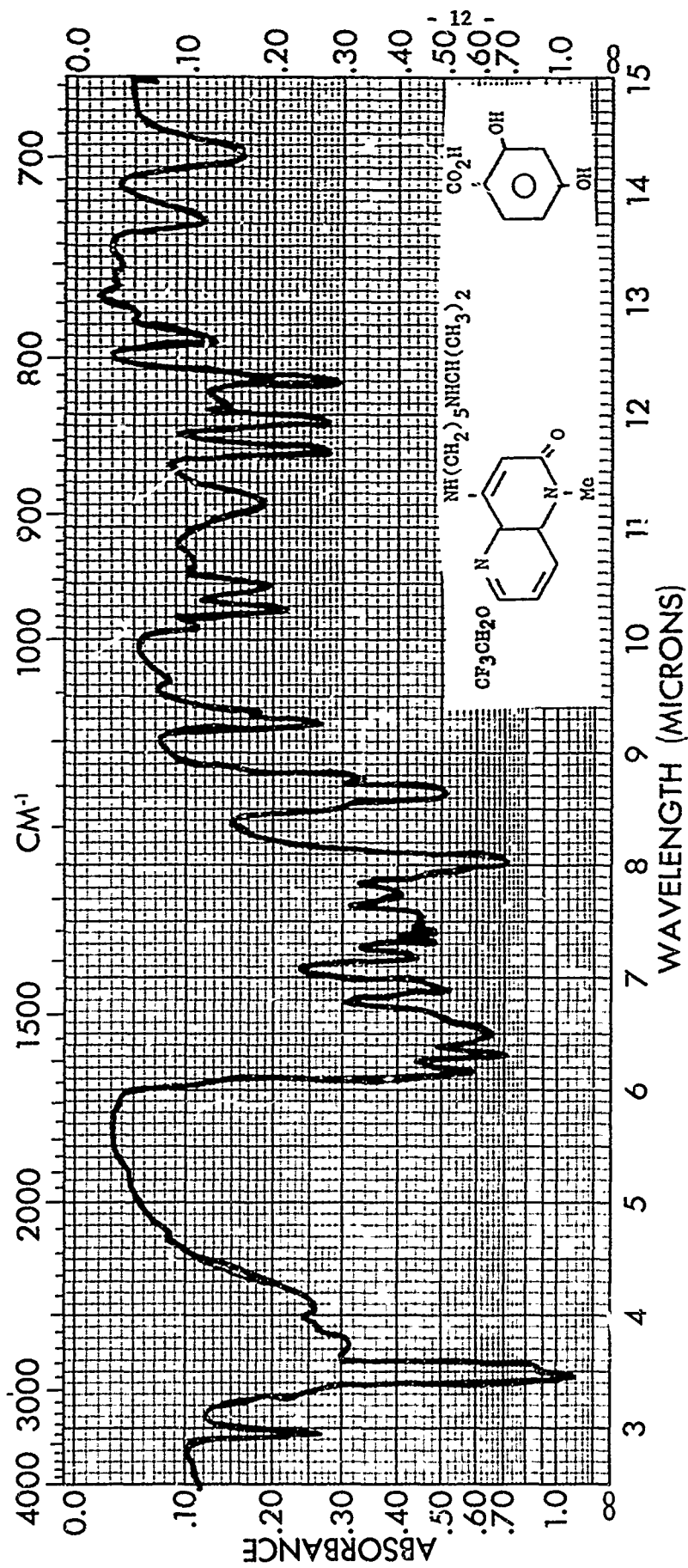


Figure 2 4-(5-isopropylaminopentylamino)-1-methyl-1-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridin-2-one β -resorcylate [NT-26]

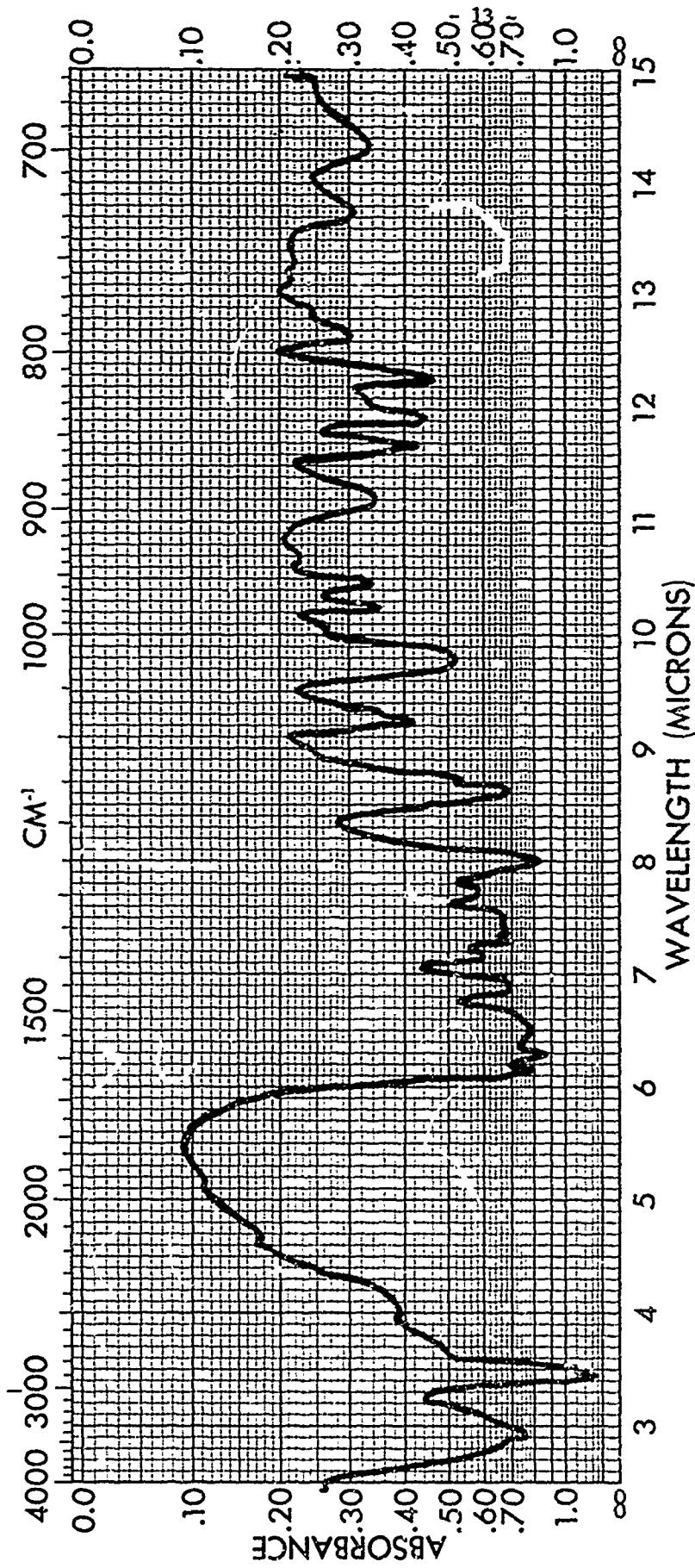
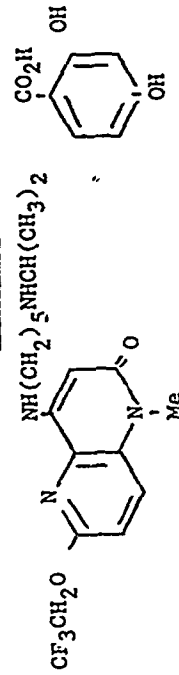


Figure 2



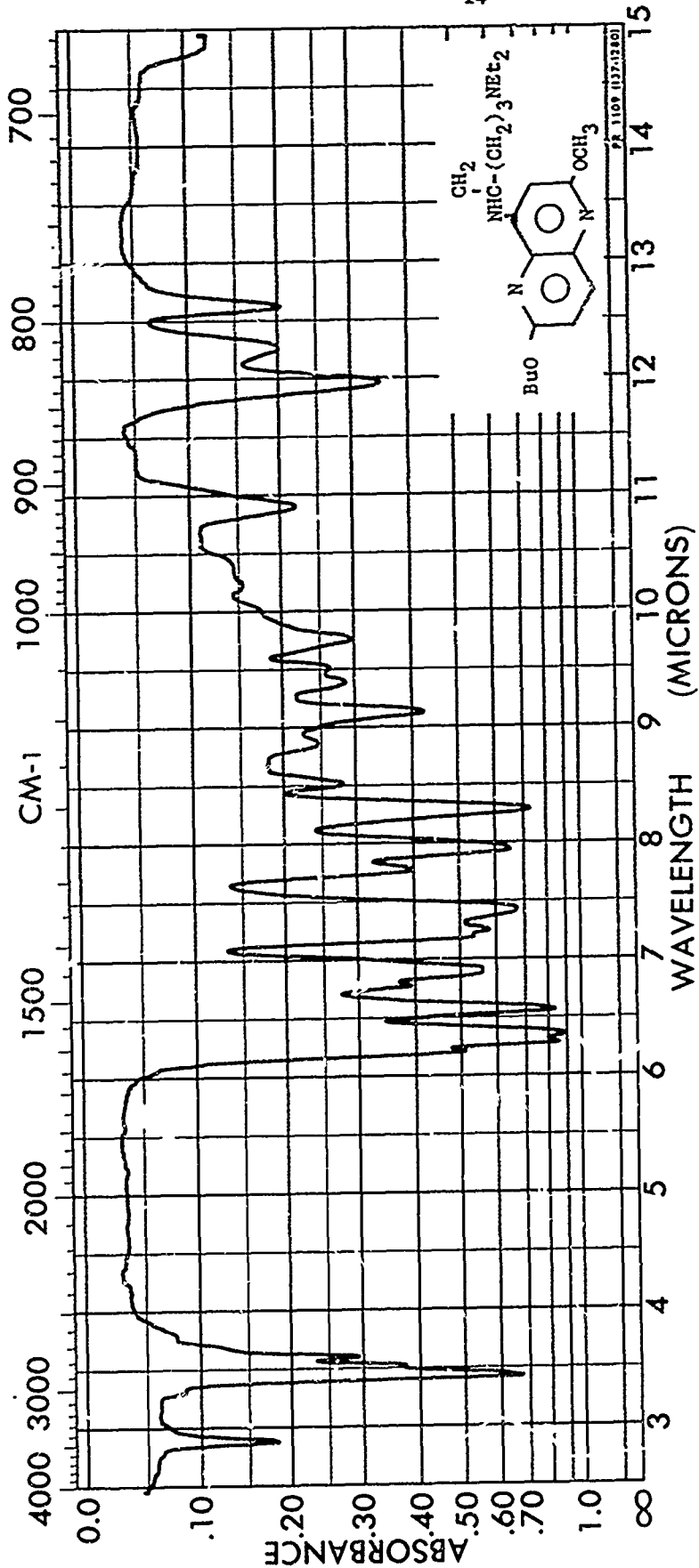
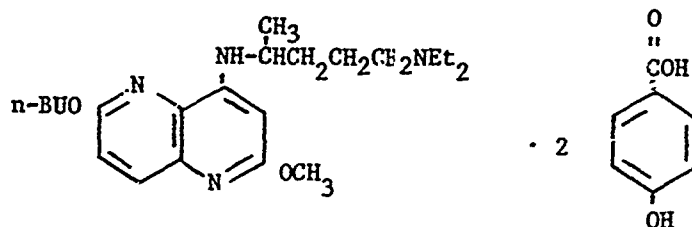


Figure 3. 6-n-Butoxy-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine [NT-24 (free base)].

4.2 4-Amino-2,6-Dialkoxy-1,5-Naphthyridine

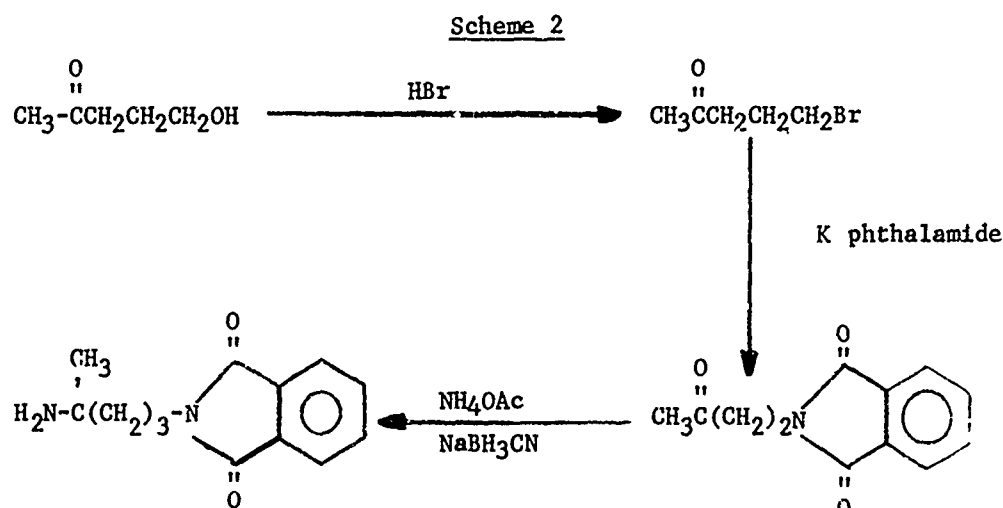
Previous efforts to introduce a basic diamino side chain at the 4-position of 2,6-disubstituted naphthyridines were plagued by accompanying loss of halide and alkoxy. Recently we found that aminolysis under less rigorous conditions than previously employed permitted introduction of the amino sidechain at the 4-position without the accompanying loss of alkoxy group(s). The specific target structure having 2- and 6-position alkoxy groups is NT-24. The spectrum of NT-24, as the free base is given in Figure 3. This target compound was submitted for testing purposes as the di- β -resorcylate.



NT-24

4.3 Primaquine Sidechain

The classical approach to introduction of the Primaquine sidechain, namely alkylation of the 8-amino quinoline, has been previously noted by us to be inoperative with 4-aminonaphthyridine⁷. The failure of this alkylation step is explicable in terms of the poor nucleophilic character of the 4-amino function resulting from the strong electron withdrawing effect of the naphthyridine ring nitrogen. Since aminolysis of 4-chloro naphthyridines is a viable route attempts to prepare a terminally blocked 1,4-diamino pentane (primaquine sidechain) were made. To our knowledge such an intermediate is unknown. The route devised to produce the desired intermediate is shown in Scheme 2.



The first two steps occur in good yield giving isolable and characterizable products. The reductive amination,⁸ under a variety of conditions, failed. Although spectral data indicated loss of the keto function and the appearance of the primary amino group no single material could be isolated by chromatographic or other techniques.

5. EXPERIMENTAL

5.1 6-n-Butoxy-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine di- β -resorcyate [NT-24]

A mixture of 3.7 g of 6-butoxy-4-chloro-2-methoxy-1,5-naphthyridine, 20 g of 4-diethylamino-1-methylbutyl amine, and 1.42g of K_2CO_3 were heated at 140° for 2.5 days. The cooled reaction was treated with 50 ml of 5N NaOH, extracted with ether and dried. The ether and excess amine were removed at reduced pressure and the dark amber residue chromatographed through neutral alumina (activity grade 1). The starting naphthyridine eluted with chloroform; NT-24 (free base) appeared in acetone and THF eluates.

The free base of NT-24 was reacted with three equivalents of β -resorcylic acid in ether, filtered and washed with large volumes of ether. NT-24, mp = $80-3^\circ$ was isolated as a white solid.

Anal calcd for $C_{36}H_{48}N_4O_{10}$: %C, 62.07; %H, 6.90; %N, 8.05. Found: %C, 62.21; %H, 7.13; %N, 8.27.

5.2 4-(5-Isopropylaminopentylamino)-1-methyl-1,5-naphthyridin-2-one β -resorcyate [NT-25]

A mixture of 1.3g of 4-chloro-1-methyl-1,5-naphthyridin-2-one (NI-62), 5 g of 5-isopropylamino pentylamine, and 0.3g of copper-bronze was stirred at 175° for 20 hrs. After removal of excess amine, at reduced pressure the residue was dissolved in water, made strongly alkaline, and extracted with ether. The dried ether solution was charcoal treated, concentrated, and added to 2g of β -resorcylic acid in a minimum of ether. The precipitated product was filtered (very hygroscopic at this stage), quickly washed with large volumes of ether, and vacuum dried. Recrystallization from methanol yielded 1g of NT-25, mp = $194-6^\circ$.

Anal calcd for $C_{24}H_{32}N_4O_5$: %C, 63.16; %H, 7.02; %N, 12.20. Found: %C, 62.87; %H, 6.74; %N, 12.07.

5.3 4-(5-Isopropylaminopentylamino)-1-methyl-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridin-2-one β resorcyate [NT-26]

4-Chloro-1-methyl-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridin-2-one was converted to NT-26 in the manner described for the preparation of NT-25. The product was isolated as an off-white powder mp = $200-1^\circ$ (MeOH).

Anal calcd for $C_{26}H_{33}F_3N_4O_6$: % C, 56.32; % H, 5.96; % N, 10.11; Found: % C, 56.51; % H, 5.35; % N, 10.04

5.4 4-Chloro-2-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine [NI-73]

2,4-Dichloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine was converted to the title compound in 25% via the procedure reported for the preparation of NI-17. Mp = 233-5° (EtOH-H₂O).

5.5 4-Chloro-1-methyl-6-(2,2,2-trifluoroethoxy)-1,5-naphthridin-2-one [NI-74]

Methylation of NI-73 was effected in the manner detailed for NI-62 in 40% yield. Mp = 139-140° (heptane).

Anal calcd for C₁₁H₈ClF₃N₂O₂. % C, 45.20; %H, 2.74; %N, 9.59:
Found: %C 45.28; %H, 2.97; %N, 9.85

5.6 5-Bromo-2-pentanone [NP-70]

To a cooled solution of 100 ml of concentrated H₂SO₄ and 200 ml of 48% HBr was added, dropwise, 100.5 g of 5-hydroxy-2-pentanone. After stirring at ambient temperature overnight the reaction was extracted with ether and the ether backwashed with dilute NaHCO₃, dried, and distilled. The titled compound was isolated in 71% yield, b₁₅ mm = 78-80° (lit,⁹ b₁₆ = 83-5°).

5.7 1-Phthalamido-4-pentanone [NP-71]

Potassium phthalamide (305 g) and 137 g of 5-bromo-2-pentanone were stirred and heated, at reflux, in 825 ml of dimethylformamide for 4 hours. The cooled reaction was diluted with three volumes of water and extracted with 3 x 500 ml of benzene. The benzene was evaporated and the residue recrystallized from MeOH/H₂O. Mp 73-74° (b₁₃ mm = 169-173°).

Anal calcd for C₁₃H₁₃N₂O₃: % C, 67.50; % H, 5.62; % N, 6.06.
Found: % C, 67.52, % H, 5.84; % N, 6.00.

6. REFERENCES

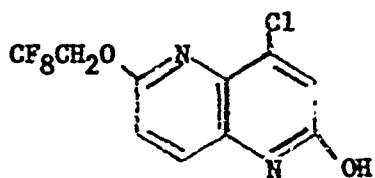
1. P.E. Thomson and L.M. Werbel, "Antimalarial Agents, Chemistry and Pharmacology", Academic Press, New York, N.Y. (1972).
2. D.J. McAustland and C.C.Cheng, J. Heterocycl. Chem., 1, 467 (1970).
3. F.Y. Wiselogle, "A Survey of Antimalarial Drugs", J.W. Edwards, Ann Arbor, Michigan, Vol. II, Pt. 2, p. 1365 (1946).
4. J.T. Adams, C.K. Bradsher, D.S. Breslow, S.T. Amore, and C.R. Hauser, J. Am. Chem. Soc., 68, 1317 (1946).
5. A.A. Goldberg, R.S. Theobald and W. Williamson, J. Chem. Soc., 2357 (1954).
6. "Naphthyridine Antimalarial Agents", Exxon Annual Technical Report", by John Pilot, Exxon Research and Engineering Co., GRU.5.BJJB.74, April 1, 1973-March 31, 1974.
7. "Naphthyridine Antimalarial Agents", Exxon Annual Technical Report", by John Pilot, Exxon Research and Engineering Co., GRU.9.BJJB.75, April 1, 1974-March 31, 1975.
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9. Ya. M. Slobodin and I.U. Shokhor, Chem. Abst. 46:7059h.
10. T. S. Osdene, P. B. Russell, and L. Rane, J. Med. Chem., 10, 431 (1967).

7. APPENDICES

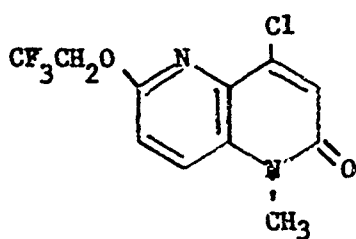
7.1 Naphthyridine Intermediates (NI-73-74)

Structure

Code No.



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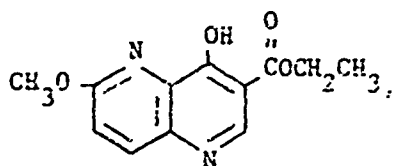


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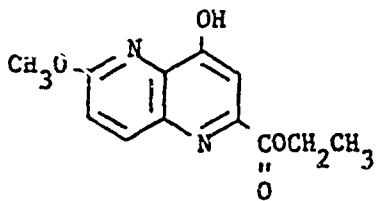
7.2 Naphthyridine Intermediates (NI-1 through NI-4)⁶

Structure

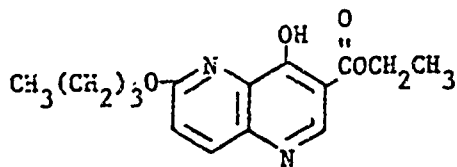
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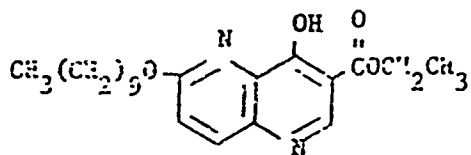
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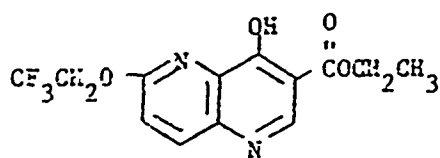
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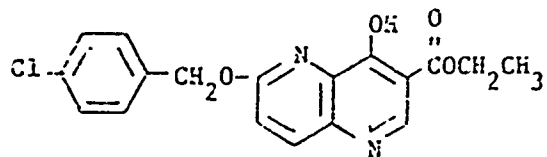
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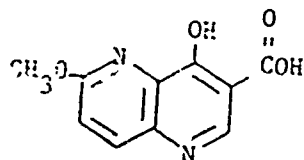
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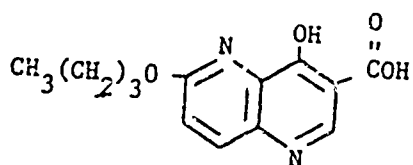
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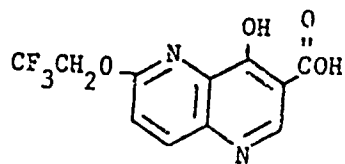
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(BD 26486)



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(BD 26495)

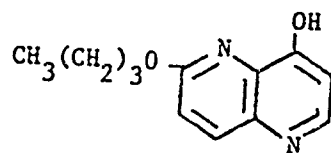


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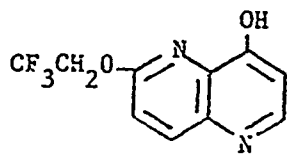


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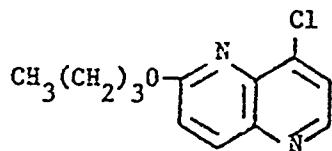
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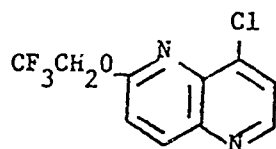
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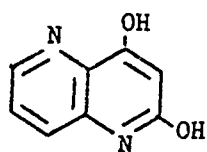
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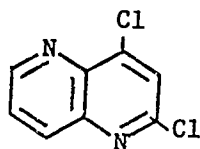
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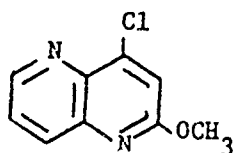
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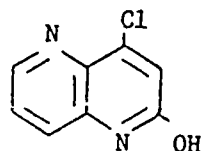
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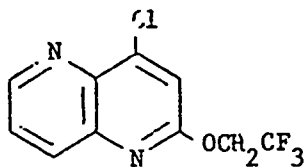
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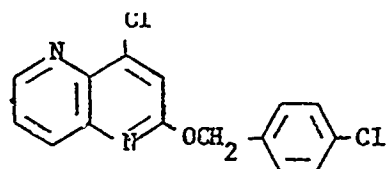
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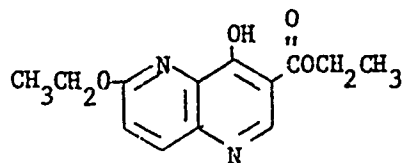
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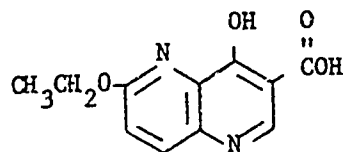
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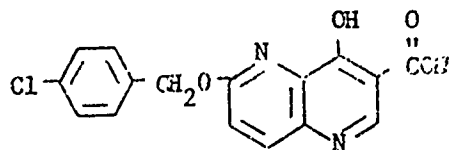


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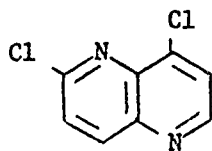


1/2 H₂O

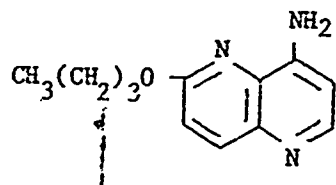
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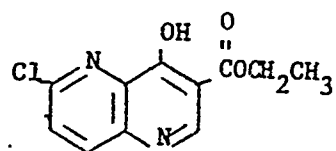
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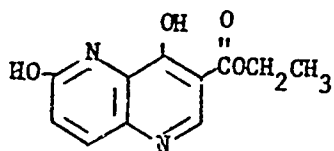
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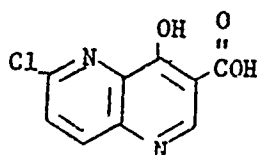
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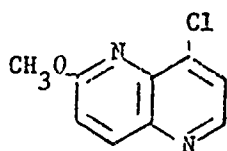
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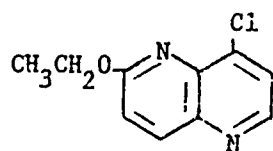
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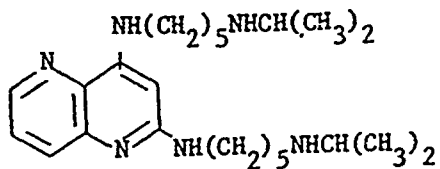
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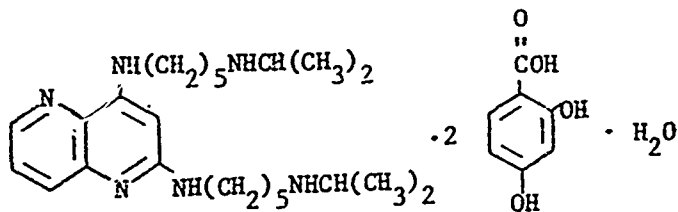
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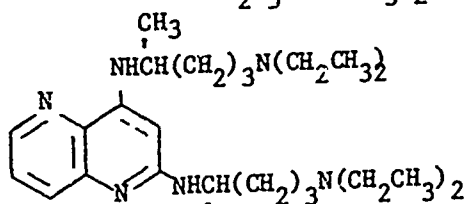
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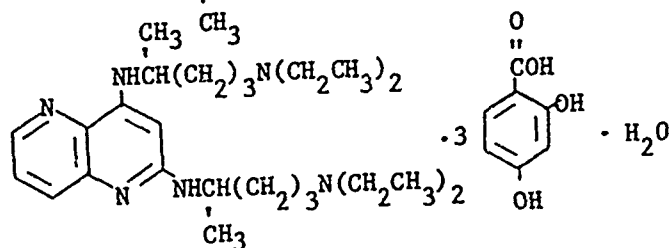
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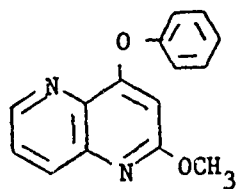
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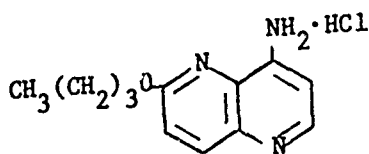
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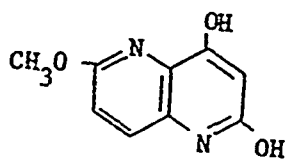
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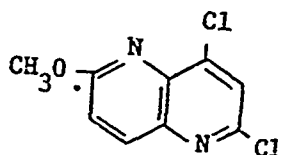
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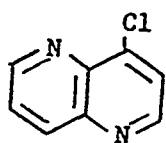
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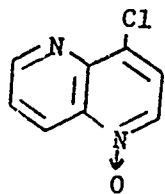
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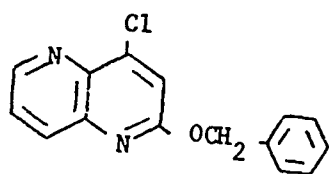
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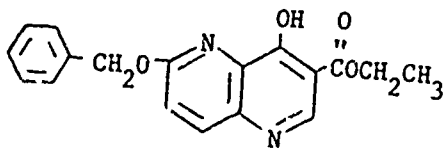
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NI-39
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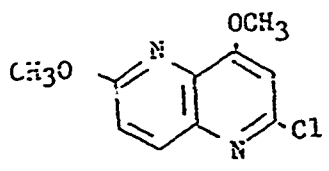
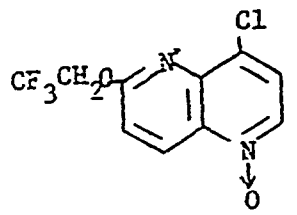
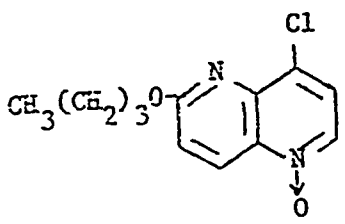
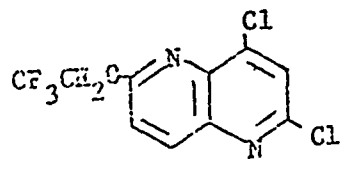
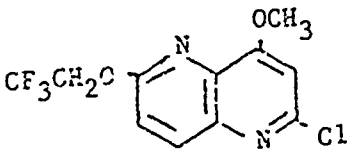


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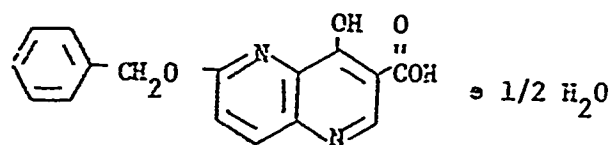
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Naphthyridine Intermediates (NI-42 through NI-72)⁷

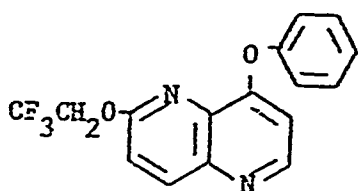
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Structure

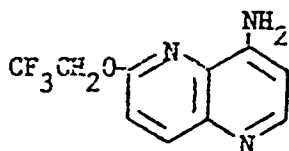
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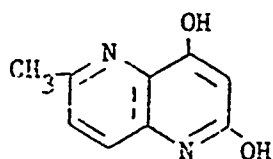
NI-47
(BE 17188)



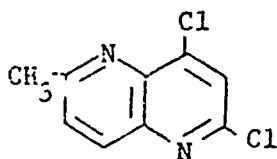
NI-48
(BE 17197)



NI-49
(BE 17204)



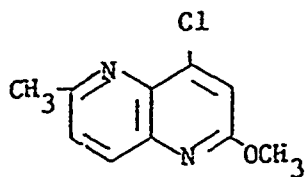
NI-50
(BE 43757)



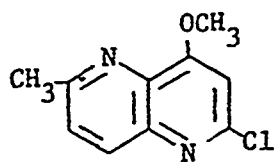
NI-51
(BE 43866)

Structure

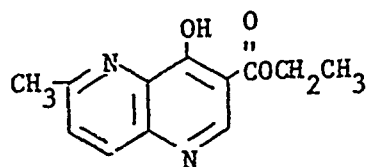
Code Number



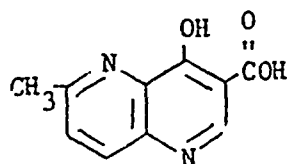
NI-52
(BE 43875)



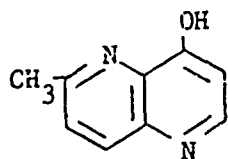
NI-53
(BE 43884)



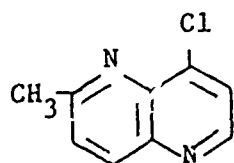
NI-54
(BE 43893)



NI-55
(EE 43900)



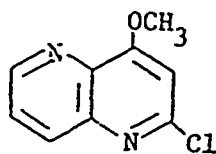
NI-56
(BE 43919)



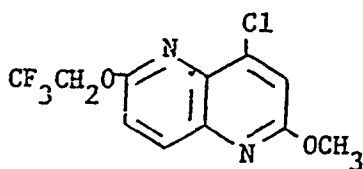
NI-57
(BE 43928)

Structure

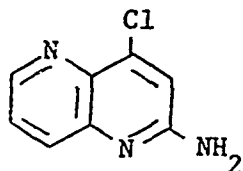
Code Number



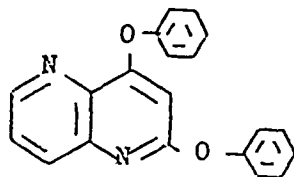
NI-58
(BE 43937)



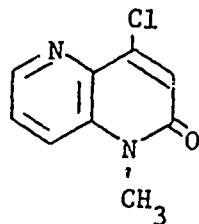
NI-59
(BE 43946)



NI-60
(BE 43955)



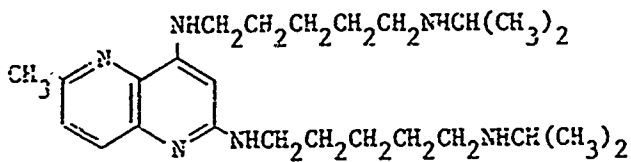
NI-61
(BE 43964)



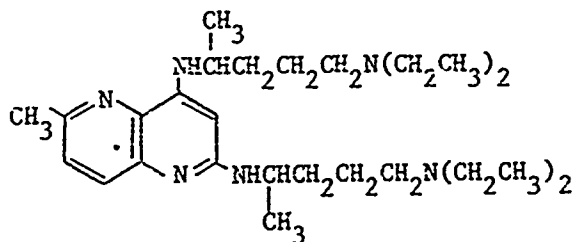
NI-62
(BE 43973)

Structure

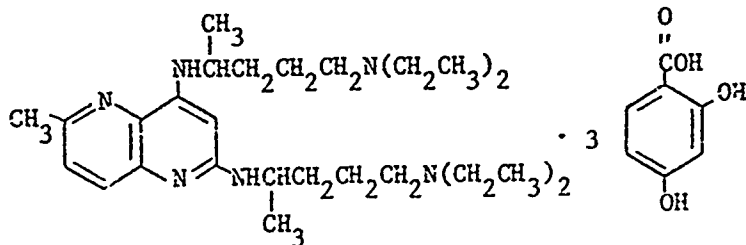
Code Number



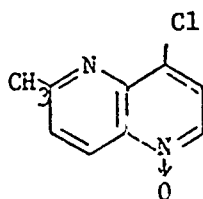
NI-63
(BE 57333)



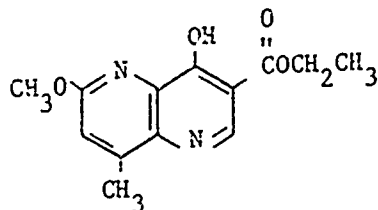
NI-64
(BE 57342)



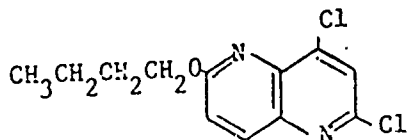
NI-65
(BE 57351)



NI-66
(BE 57360)



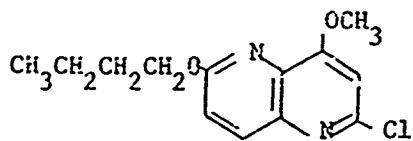
NI-67
(BE 57379)



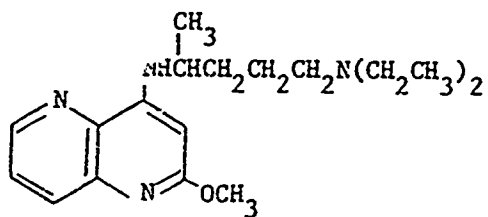
NI-68
(BE 47388)

Structure

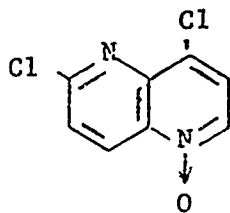
Code Number



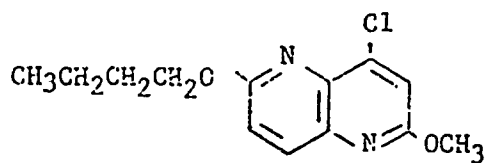
NI-69
(BE 57397)



NI-70
(BE 57404)

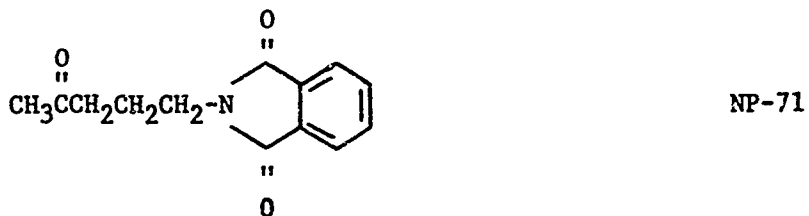


NI-71
(BE 80207)

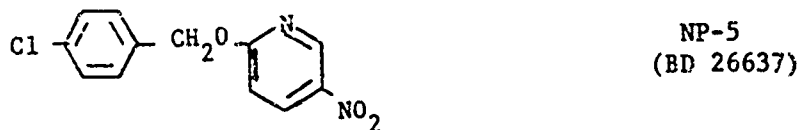
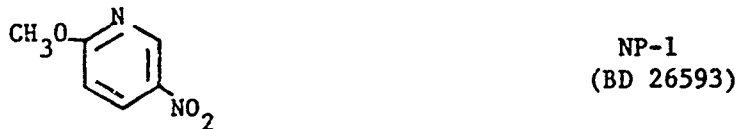


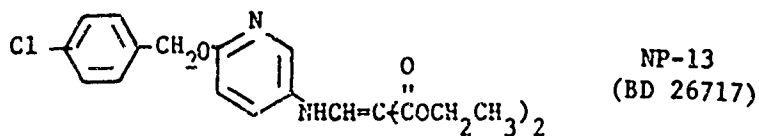
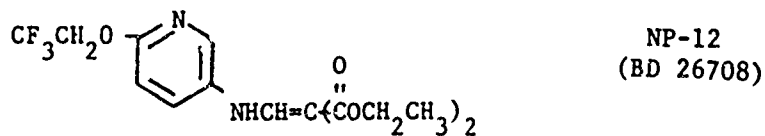
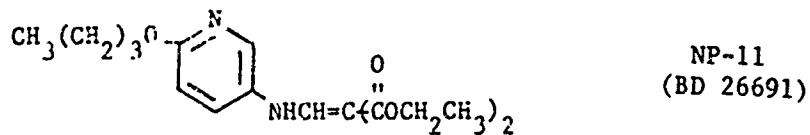
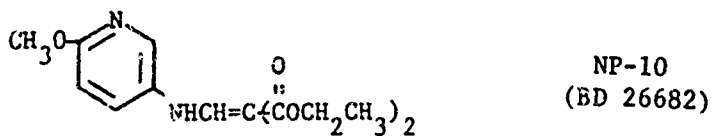
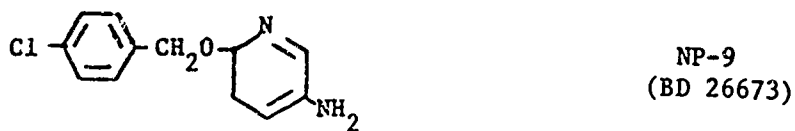
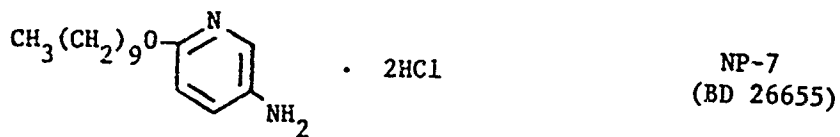
NI-72
(BE 80216)

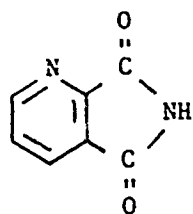
7.3 Naphthyridine Precursors (NP-70-71)



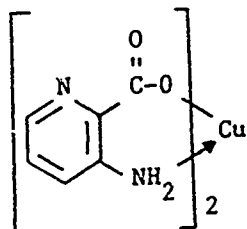
7.4 Naphthyridine Precursors (NP-1 through NP-43)⁶



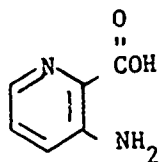




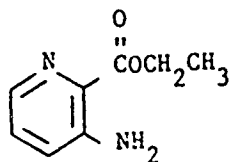
NP-14
(BD 26726)



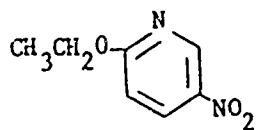
NP-15
(BD 26735)



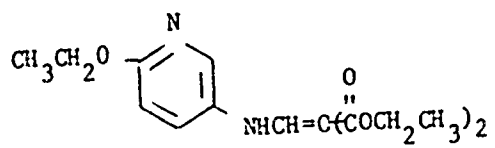
NP-16
(BD 26744)



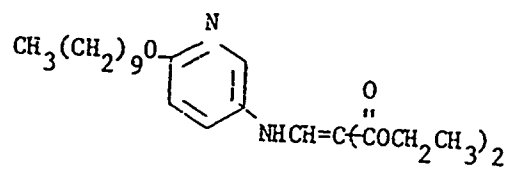
NP-17
(BD 26753)



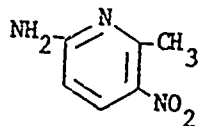
NP-18
(BD 54640)



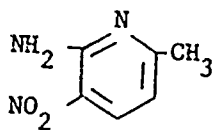
NP-19
(BD 54588)



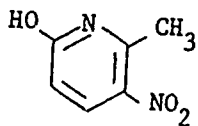
NP-20
(BD 54668)



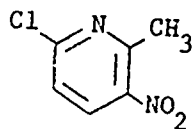
NP-21
(BD 54677)



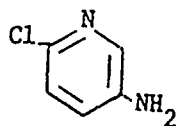
NP-22
(BD 54686)



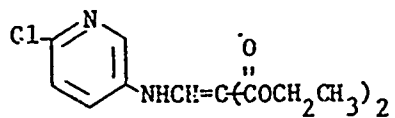
NP-23
(BD 54695)



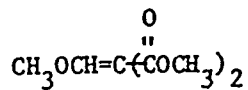
NP-24
(BD 54702)



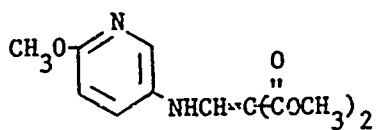
NP-25
(BE 10885)



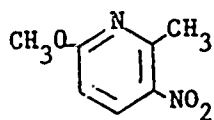
NP-26
(BE 10894)



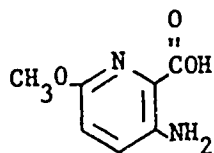
NP-27
(BE 10901)



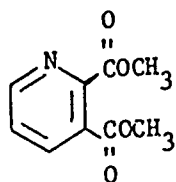
NP-28
(BE 10910)



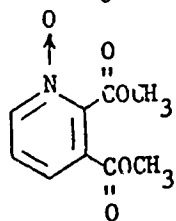
NP-29
(BE 10929)



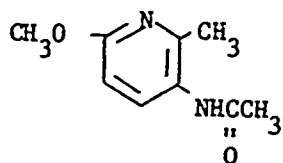
NP-30
(BE 10938)



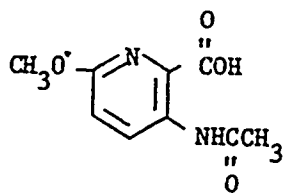
NP-31
(BE 10947)



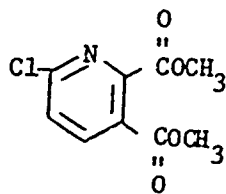
NP-32
(BE 10956)



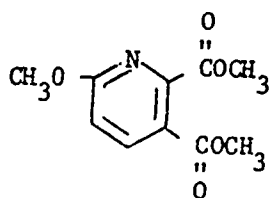
NP-33
(BE 13386)



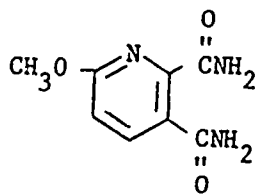
NP-34
(BE 13395)



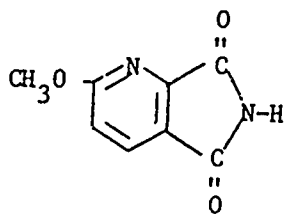
NP-35
(BE 13402)



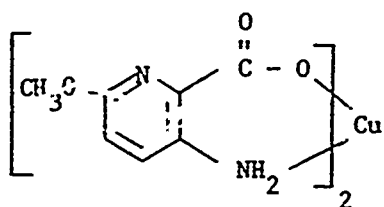
NP-36
(BE 13411)



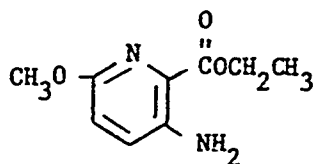
NP-37
(BE 13420)



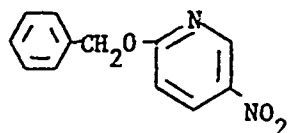
NP-38
(BE 13439)



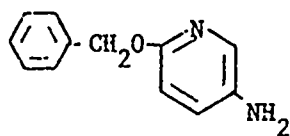
NP-39
(BE 13448)



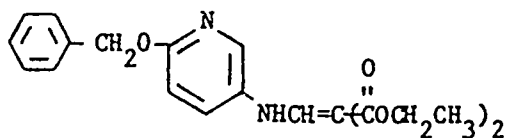
NP-40
(BE 13457)



NP-41
(BE 13466)



NP-42
(BE 13475)

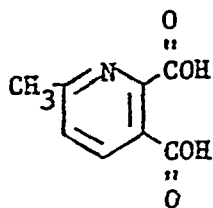


NP-43
(BE 13493)

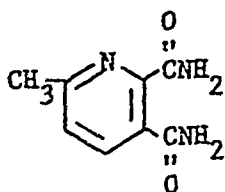
Naphthyridine Precursors (NP-44 through NP-69)⁷

Structure

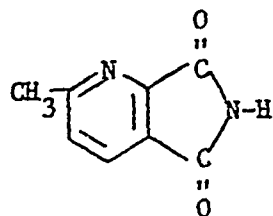
Code Number



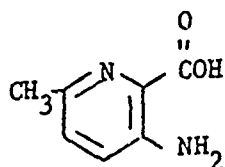
NP-44
(BE 17213)



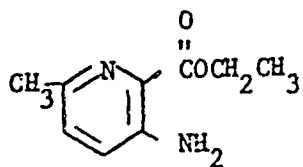
NP-45
(BE 17222)



NP-46
(BE 17231)



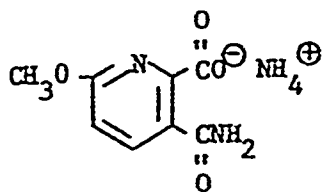
NP-47
(BE 17240)



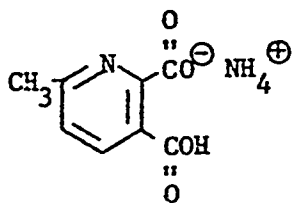
NP-48
(BE 17259)

Structure

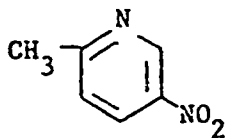
Code Number



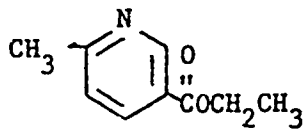
NP-49
(BE 17268)



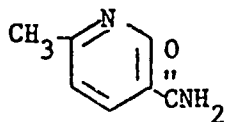
NP-50
(BE 17277)



NP-51
(BE 43982)



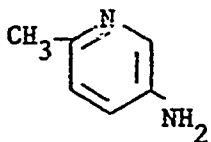
NP-52
(BE 43991)



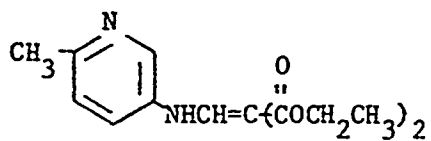
NP-53
(BE 44005)

Structure

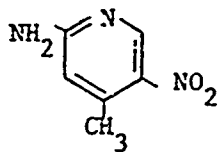
Code Number



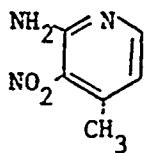
NP-54
(BE 44014)



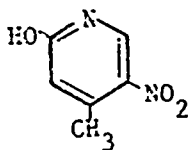
NP-55
(BE 44023)



NP-56
(BE 57413)



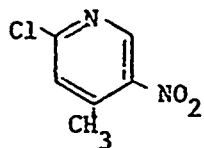
NP-57
(BE 57422)



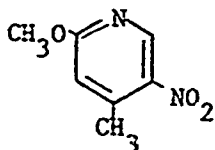
NP-58
(BE 57431)

Structure

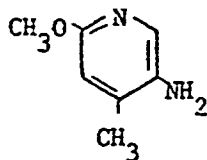
Code Number



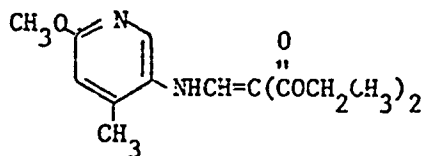
NP-59
(BE 57440)



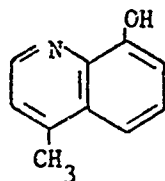
NP-60
(BE 57459)



NP-61
(BE 57468)



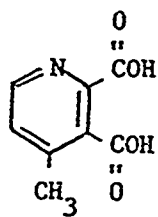
NP-62
(BE 57477)



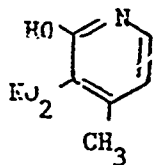
NP-63
(BE 57486)

Structure

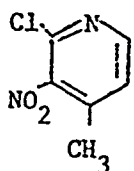
Code Number



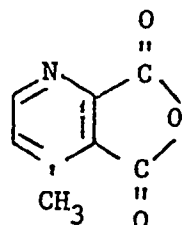
NP-64
(BE 57495)



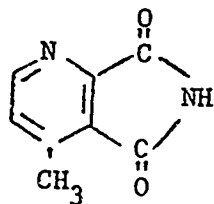
NP-65
(BE 57502)



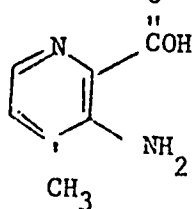
NP-66
(BE 57511)



NP-67
(BE 80172)



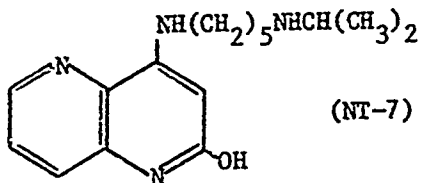
NP-68
(BE 80181)



NP-69
(BE 80190)

7.5 Biological Activity Data

Test results in the Rhesus monkey infected with sporozoites of the B strain of P. cynomolgi have been obtained for most of the target drugs which have been submitted to WRAIR. In general, no significant prophylactic activity has been observed in the Rhesus monkey in the lower dosage range (1 mg/kg). However, one target compound, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-7), continues to afford protection after more than seventy days at a dosage level of 10 mg/kg.



While biologic testing data are not yet complete in the P. berghei/mouse curative screen (10), we have included below a summary of the activity data received to date.

Compound		Activity (T-C)						
Code No.	WRAIR No.	10 mg	20	40	80	160	320	640
NT-2	BD 26413	0.2	0.2	1.2	2.8	5.2	9.2	
NT-4	BD 54711		0.1		0.3		0.9(2)	
NT-5	BD 54720			0.1		0.1		0.1
NT-6	BD 54739			0.1		0.1		0.3
NT-8	ED 54757	0.3	0.3	2.9	3.7	5.9	7.9(2)	
NT-9	BD 54766		0.1	0.5	2.1	4.1	6.9	8.9
NT-10	BD 54775			0.1		0.1		0.3
NT-13	BE 10983		0.5	0.7	1.7	3.7	4.5	0.0(5)
NT-14	BE 10992			0.3		0.0(5)		0.0(5)
NT-15	BE 11006	0.1	0.3	0.3	0.5	2.5	5.3	
NT-17	BE 11024			0.3		0.4(1)		0.0(5)
NT-19	BE 13500			0.3		0.5		0.0(5)
NT-20	BE 17286			0.3		0.5		0.0(5)
NT-21	BE 17295			0.3		0.7		1.1

In addition, NP-18 through NP-50 and NI-17 through NI-49 (excluding NI-26 and NI-33) have also been tested in the therapeutic screen at dosage levels of 40, 160 and 640 mg/kg. None of these precursors and intermediates exhibited a T-C in excess of 1.0 day at any dosage level.