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SYNTHESIS OF POTENTIAL TRYPANOCIDES

Annual/Final Report

December 1987

Richard J. Sundberg

Charlottesville, VA 22901

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U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland, 21701-5012

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University of Virginia,

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Final for the period 1 October 1984 - 31 December 1987

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FIELD	GROUP	SUB-GROUP
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06	18	

18. SUBJECT TERMS *(Continue on reverse if necessary and identify by block number)*

Keywords: antiparasitic, trypanosomiasis, chemotherapy, trypanocides, synthesis, heteroaromatic, heterocyclic

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

This report describes the synthesis of new compounds for evaluation as antiparasitic agents. Most of the biological data pertain to activity against Trypanosoma rhodesiense but limited data pertaining to leishmania, filarius and plasmodium are also included. Biological data is included for compounds prepared in an earlier contract DAMD-17-83-C-3127. The salts are derivatives of imidazole, pyridine, thiazole, benizimidazole and imidazo[1,2-a]pyridine. High levels of in vivo activity are reported for many of the commpounds.

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22a. NAME OF RESPONSIBLE INDIVIDUAL: Mary Frances Bostian

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DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

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Summary

This report covers the research during the period of October, 1984 through March 1987, undertaken under Contract DAMD17-85-C-5004. During this period 164 new compounds were prepared and submitted for evaluation as antiparasitic agents. The report presents the structures of these compounds and gives the experimental methods for their preparation.

Biological data was obtained for most of these compounds and also for related compounds prepared under the preceding contracts DAMD17-78-C-8016 included in the report and the significance of the data is discussed. Several compounds are recommended for further study on the basis of high potency, low toxicity and oral activity.

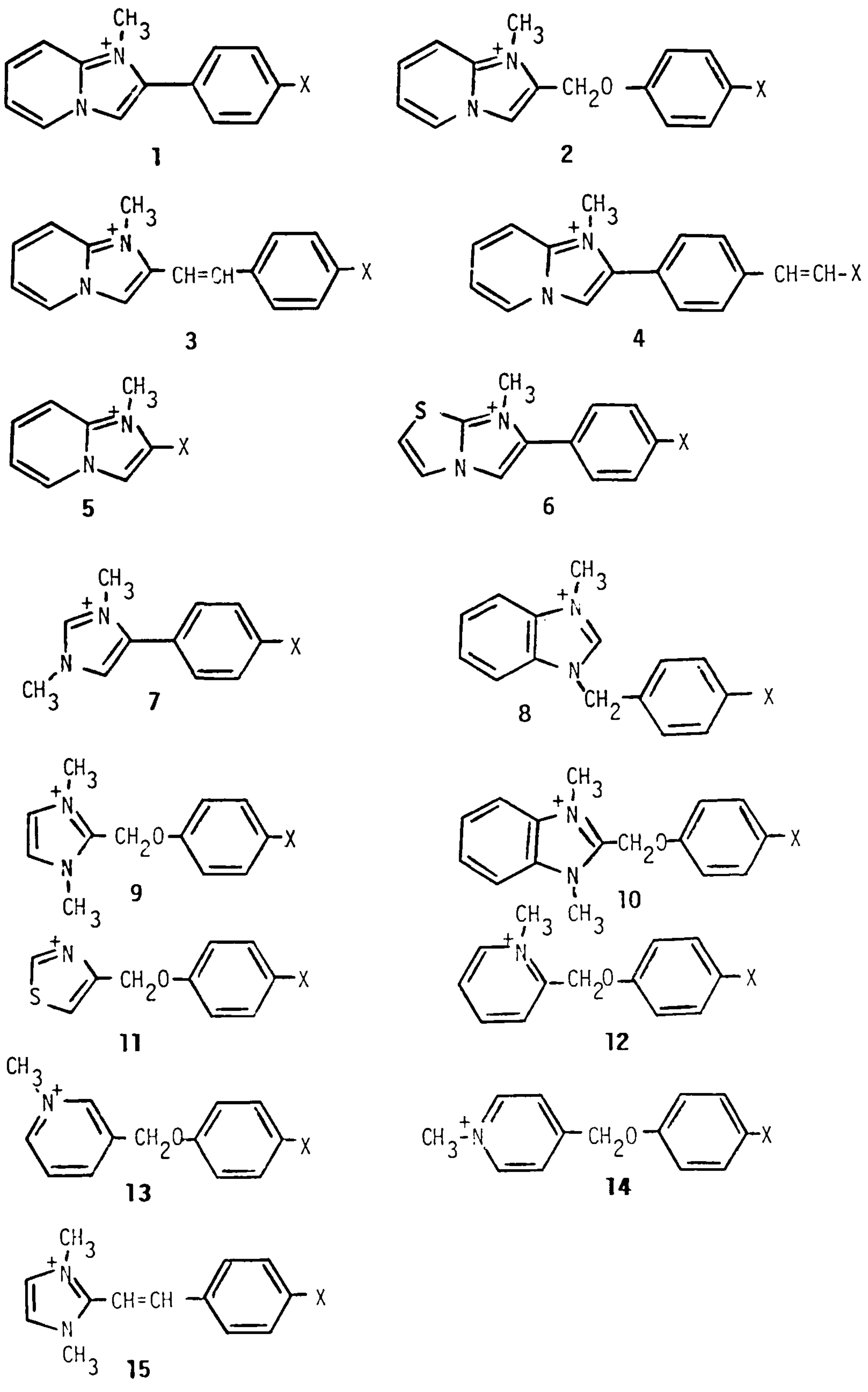
I. Compounds Submitted

The compounds which were submitted are listed in order of date of submission in Table I. Our sample number, the WRAIR bottle number, structure and date of submission are given.

The compounds can be subdivided into several groups on the basis of structure. This subdivision corresponds to those used in the tables of biological data. The structures are defined as a combination of a ring structure and functional groups as *defined in Scheme* 1 and 2. The level of effort for the varions functional group types defined in Scheme 2 was as follows: **Functional Groups 1-9** - Acetamido and Related Functions. No new examples of this type were prepared since they are generally not highly active. **Fuctional Groups 10-27.** Several examples of this class, especially functional groups 22, were prepared. **Functional Groups 28-36.** No new examples of this class were prepared. **Functional Groups 37 and 38.** No new examples of this class were prepared. ***Functional Groups* 39-62.** Guanylhydrazones and N-Alkyl Guanylhydrazones. Many new examples of this class were prepared. **Functional Groups 63-65.** Several examples of this class, primarily N-hydroxyguanylhydrazones were prepared. **Functional Groups 66-78.** A few new examples were prepared.

Extensive investigation of modification of the heterocyclic ring system was done. The structure of the ring systems which were investigated are defined in Scheme 1. The modifications include insertion of a linking group, $-CH_2O-$ or $-CH=CH-$, between the imidazo[1,2-a]pyridine and the phenyl ring, ring structures 2 and 3, introduction of a $-CH=CH-$ group between the phenyl ring and its 4'-substituent, ring structure 4, elimination of the phenyl ring so as to place the substituent directly on the imidazo[1,2-a]pyridine ring, structure 5, replacement of the imidazo[1,2-a]pyridine ring by imidazo[2,1-b]thiazole, structure 6, or by imidazole, structure 7, and incorporation of other rings such as benzimidazole (8, 10) imidazole (9, 15) thiazole (11) and pyridine (12-14) into ether-linked and vinyl-linked structures.

SCHEME 1
HETEROAROMATIC RINGS

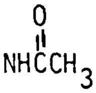


RING MODIFIERS FOR IMIDAZO[1,2-a]PYRIDINE STRUCTURES **1-5**

a	N-CH_3
b	N-$CH_2CH{=}CH_2$
c	5,6-benzo
d	7,8-benzo
e	6-Cl
f	6-I
g	5-CH_3
h	6-CH_3
i	7-CH_3
j	CF_3
k	6-CO_2CH_3
l	7-CO_2CH_3
m	6-C_2H_5S
n	6-C_2H_5SO-
o	6-$C_2H_5SO_2$-
p	6-C_3H_7S-
q	6-C_4H_9S-
r	6-C_6H_5S-
s	6-CH_3O-
t	6-CH_3CONH-
u	3-NO_2
v	3-Br
w	3-CH_3
x	5,6,7,8-tetrahydro

SCHEME 2

FUNCTIONAL GROUPS

1 
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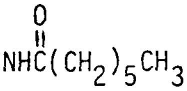
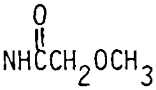
2 $NHCO_2C_2H_5$

3 
$NHC(=O)(CH_2)_5CH_3$

4 
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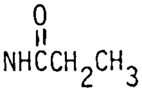
5 
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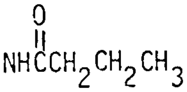
6 
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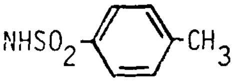
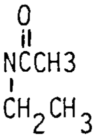
7 $NHSO_2CH_3$

8 

9 
$N(CH_2CH_3)C(=O)CH3$

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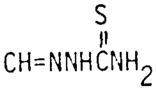
11 
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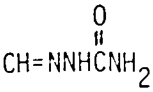
12 
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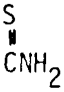
13 
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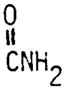
14 
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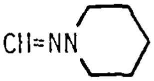
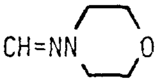
15 

16 

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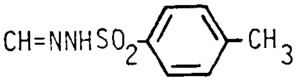
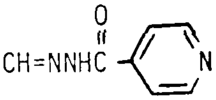
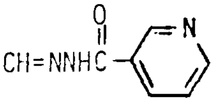
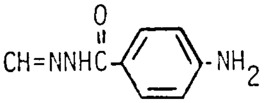
18 $CH{=}NNHSO_2CH_3$

19 

20 

21 

22 

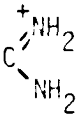
23 CO_2CH_3

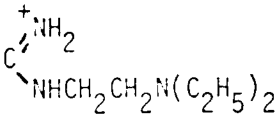
24 Br

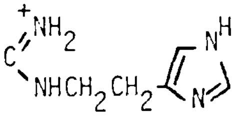
25 $CH(CH_3)_2$

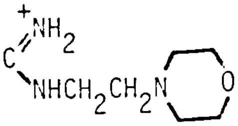
26 NO_2

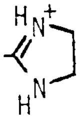
27 OCH_3

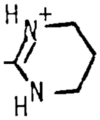
28 
$C(={}^{+}NH_2)NH_2$

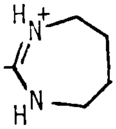
29 
$C(={}^{+}NH_2)NHCH_2CH_2N(C_2H_5)_2$

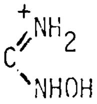
30 

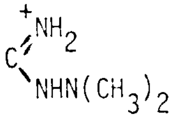
31 

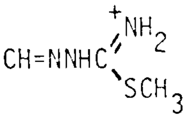
32 

33 

34 

35 
$C(={}^{+}NH_2)NHOH$

36 
$C(={}^{+}NH_2)NHN(CH_3)_2$

37 
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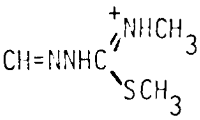
38 
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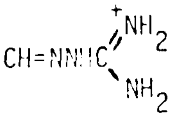
39 
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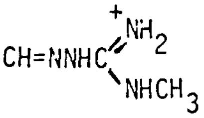
40 
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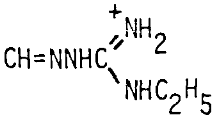
41 
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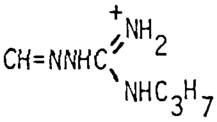
42 
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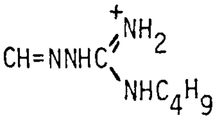
43 
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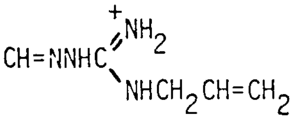
44 
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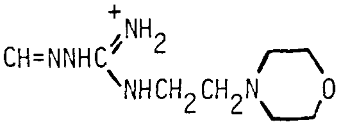
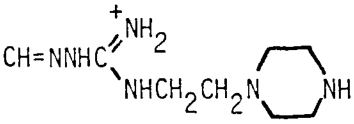
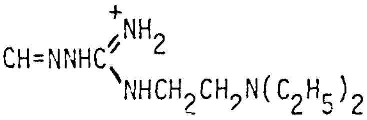
45 

46 

47 
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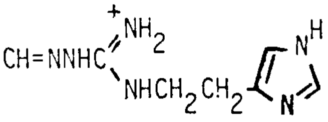
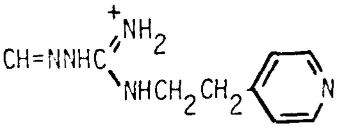
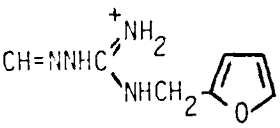
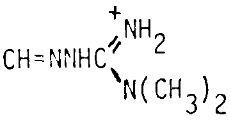
48 

49 

50 

51 
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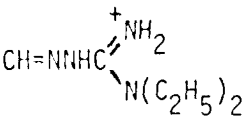
52 
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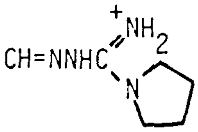
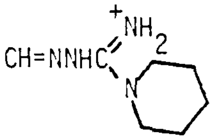
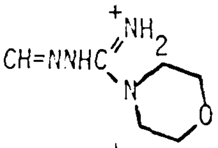
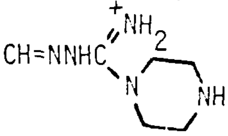
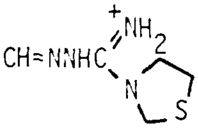
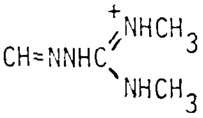
53 

54 

55 

56 

57 

58 
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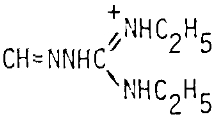
59 
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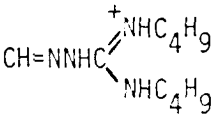
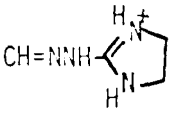
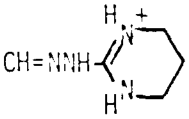
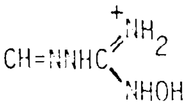
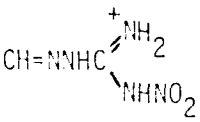
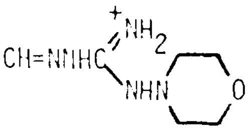
60 
$CH{=}NNHC(={}^{+}NHC_4H_9)NHC_4H_9$

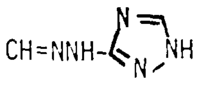
61 

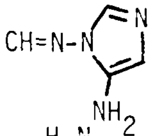
62 

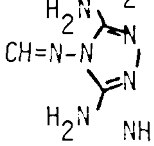
63 
$CH{=}NNHC(={}^{+}NH_2)NHOH$

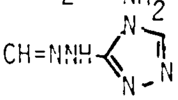
64 
$CH{=}NNHC(={}^{+}NH_2)NHNO_2$

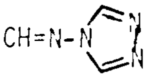
65 

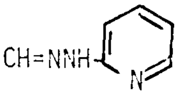
66 

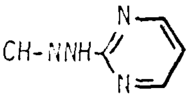
67 

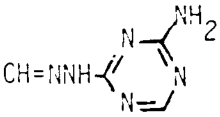
68 

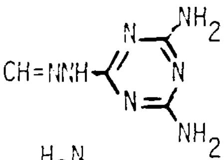
69 

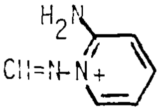
70 

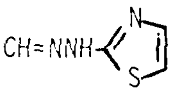
71 

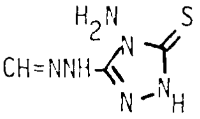
72 

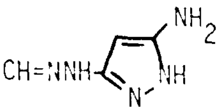
73 

74 

75 

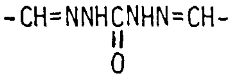
76 

77 

78 

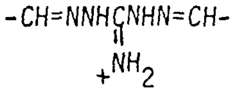
DIFUNCTIONAL LINKS

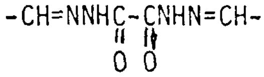
1 $-CH{=}N{-}N{=}CH-$

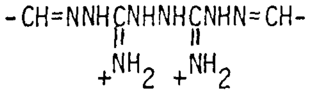
2

$-CH{=}NNH\underset{\overset{\|}{O}}{C}NHN{=}CH-$

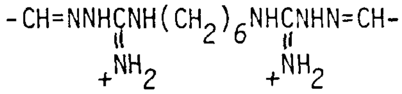
3

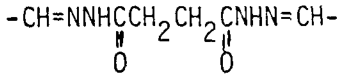
$-CH{=}NNH\underset{\overset{\|}{S}}{C}NHN{=}CH-$

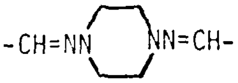
4

$-CH{=}NNH\underset{\overset{\|}{{}^{+}NH_2}}{C}NHN{=}CH-$

5

$-CH{=}NNH\underset{\overset{\|}{O}}{C}-\underset{\overset{\|}{O}}{C}NHN{=}CH-$

6

$-CH{=}NNH\underset{\overset{\|}{{}^{+}NH_2}}{C}NHNH\underset{\overset{\|}{{}^{+}NH_2}}{C}NHN{=}CH-$

7

$-CH{=}NNH\underset{\overset{\|}{{}^{+}NH_2}}{C}NH(CH_2)_6NH\underset{\overset{\|}{{}^{+}NH_2}}{C}NHN{=}CH-$

8

$-CH{=}NNH\underset{\overset{\|}{O}}{C}CH_2CH_2\underset{\overset{\|}{O}}{C}NHN{=}CH-$

9


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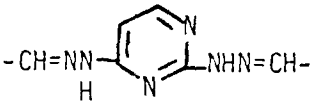

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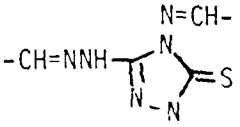

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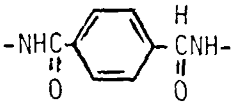

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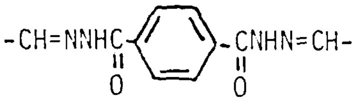

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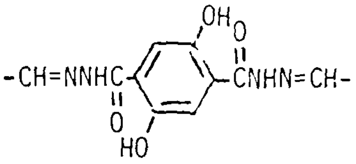

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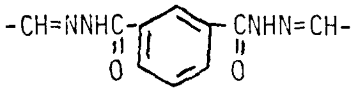

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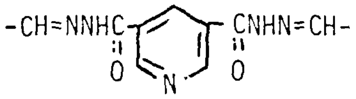


II. Chemical Methods

The methods for synthesis of the compounds of general structure 1-15 in Scheme 1 are as follows: Structure 1 was obtained by cyclization of a 2-aminopyridine with a 4-substituted bromomethyl aryl ketone (substituted α-bromoacetophenone). Structure 2 was obtained by reaction of 2-(chloromethyl)imidazo[1,2-a]pyridine with the 4-formylphenoxide ion. Structure 3 was obtained by reaction of 2-formylimidazo[1,2-a]pyridine with diethyl 4-cyanobenzylphosphonate in a Wittig-Horner-Emmons reaction. Structure 5 was obtained by cyclization of a 2-aminopyridine with ethyl 3-bromo-2-oxopropanoate. Structure 6 was obtained by cyclization of 2-aminothiazole with bromomethyl 4-iodophenyl ketone. Structure 7 was obtained by cyclization of bromomethyl 4-bromophenyl ketone with formamide. Structure 8 was obtained by N-alkylation of benzimidazole with 4-cyanobenzyl bromide. Structures 9-14 were obtained by reaction of the appropriate chloromethyl heterocycle with 4-formylphenoxide ion. Structure 15 was obtained by reaction of 1-methyl-2-formylimidazole with diethyl 4-cyanobenzylphosphonate.

When cyclization gave X = Br or I the halide was displaced with cuprous cyanide to give X = CN. These intermediates as well as intermediates 3, 8 and 15, X = CN, were converted to aldehydes by one of several reduction methods, e.g. diisobutyl aluminum hydride or Raney nickel in formic acid. In structure 5, X = $CO_2C_2H_5$ was reduced to CH_2OH with lithium aluminum hydride and then oxidized to X = CH=O with MnO_2. The pentultimate step in all syntheses was the quaternization of the heterocyclic aldehydes to give structures 1-15 with X = CH=O. The quaternizations were usually done with methyl p-toulenesulfonate.

The final step in the synthesis of each target compound was the reaction of the aldehyde with a substituted hydrazine or hydrazide to give the final compound. The salts were purified by recrystallization and characterized by elemental analysis. The analytical data are given for each compound in the experimental section. Infrared and proton NMR spectra were also recorded for each sample and were consistent with the assigned structures.

TABLE I. *Compounds Submitted During the Contract Period*

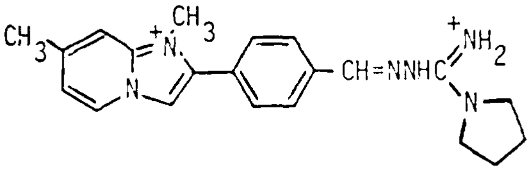
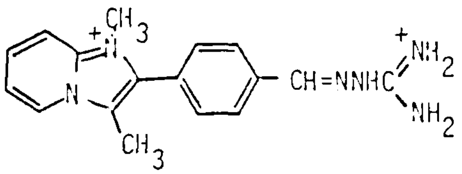
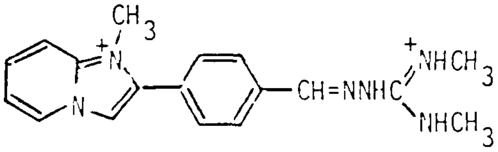
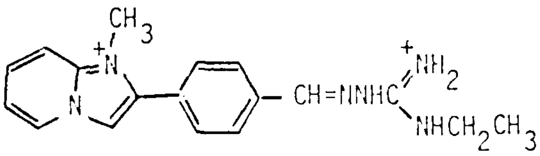
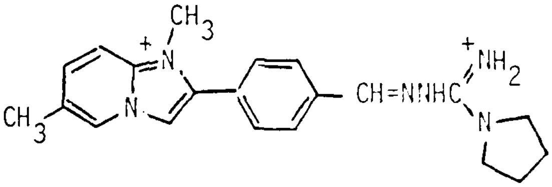
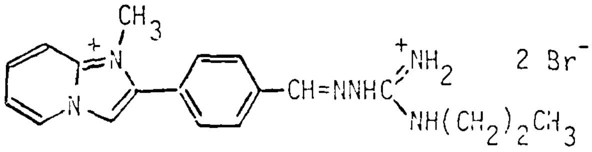
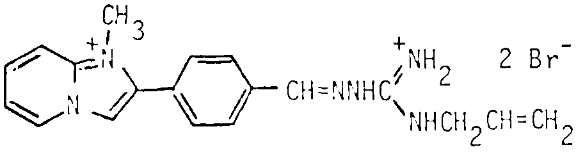
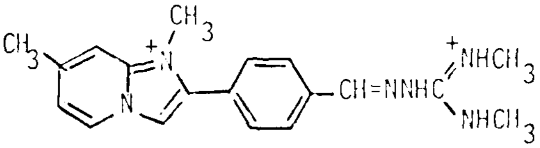
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Day-Y
V-40-GM	BK96700	 2 Br^-	11-7-84
III-88-MJB	BK96719	 2 Br^-	11-7-84
V-32-GM	BK96728	 2 I^-	11-7-84
V-38-GM	BK96737	 2 Br^-	11-7-84
V-39-GM	BK96746	 2 Br^-	11-7-84
V-43-GM	BK96755	 2 Br^-	11-7-84
V-42-GM	BK96764	 2 Br^-	11-7-84
V-41-GM	BK96773	 2 Br^-	11-7-84

TABLE I (cont.)

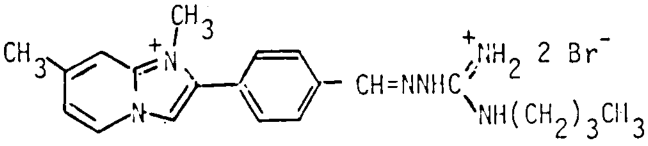
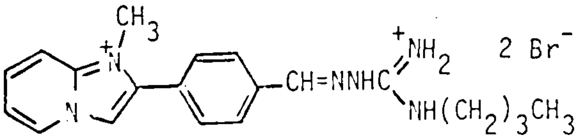
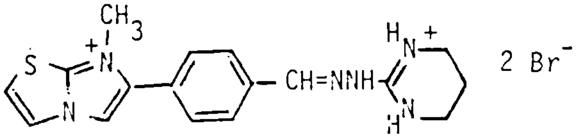
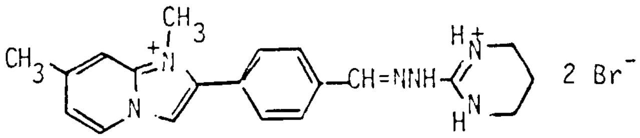
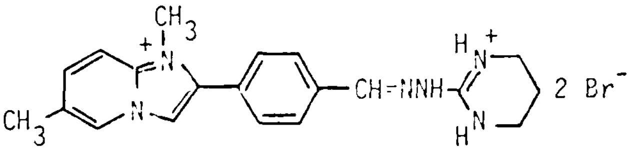
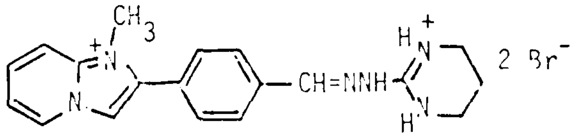
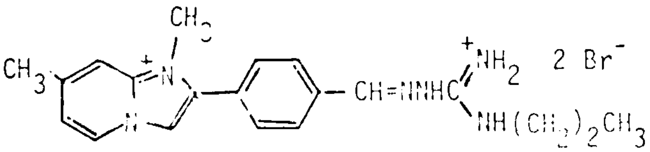
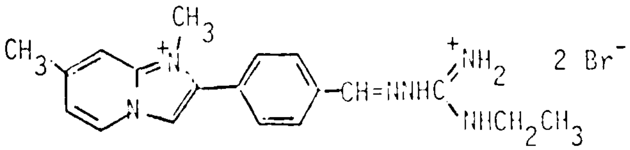
Our Sample Number	WRAIR Number		Date Submitted (Mo-Day-Yr)
V-56-GM	BK98526		11-30-84
V-55-GM	BK98535		11-30-84
V-52-GM	BK98544		11-30-84
V-51-GM	BK98553		11-30-84
V-50-GM	BK98571		11-30-84
V-49-GM	BK98580		11-30-84
V-47-GM	BK98599		11-30-84
V-46-GM	BK98599		11-30-84

TABLE I. (cont.)

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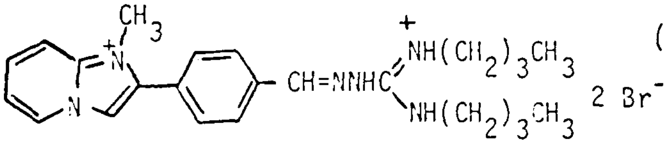
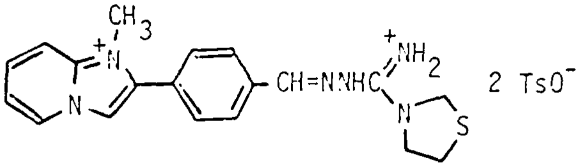
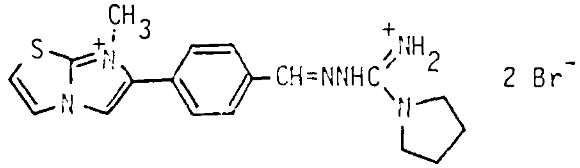
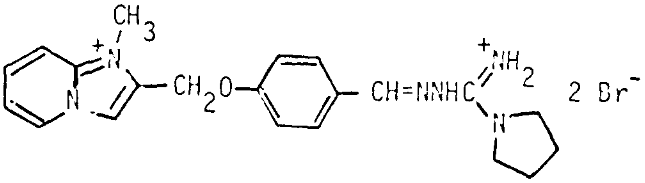
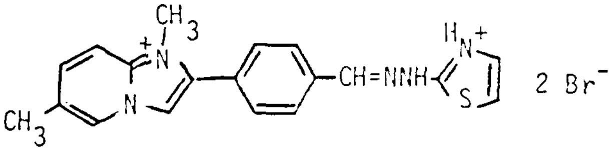
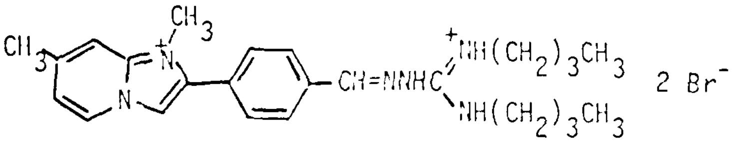
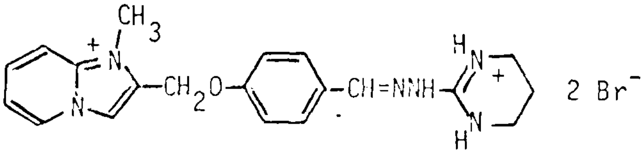
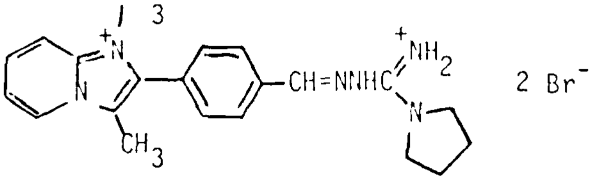
V-48-GM	BL00003		12-28-84
V-54-GM	BL00012		12-28-84
V-57-GM	BL00021		12-28-84
V-58-GM	BL00030		12-28-84
V-59-GM	BL00049		12-28-84
V-60-GM	BL00058		12-28-84
V-64-GM	BL00067		12-28-84
V-68-GM	BL00076		12-28-84

TABLE I. (continued)

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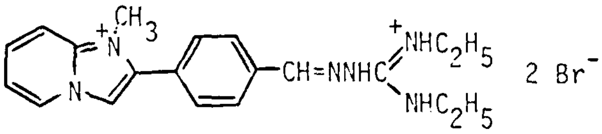
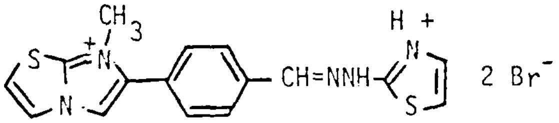
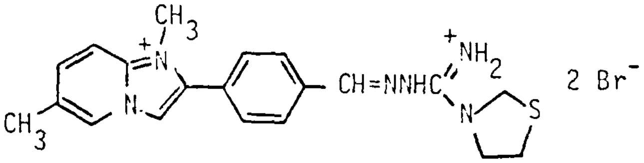
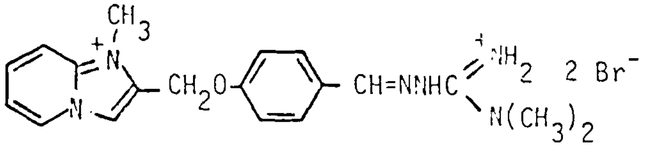
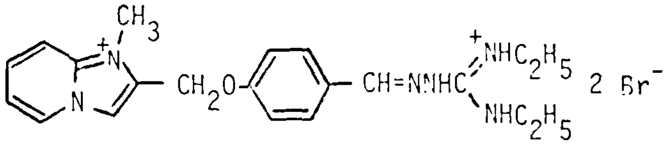
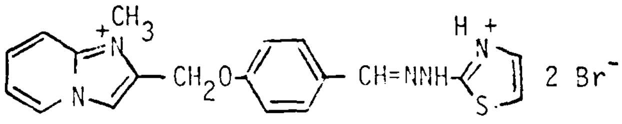
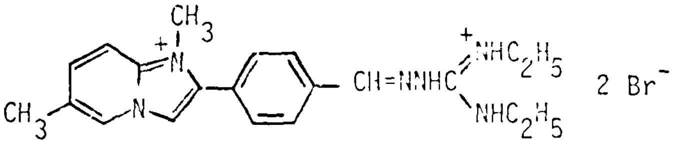
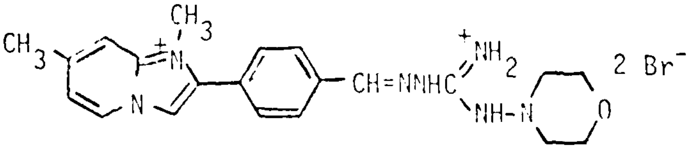
V-62-GM	BL03899		2-20-85
V-63-GM	BL03906		2-20-85
V-70-GM	BL03915		2-20-85
V-75-GM	BL03924		2-20-85
V-76-GM	BL03933		2-20-85
V-65-GM	BL05320		3-21-85
V-66-GM	BL05339		3-21-85
V-73-GM	BL05348		3-21-85

TABLE I. (continued)

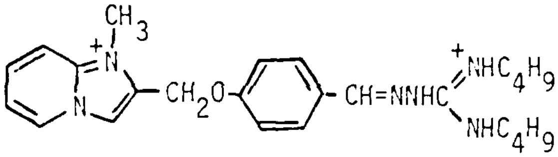
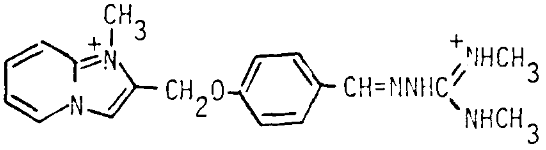
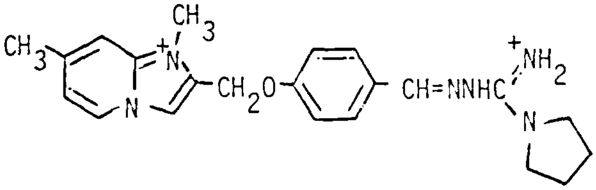
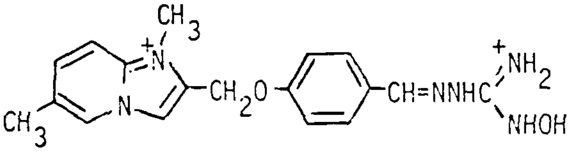
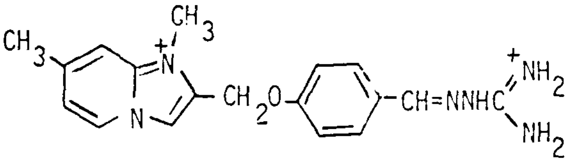
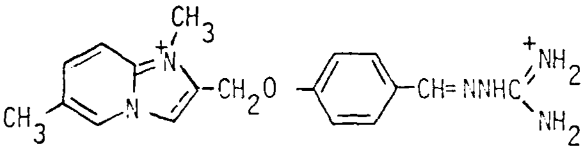
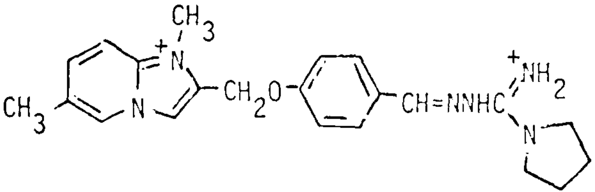
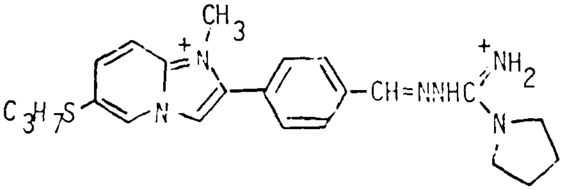
Our Sample *Number*	WRAIR *Number*	Structure	Date Submitted (Mo-Da-Yr)
V-77-GM	BL05357	 2 Br$^-$	3-21-85
V-80-GM	BL05366	 2 Br$^-$	3-21-85
V-92-GM	BL06934	 2 Br$^-$	4-24-85
V-91-GM	BL06943	 2 Br$^-$	4-24-85
V-90-GM	BL06952	 2 Br$^-$	4-24-85
V-88-GM	BL06961	 2 Br$^-$	4-24-85
V-89-GM	BL06970	 2 Br$^-$	4-24-85
V-86-GM	BL06989	 2 Br$^-$	4-24-85

TABLE I. (continued)

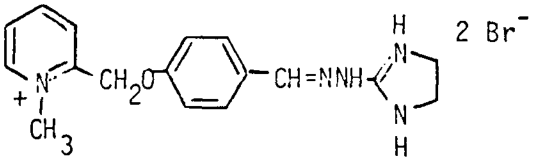
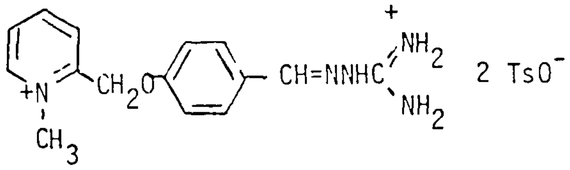
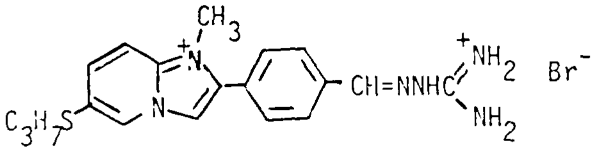
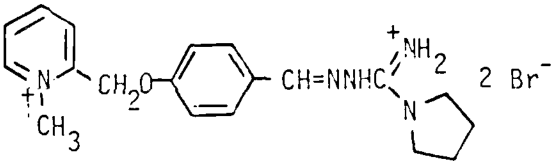
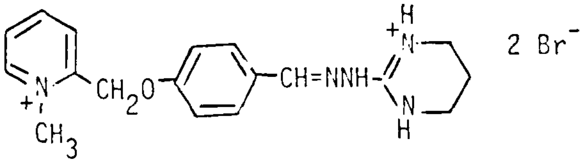
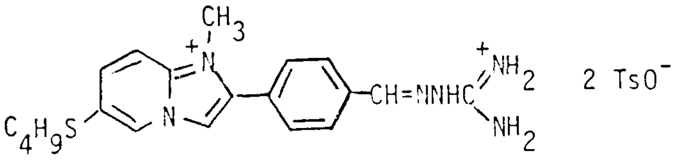
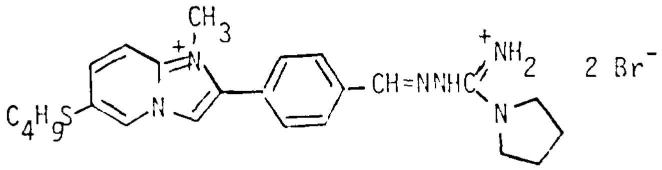
Our Sample Number	WRAIR Number	Structure	Date Submitte (Mo-Da-Y
I-005-AB	BL06998		4-24-85
I-006-AB	BL07002		4-24-85
V-85-GM	BL07039		4-24-85
A-I-9	BL07633		5-23-85
A-1-10	BL07646		5-23-85
V-93-GM	BL07655		5-23-85
V-94-GM	BL07664		5-23-85

TABLE I. (continued)

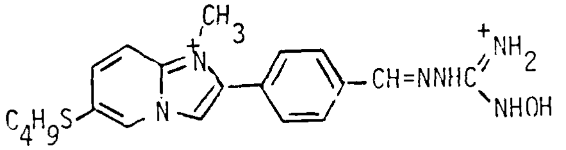
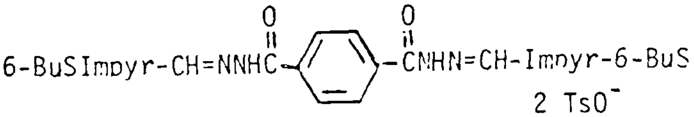
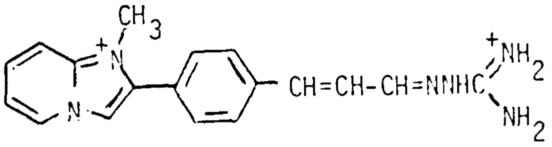
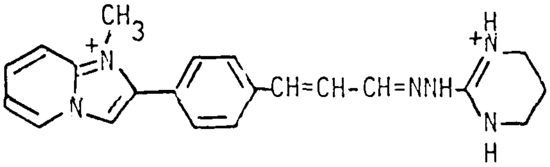
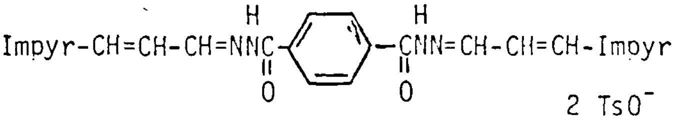
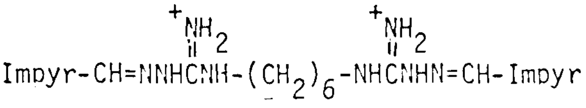
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
V-95-GM	BL07673	 2 Br$^-$	5-23-85
V-96-GM	BL07806	 2 TsO$^-$	6-13-85
V-98-GM	BL07815	 2 TsO$^-$	6-13-85
V-99-GM	BL07824	 2 Br$^-$	6-13-85
V-101-GM	BL07833	 2 TsO$^-$	6-13-85
V-103-GM	BL07842	 $\text{Impyr-CH=NNH}\overset{^{+}NH_2}{\overset{\|}{C}}\text{NH-}(CH_2)_6\text{-NH}\overset{^{+}NH_2}{\overset{\|}{C}}\text{NHN=CH-Impyr}$ 4 I$^-$	6-13-85

Table I. (continued)

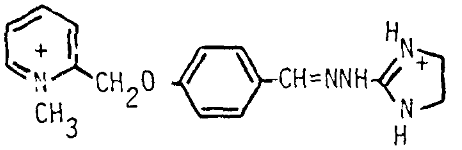
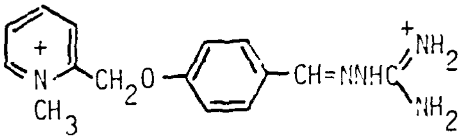
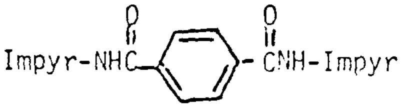
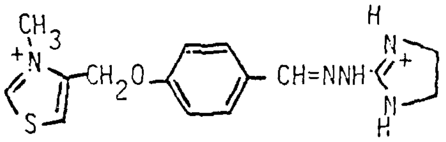
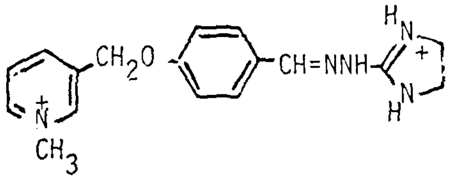
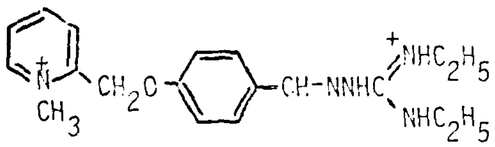
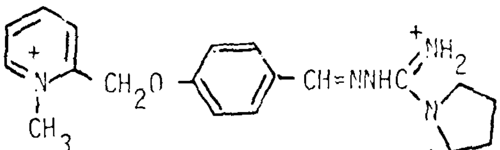
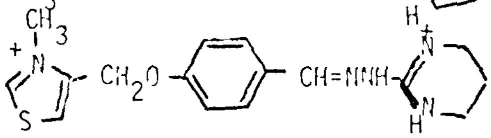
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
I-0005-AB (resubmission)	BL08205	 2 Br$^-$	7-5-85
I-006-AB (resubmission)	BL08214	 2 TsO$^-$	7-5-85
V-104-GM	BL08223	 2 TsO$^-$	7-5-85
I-25-A	BL08232	 2 Br$^-$	7-5-85
I-29-A	BL08241	 2 Br$^-$	7-5-85
I-12-A	BL08250	 2 Br$^-$	7-5-85
A-I-9 (resubmission)	BL09006	 2 Br$^-$	8-1-85
I-39-A	BL09015	 2 Br$^-$	8-1-85

TABLE I. (continued)

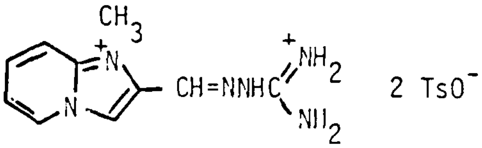
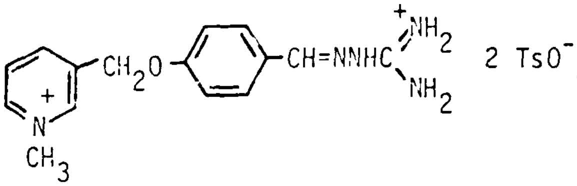
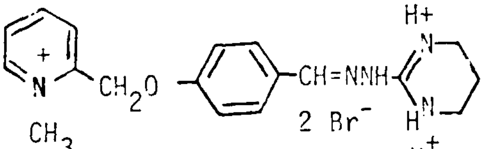
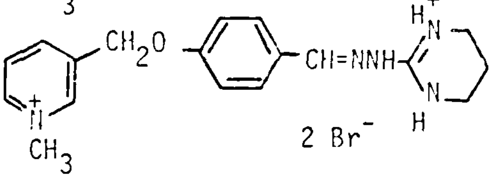
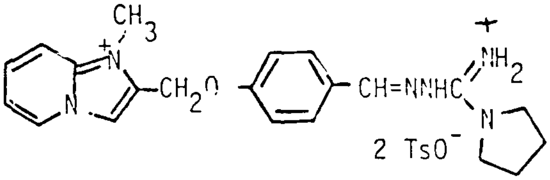
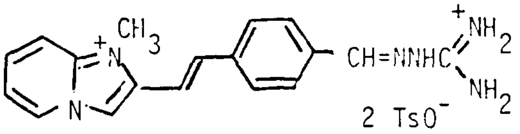
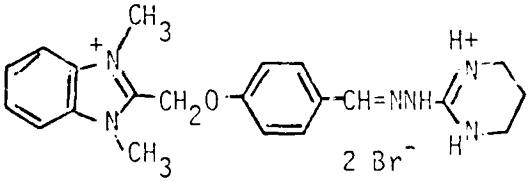
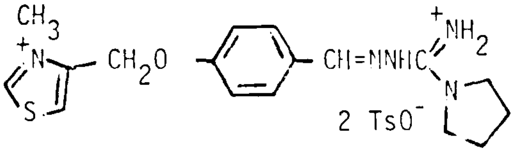
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
II-20-VS	BL09024	 2 TsO$^-$	8-1-85
I-31-A	BL09033	 2 TsO$^-$	8-1-85
A-I-10 (resubmission)	BL09042	 2 Br$^-$	8-1-85
I-34-A	BL09051	 2 Br$^-$	8-1-85
II-33-VS	BL09453	 2 TsO$^-$	8-23-85
II-36A-VS	BL09462	 2 TsO$^-$	8-23-85
I-38-A	BL09471	 2 Br$^-$	8-23-85
I-43-A	BL09480	 2 TsO$^-$	8-23-85

TABLE I. (continued)

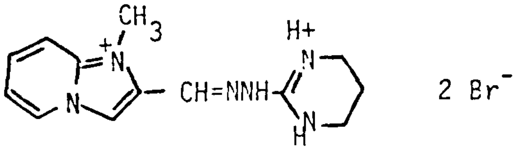
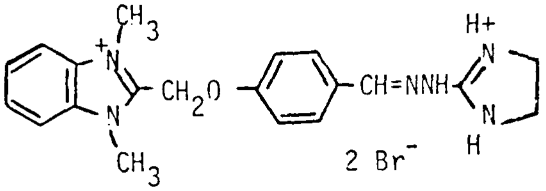
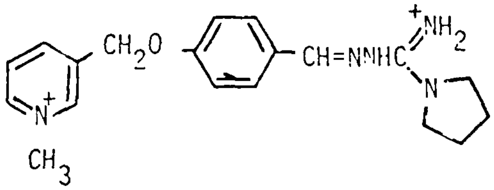
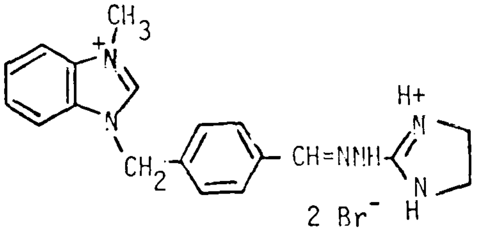
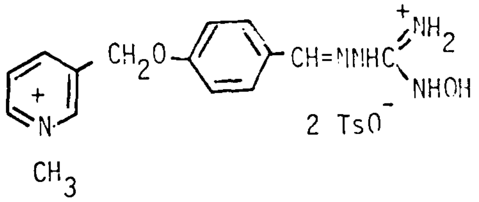
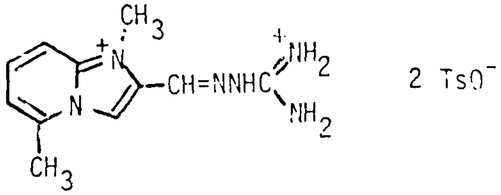
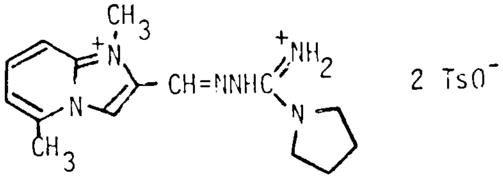
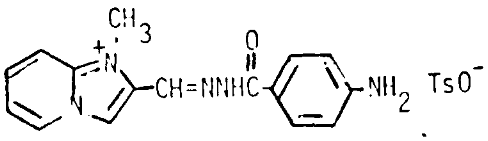
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
II-21A-VS	BL09499		8-23-85
I-50-A	BL10018		9-26-85
I-51-A	BL10027		9-26-85
I-57-A	BL10036		9-26-85
I-58-A	BL10045		9-26-85
II-38-VS	BL10054		9-26-85
II-39-VS	BL10063		9-26-85
II-41-VS	BL10072		9-26-85

Table I. (continued)

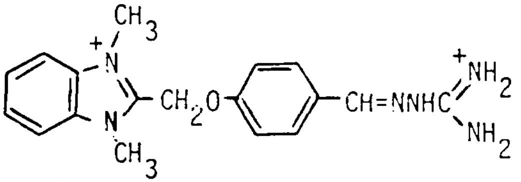
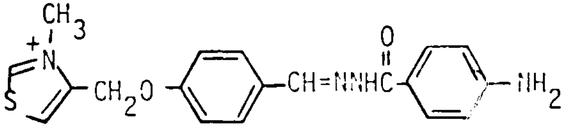
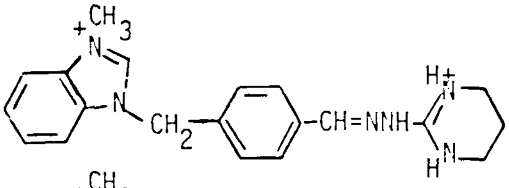
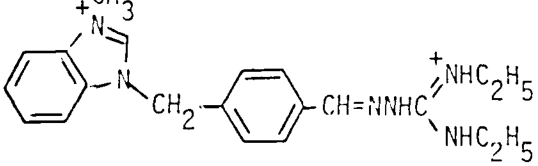
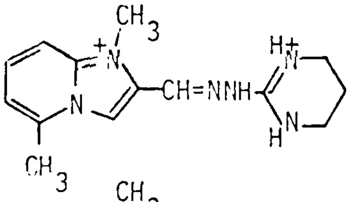
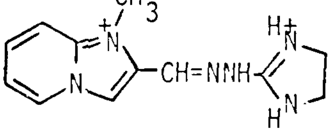
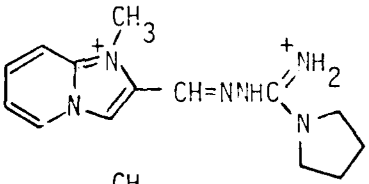
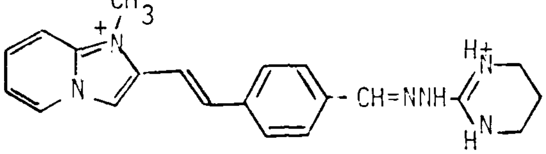
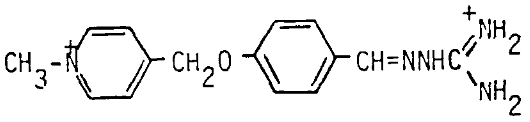
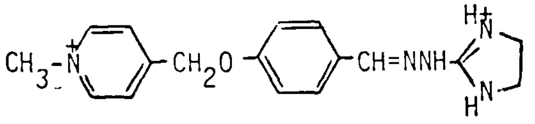
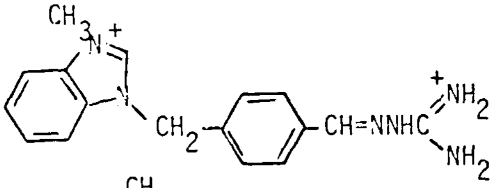
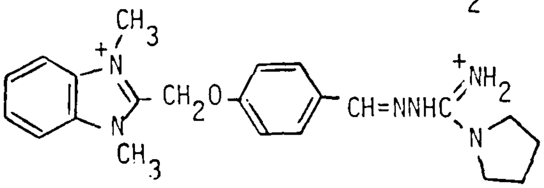
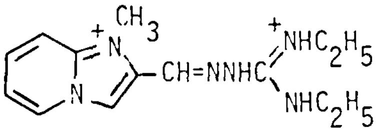
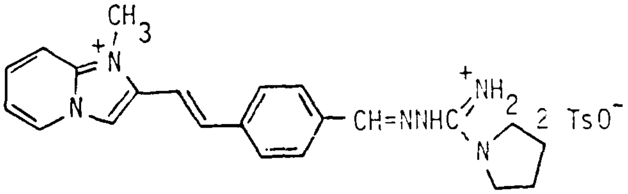
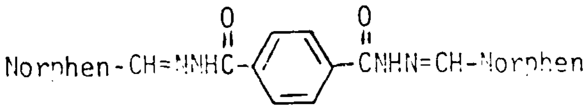
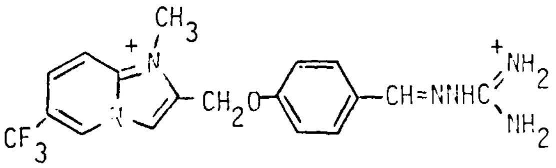
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Day-Yr)
I-49-A	BL11131	 2 Br$^-$	10-31-85
I-54-A	BL11140	 TsO$^-$	10-31-85
I-62-A	BL11159	 2 Br$^-$	10-31-85
I-67-A	BL11168	 2 Br$^-$	10-31-85
II-39A-VS	BL11177	 2 Br$^-$	10-31-85
II-44-VS	BL11186	 2 Br$^-$	10-31-85
II-49B-VS	BL11195	 2 Br$^-$	10-31-85
II-54-VS	BL11202		10-31-85

Table I. (cont.)

Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Day-Yr)
I-32-A	BL12110	 $2\ TsO^-$	12-9-85
I-33-A	BL12129	 $2\ Br^-$	12-9-85
I-60-A	BL12138	 $2\ Br^-$	12-9-85
I-79-A	BL12147	 $2\ TsO^-$	12-9-85
II-46-VS	BL12156	 $2\ Br^-$	12-9-85
II-57-VS	BL12165	 $2\ TsO^-$	12-9-85
II-78-VS	BL12174		12-9-85
II-79-VS	BL12183	 $2\ TsO^-$	12-9-85

Norphen = 1-Methylimidazo[1,2-a]pyridinium

Table I. (continued)

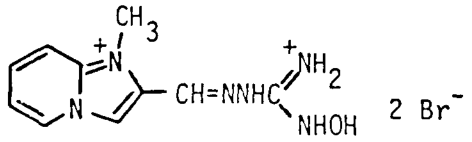
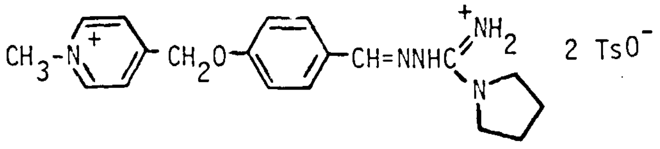
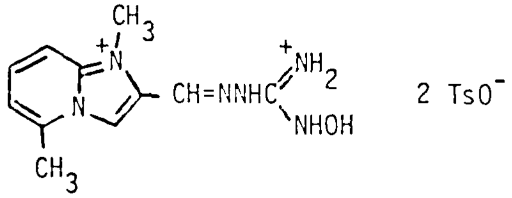
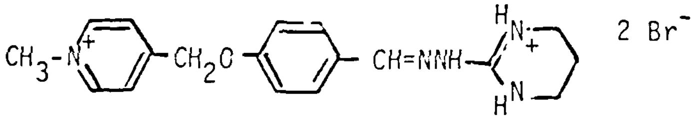
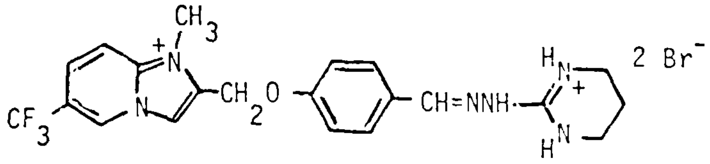
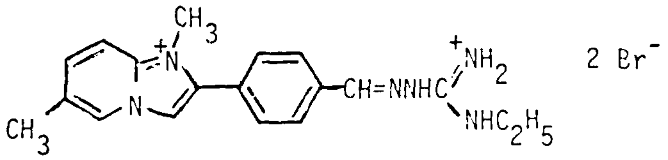
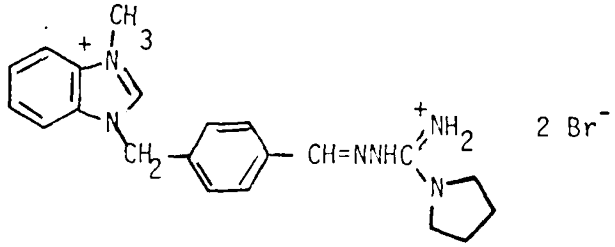
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
II-22C-VS	BL12718		1-10-86
I-87-A	BL12727		1-10-86
II-94-VS	BL12736		1-10-86
I-86-A	BL12745		1-10-86
II-80A-VS	BL12754		1-10-86
II-95-VS	BL12763		1-10-86
I-61-A	BL12772		1-10-86

TABLE I. (continued)

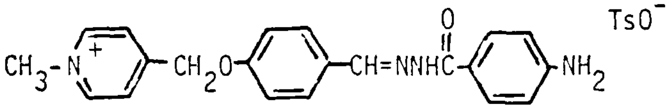
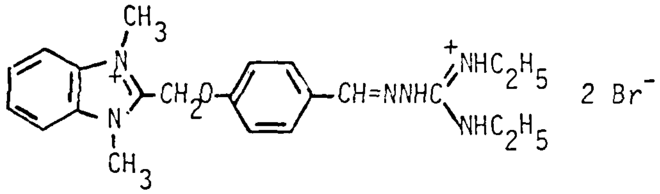
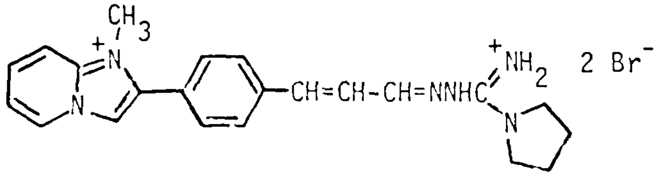
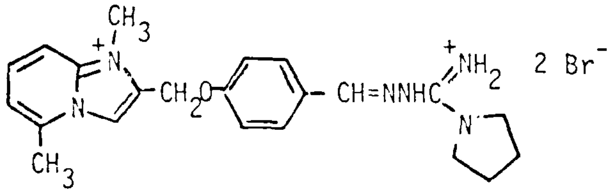
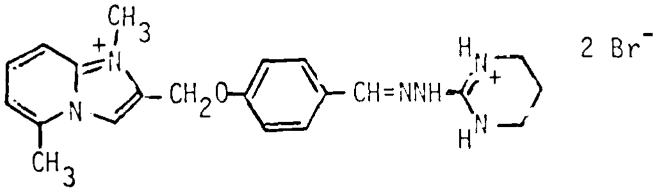
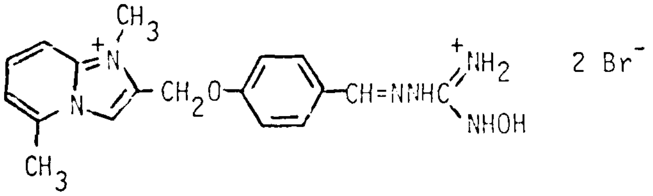
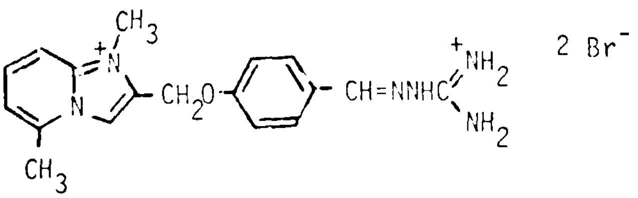
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
I-30-A	BL18514		2-12-86
I-32-A	BL18523		2-12-86
II-39-VS	BL18532		2-12-86
III-15-VS	BL18541		2-12-86
III-18-VS	BL18550		2-12-86
III-19-VS	BL18569		2-12-86
III-11B-VS	BK40673		3-27-86

TABLE I. (continued)

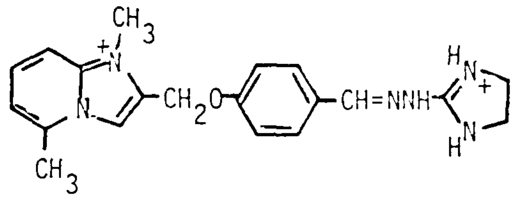
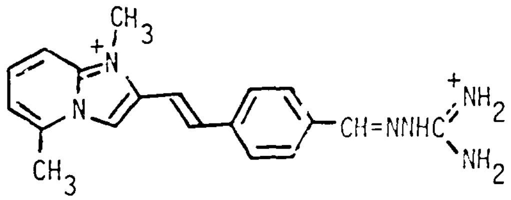
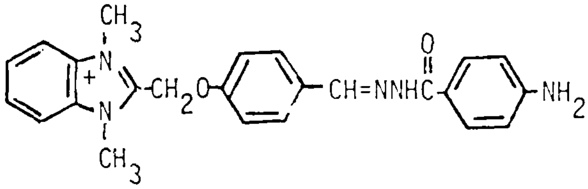
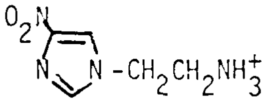
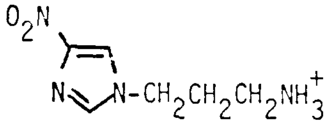
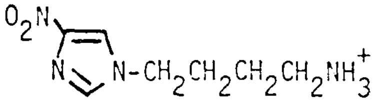
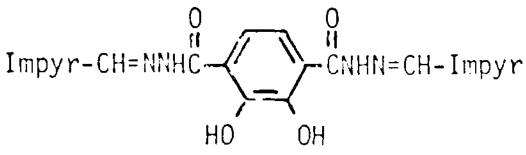
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
III-25-VS	BK40664	 2 Br^-	3-27-86
III-27-VS	BK40655	 2 TsO^-	3-27-86
I-91-A	BK40726	 TsO^-	3-27-86
II-10-A	BK40691	 Cl^-	3-27-86
I-97-A	BK40717	 Cl^-	3-27-86
II-6-A	BK40708	 Cl^-	3-27-86
II-69D-VS	BK40682	 2 Br^-	3-27-86

Table I. (continued)

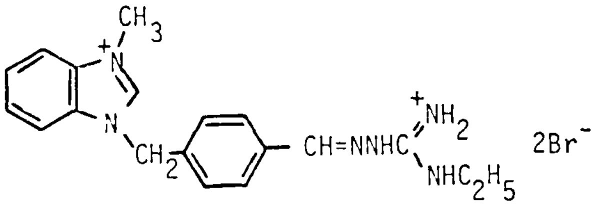
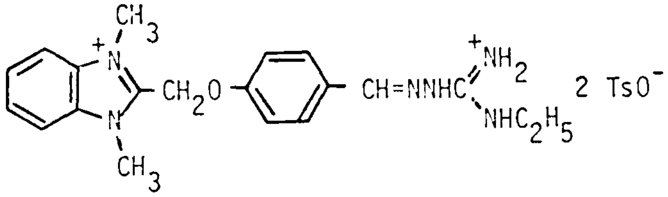
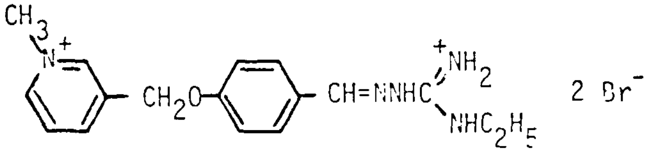
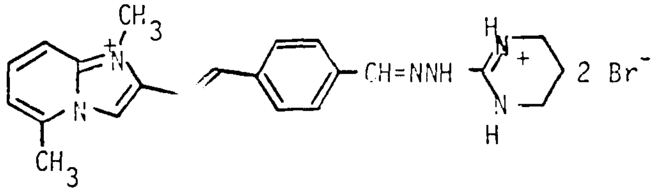
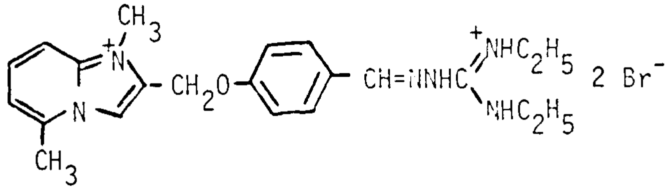
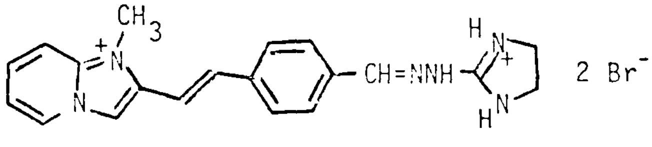
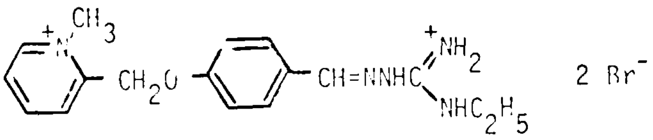
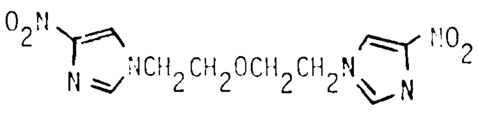
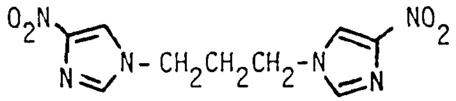
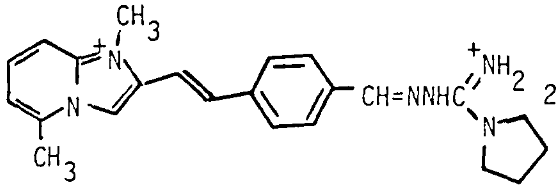
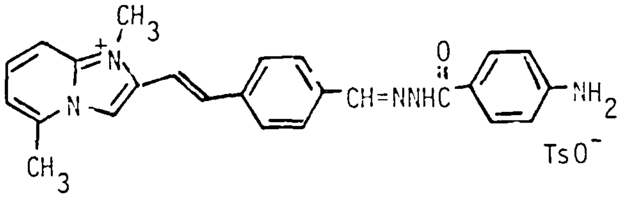
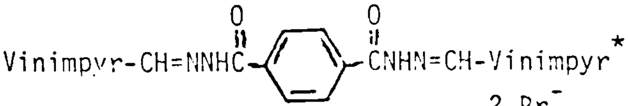
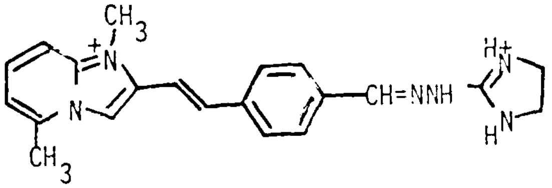
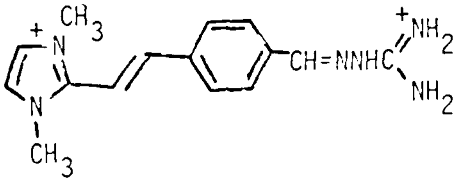
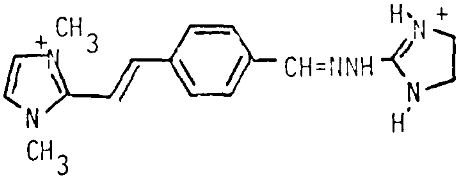
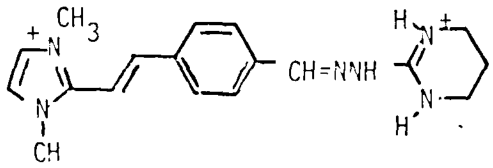
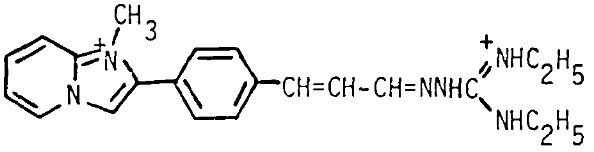
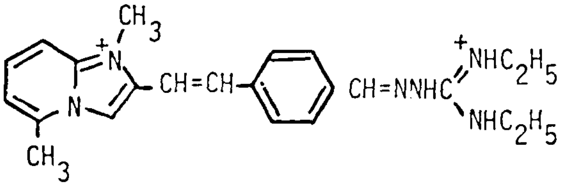
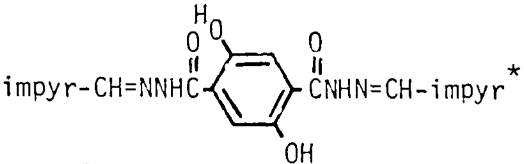
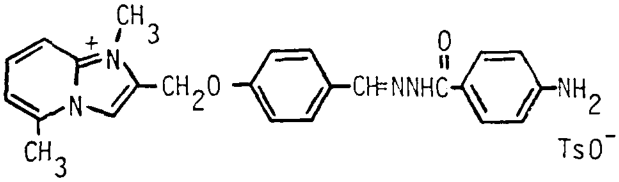
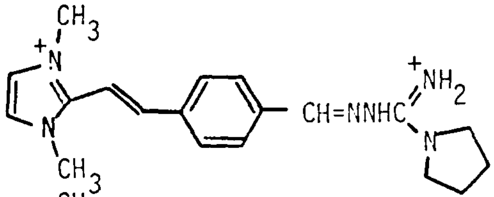
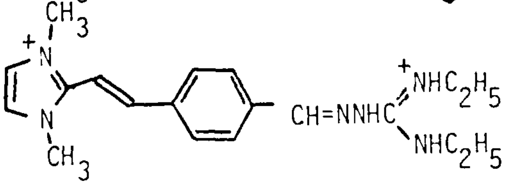
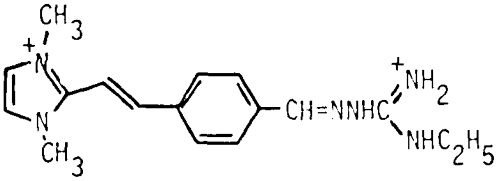
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-T
II-15-A	BL19771		5-6-86
II-16-A	BL19780		5-6-86
II-17-A	BL19799		5-6-86
III-28-VS	BL19806		5-6-86
III-32-VS	BL19815		5-6-86
III-33-VS	BL19824		5-6-86
II-18-A	BL20658		6-6-86
II-19-A	BL20667		6-6-86

Table 1. (continued)

Our Sample Number	WRAIR Number	Structure	Date Submittec (Mo-Da-Yr
II-20-A	BL20676		6-6-86
III-31A-VS	BL20685	 $2\ Br^-$	6-6-86
III-37-VS	BL20694	 TsO^-	6-6-86
III-38-VS	BL20701	 Vinimpyr-CH=NNHC(O)-C₆H₄-C(O)NHN=CH-Vinimpyr* $2\ Br^-$	6-6-86
III-41-VS	BL20710	 $2\ Br^-$	6-6-86
II-26-A	BL21600	 $2\ TsO^-$	7-8-86
II-27-A	BL21593	 $2\ Br^-$	7-8-86
II-28-A	BL21584	 $2\ Br^-$	7-8-86

* Vinimpyr = 1-methyl-2-(phenylethenyl)imidazo[1,2-a]pyridinium

Table I. (continued)

Our Sample Number	WRAIR Number	Structure	Date Submit (Mo-Da-
II-98-VS	BL21575	 $2\ Br^-$	7-8-8
III-46-VS	BL21566	 $2\ Br^-$	7-8-8
III-35C-VS	BL21548	 $2\ Br^-$	7-8-86
III-45-VS	BL21557	 TsO^-	7-8-86
II-31-A	BL22250	 $2\ TsO^-$	8-15-8
II-32-A	BL22269	 $2Br^-$	8-15-8
II-34-A	BL22278	 $2\ TsO^-$	8-15-8

* impyr = 1-methyl-2-phenylimidazo[1,2-a]pyridinium

Table I. (cont.)

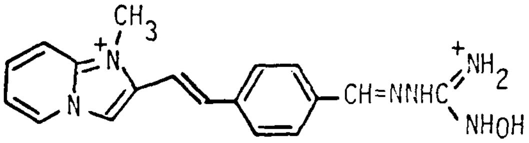
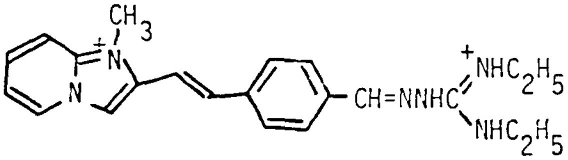
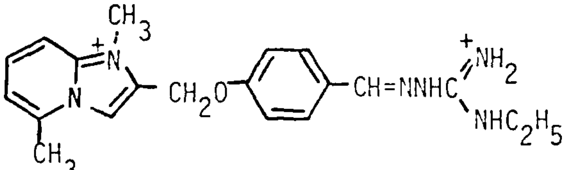
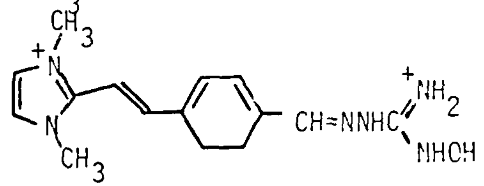
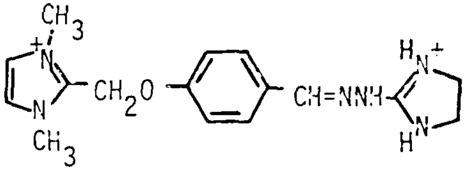
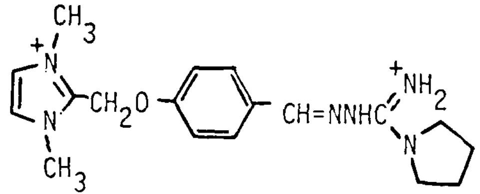
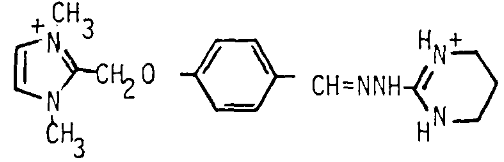
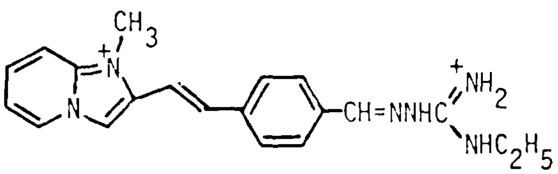
Our Sample Number	WRAIR Number	Structure	Date Submitte (Mo-Da-
II-96D-VS	BL22287	 2 Br$^-$	8-15-8
III-47A-VS	BL22296	 2 Br$^-$	8-15-8
III-55A-VS	BL22303	 2 Br$^-$	8-15-86
II-33-A	BL24094	 2 Br$^-$	9-22-86
II-24-A	BL24085	 2 Br$^-$	9-22-86
II-36-A	BL24101	 2 TsO$^-$	9-22-86
II-41-A	BL24110	 2 Br$^-$	9-22-86
III-57A-VS	BL24129	 2 Br$^-$	9-22-86

Table I. (cont)

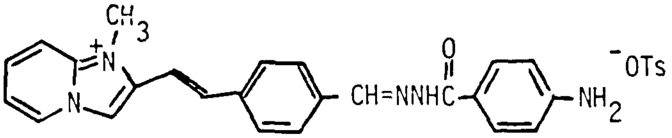
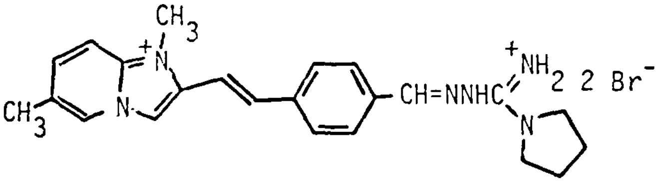
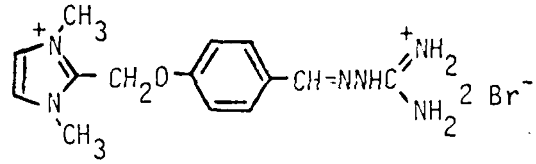
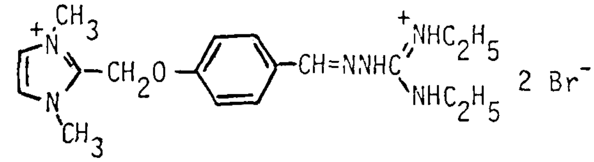
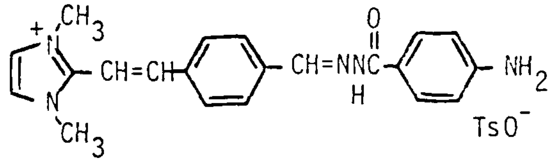
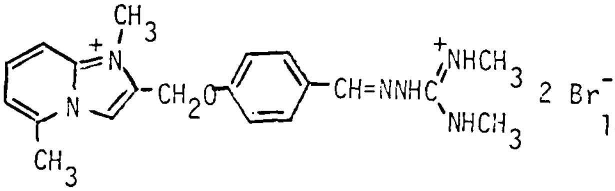
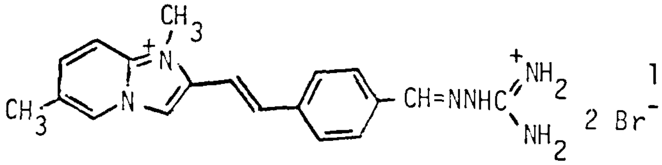
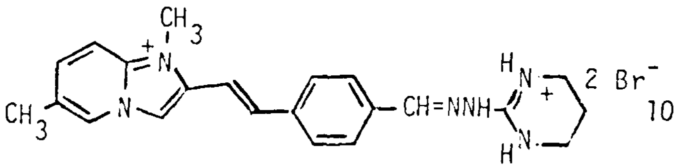
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr.
III-64-VS	BL24138		9-22-86
III-71-VS	BL24147		9-22-86
II-37-A	BL28029		10-31-86
II-40-A	BL28038		10-31-86
II-42-A	BL28047		10-31-86
III-66B-VS	BL28056		10-31-86
III-70B-VS	BL28065		10-31-86
III-72A-VS	BL28074		10-31-86

Table I. (cont.)

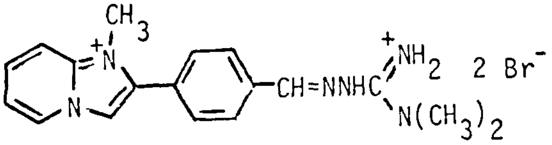
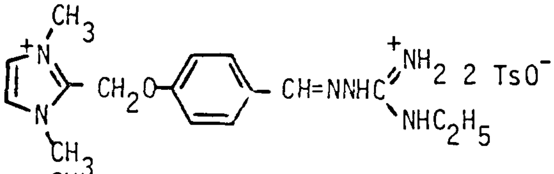
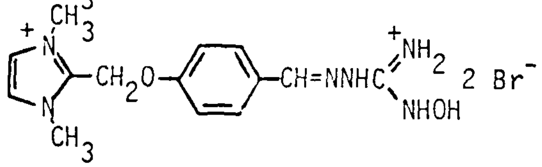
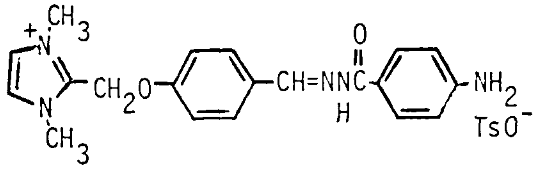
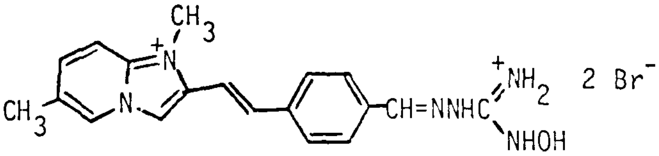
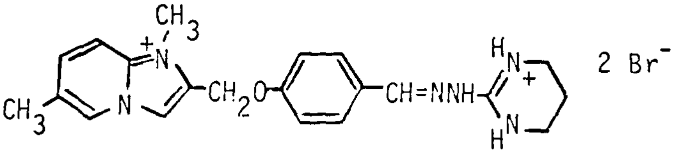
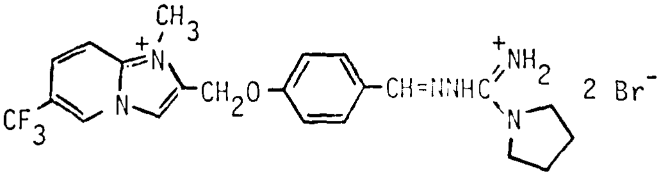
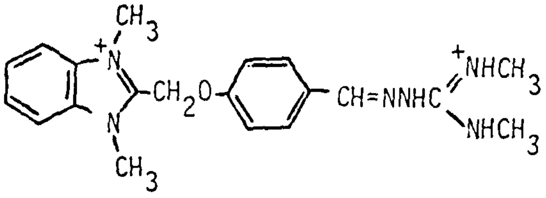
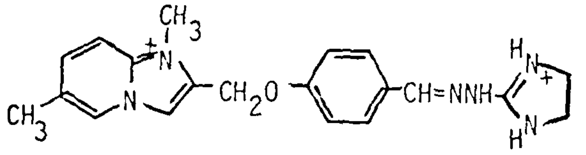
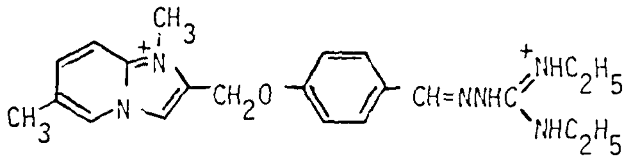
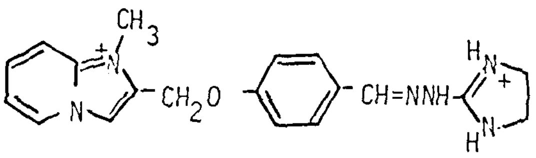
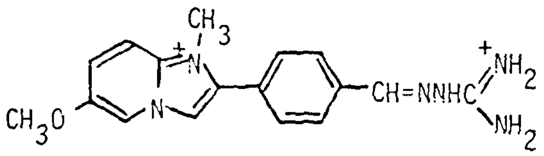
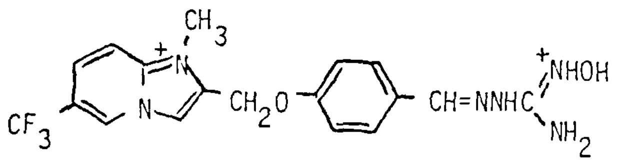
Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
III-24-GM (resubmission)	BL28083		11-5-86
II-38-A	BL31017		12-12-86
II-39-A	BL31026		12-12-86
II-43-A	BL31035		12-12-86
III-74C-VS	BL31044		12-12-86
III-87A-VS	BL31053		12-12-86
III-89-VS	BL31062		12-12-86

Table I. (cont.)

Our Sample Number	WRAIR Number	Structure	Date Submitted (Mo-Da-Yr)
II-47-A	BL35542	 $2\ Br^-$	2-20-87
III-94-VS	BL35579	 $2\ Br^-$	2-20-87
III-90A-VS	BL35560	 $2\ Br^-$	2-20-87
III-11-MJB (resubmission)	BL35533	 $2\ Br^-$	2-20-87
III-60-GM (resubmission)	BL35551	 $2\ TsO^-$	2-20-87
III-92-VS	BL39700	 $2\ Br^-$	4-14-87

III. Biological Evaluation

A. Activity Against T. rhodesiense

Nearly all of the compounds were examined for in vivo activity in trypanosomiasis (T. rhodesiense) infections in mice. A standard protocol was used in which groups of five mice were treated by subcutaneous injection with a specified dose of the compound. Data were reported as toxic deaths, an increased life span versus controls or survival (cure) of greater than 30 days. This data has been summarized for each compound by giving the dose range at which the compound caused lethal toxicity (toxic), the dose range in which all test animals survived 30 days (100% cures), the dose range in which some but not all animals were cured (partial cures) and the lowest dose at which at least 50% of the test animals were 30-day survivors (50% cures = ED_{50}).

For each compound for which sufficient data is available an index of curative effectiveness (i.c.e.) was calculated as the fraction of all animals cured in the dose range 0.4 through 424 mg/kg. The calculation was done by taking the average of the fraction cured at each of the 11 dose rates within this range. An inactive compound would be scored 0 since no animals are cured. A completely toxic compound would also be scored 0. A compound which cured all animals at all 11 doses would score the maximum value of 1.0. The index rates the relatively nontoxic compounds higher than less toxic ones, since the less toxic compounds have broader curative ranges. A sample calculation is given for BK50311.

dose	0.4	0.8	1.6	3.3	6.6	13	26	53	106	212	424
cures	2/5	8/10	9/10	5/5	3/5	10/10	8/10	2/5	1/5	1/5	0/5
toxic	0/5	0/10	0/10	0/5	0/5	0/10	0/10	3/5	4/5	4/5	5/5
fraction cured	0.4	0.8	0.9	1.0	0.6	1.0	0.8	0.4	0.2	0.2	0.0

$$\text{i.c.e.} = \frac{6.3}{11} = 0.57$$

The results of these tests are given in Tables 2-8 which are subdivided according to the functional group types as defined in Scheme 2.

Another class of compounds which were prepared and evaluated are referred to as "dimeric" compounds. These are structures in which one of the heteroaromatic ring systems defined in Scheme 1 is linked by a difunctional central group to give examples of the general structure.

(ring)---(difunctional)---(ring)

The difunctional links are defined in Scheme 3 and correspond to a special case of functional group X in Scheme 1. The activity of the dimeric compounds by SC administration is given in Table 9. Several of these dimeric structures showed significant trypanocidal activity, compounds $(Ia)_2$-12 and $(Ia)_2$-13 being particularly active.

SCHEME 3

DIFUNCTIONAL LINKS

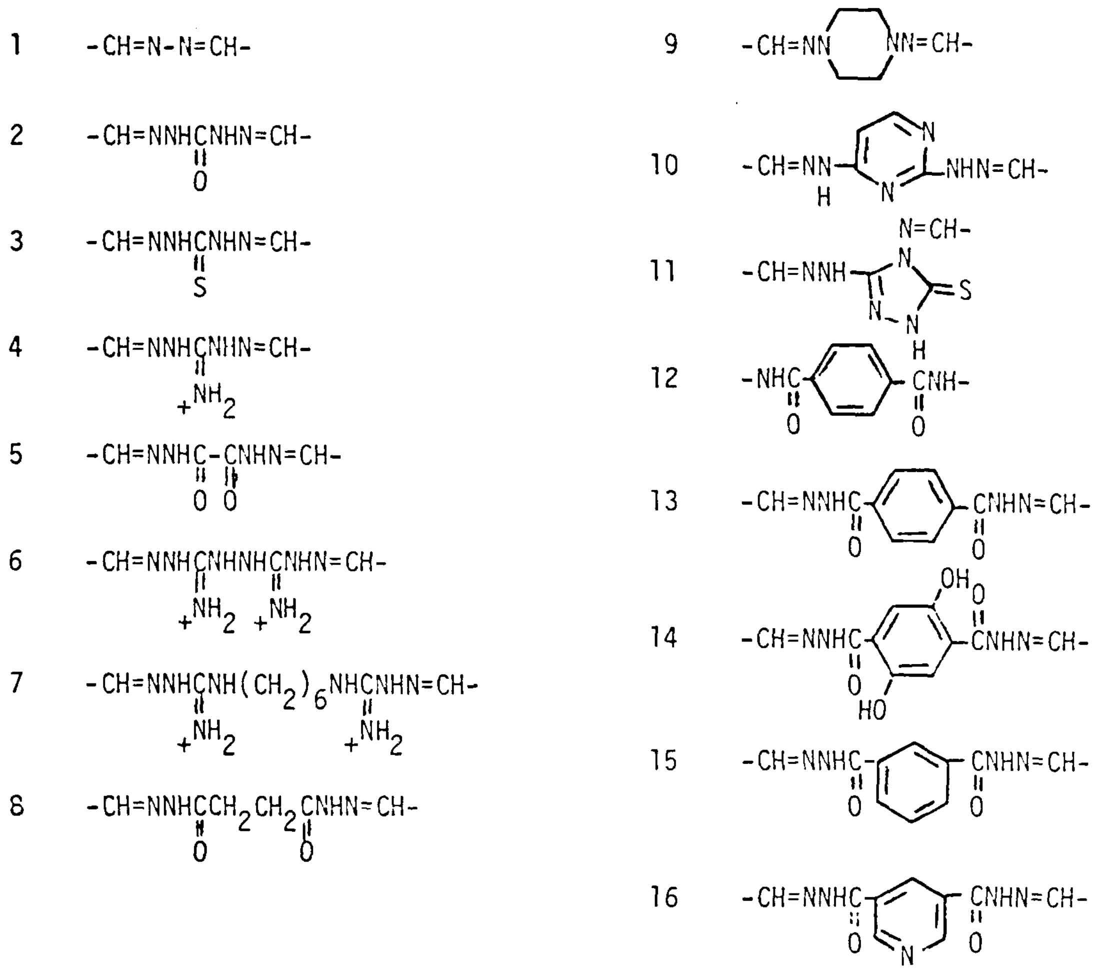


TABLE 2

Acetamido and Related Functions - Functional Groups 1-9

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
1a-1	I^-	BJ36718	0.17	212	53-212		424
1a-1	TsO^-	BJ83315	0.14	212	212-424		
1a-2	I^-	BJ83262	0.00				106-424
1a-3	TsO^-	BJ84929	0.00				106-424
1a-7	I^-	BJ92645	0.00				
1a-8	I^-	BJ92636	0.00				424
1b-1	Br^-	BJ58296	0.20	26	26		53-424
1b-4	Br^-	BJ91264	0.01		106		212-424
1b-5	Br^-	BJ91246	0.00				106-424
1b-6	Br^-	BJ91273	0.00				106-424
1b-7	Br^-	BJ92627	0.00				106-424
1b-9	Br^-	BK02566	0.04		26		106-424
1be-1	Br^-	BK11761	0.00				106-424
1bh-1	Br^-	BK02557	0.02				106-424
1c-1	Br^-	BJ83244	0.10	212			106-424
1d-1	Br^-	BJ83235	0.17	212	26-53		106-424
1e-1	TsO^-	BJ83280	0.00				106-424
1f-1	TsO^-	BJ83306	0.07		106-212		424
1h-1	TsO^-	BJ84938	0.08	424	106-424		
1j-1	TsO^-	BJ90703	0.09		26-424		
1k-1	TsO^-	BJ90758	0.02				424
1l-1	TsO^-	BJ90767	0.01		424		
1r-1	Br^-	BJ91255	0.00				
1x-1	I^-	BJ51911	0.12	212	106		424
6-1	TsO^-	BK16480	0.02				106-424
7-1	TsO^-	BK15367	0.00				424
8-1	TsO^-	BK15394	0.00				424

TABLE 3

Related Functional Groups 10-27

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
1a-10	TsO$^-$	BJ90712	0.04		106		424
1a-11	TsO$^-$	BJ90721	0.24	106	53-212	424	
1a-12	TsO$^-$	BJ90730	0.12	106	26-106		212-424
1a-13	TsO$^-$	BK11743	0.34	53	13-212		424
1a-14	TsO$^-$	BK15358	0.00				424
1a-15	TsO$^-$	BK47896	0.00				106-424
1a-16	TsO$^-$	BK47930	0.00				106-424
1a-17	2TsO$^-$	BK50222	0.00				106-424
1a-18	Cl$^-$	BK51989	0.00				106-424
1a-19	Br$^-$	BK57114	0.17	53	26-212		424
1a-20	2TsO$^-$	BK57203	0.05		3.3-13		26-424
1a-21	2Br$^-$	BK57212	0.00				26-424
1a-22	TsO$^-$	BK73690	0.57	0.8	0.8-1.6	3.3-26	53-424
1a-24	TsO$^-$	BK21883	0.00				106-424
1a-25	TsO$^-$	BK22988	0.00				26-424
1a-26	TsO$^-$	BK24053	0.00				424
1a-27	TsO$^-$	BJ84965	0.00				106-424
1b-23	Br$^-$	BK02539	0.00				424
1u-11	Br$^-$	BK57187	0.06	26			106-424
1u-16	TsO$^-$	BK50240	0.00				6.6-424
2g-22	TsO$^-$	BL21557	0.44	13	26-212		
3a-22	TsO$^-$	BL24138					
3g-22	TsO$^-$	BL20694	0.62	6.6	1.6-6.6	13-212	
5a-22	TsO$^-$	BL10072		424	106	424	
6-12	TsO$^-$	BK21918	0.05	106			106-424
6-16	TsO$^-$	BK47903	0.00				26-424
6-20	2Br$^-$	BK63658	0.05				26-424
6-21	2Br$^-$	BK64164	0.01				26-424
6-26	TsO$^-$	BK24044	0.00				424
7-12	TsO$^-$	BK23994	0.00			212-424	
9-22	TsO$^-$	BL31035					
10-22	TsO$^-$	BK40726	0.37	6.6	1.6-53		106-424
11-22	TsO$^-$	BK11140	0.18	53	13-212		424
14-22	TsO$^-$	BL18514					
15-22	TsO$^-$	BL28047		13		53	106-424

TABLE 4

Amidines, Amide Oximes and Amidrazones - Functional Groups 28-36

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
1a-28	$2Cl^-$	BK16471	0.21	26	13-26	53	106-424
1a-29	$3Cl^-$	BK23001	0.01				26-424
1a-30	$3Cl^-$	BK50259	0.12	13	13		26-424
1a-31	$3Cl^-$	BK62795	0.00				26
1a-32	$2TsO^-$	BK15349	0.00				
1a-33	$2TsO^-$	BK63603	0.00				26-424
1a-34	$2Cl^-$	BK63621	0.00				26-424
1a-35	Cl^-	BJ84974	0.29	53	26-106	212	424
1a-36	$2Cl^-$	BK21892	0.00				106-424
1e-28	$2Cl^-$	BK46148	0.00				106-424
1e-35	$2Cl^-$	BK46193	0.09	212			106-424
1e-36	$2Cl^-$	BK46157	0.00				26-424
1h-28	$2Cl^-$	BK46166	0.13	106	26-53		106-424
1h-35	$2Cl^-$	BK13087	0.16	106	53		106
1u-28	$2Cl^-$	BK42757	0.11	212	53		106-424
2a-28	$2Cl^-$	BK65330	0.26	3.3	0.8-13		26-424
6-28	$2Cl^-$	BK21874	0.23	106	26-106	212	424
6-29	$2Cl^-$	BK23010	0.04		26		53-424
6-30	$3Cl^-$	BK50204	0.04		13		26-424
6-35	$2Cl^-$	BK16499	0.12	106	26-53		106-424
6-36	$2Cl^-$	BK22997	0.00				106-424
7-28	$2Cl^-$	BK22979	0.02		106-212		424
7-29	$3Cl^-$	BK42739	0.01				26-424
7-35	$2Cl^-$	BK21865	0.02				424
7-36	$2Cl^-$	BK23029	0.00				26-424

TABLE 5

Methylthioimidoylhydrazones - Functional Groups 37 and 38

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
1a-37	$2Br^-$	BK47921	0.55	6.6	3.3-106		212-424
1a-38	$2Br^-$#	BK85645	0.24	26	13-26		106-424
1h-37	$2Br^-$	BK62811	0.38	26	13-53		106-424
1i-38	$2Br^-$#	BK85645	0.38	26	13-26	53	106-424
1m-37	$2Br^-$	BK70993	0.16	106	106-424	424	
1n-37	$2Br^-$	BK73770	0.00				106-424
1o-37	$2Br^-$	BK72835	0.00				106-424
1s-37	$2Br^-$	BK75158	0.47	13	13-106	212-424	
2a-37	$2Br^-$	BK65027	0.44	26	6.6-53	106-212	424
6-37	$2Br^-$	BK50231	0.11	26	6.6-53		106-424

isolated as mixed bromide-iodide salt

TABLE 6

Guanylhydrazones and N-Alkyl Guanylhydrazones - Functional Groups 39-62

Structure Code	Counter Ions	WRAIR Number	i.c.e	50% Cures	Partial Cures	100% Cures	Toxic
1a-39	$2TsO^-$	BJ90749	0.54	0.8	0.2-0.8	.6-13	26-424
1a-40	$2Br^-$	BK46200	0.40	0.8	0.4-1.6	3.3-6.6	13-424
1a-41	$2Br^-$	BK96737	0.59*	0.1	0.06-0.1	0.2-13	26-424
1a-42	$2Br^-$	BK96755	0.59*	0.1	0.1-1.6	3.3-13	26-424
1a-43	$2Br^-$	BK98535	0.50	0.8	0.4-0.8	1.6-6.6	13-424
1a-44	$2Br^-$	BK96764	0.65	0.2	0.2-0.8	1.6-53[a]	106-424
1a-45	$3Br^-$	BK62777	0.45	0.8	0.4-1.6	3.3-13	26
1a-46	$4Br^-$#	BK64100	0.00				6.6-424
1a-47	$2Br^-$	BK46175	0.06				1.6-424
1a-48	$3Br^-$#	BK63596	0.38	1.6	0.8	1.6-13[b]	26-424
1a-49	$3Br^-$	BK57123	0.41	0.8	0.4-6.6	13	26-424
1a-50	$2Br^-$	BK96086	0.46	1.6	0.8-6.6	13	26-424
1a-51	$2I^-$	BK47976	0.48	0.2		0.2-6.6	13-424
1a-52	$2Br^-$	BK50286	0.35	0.2	0.06-3.3		6.6-424
1a-53	$2Br^-$	BK50277	0.39*	0.06	0.06-0.8	1.6-3.3	6.6-424
1a-54	$2Br^-$	BK96095	0.44	0.8	0.1-0.8	1.6-6.6[c]	13-424
1a-55	$2Br^-$	BK90677	0.33	0.4	0.4-1.6	3.3	6.6-424[d]
1a-56	$2.75Br^-$	BK96068	0.21	3.3	1.6-6.6		13-424
1a-57	$2TsO^-$	BL00012	0.30	13		13-53	106-424
1a-58	$2I^-$	BK96728	0.58	0.2	0.2-0.4	0.8	26-424
1a-59	$2Br^-$	BL03899	0.57	1.6	0.4-1.6	3.3-13	26-424
1a-60	$2Br^-$	BL00003	0.05	13	13		26-424
1a-61	$2Br^-$	BK50311	0.57	0.8	0.4-6.6	13-26[e]	53-424
1a-62	$2Br^-$	BK98571	0.67*	0.1	0.06-1.6	3.3-13	26-424
1b-39	$2Br^-$	BK11770	0.43	0.4	0.2-1.6	13	26-424
1e-39	$2TsO^-$	BK13069	0.45	0.8	0.2-0.4	0.8-6.6	13-424
1h-39	$2TsO^-$	BK13078	0.83	0.2	0.06-0.4	0.8-53[f]	106-424
1h-41	$2Br^-$	BL12763	0.67	0.4	0.2-0.8	1.6-13	26-424
1h-51	$2Br^-$	BK96102	0.43	0.8	0.4-1.6	3.3-6.6	13-424
1h-53	$2Br^-$	BK96746	0.49	0.1	0.03-0.2	0.4-6.6[g]	13-424
1h-55	$2Br^-$	BK96040	0.47	0.8	0.2-3.3	6.6	13-424
1h-57	$2TsO^-$	BL03915	0.39	6.6	6.6-26	53	106-424
1h-59	$2Br^-$	BL05339	0.66	1.6	1.6-53[+]	106-424	
1h-62	$2Br^-$	BK98562	0.76	0.2	0.06-0.1	0.2-53	106-424
1i-39	$2TsO^-$	BK46219	0.55	1.6	0.8	1.6-26	53-424
1i-41	$2Br^-$	BK98599	0.57*	0.1	0.1-1.6	3.3-6.6	13-424
1i-42	$2Br^-$	BK98580	0.63*	0.2	0.06-0.8	1.6-6.6	13-424
1i-43	$2Br^-$	BK98526	0.71	0.4	0.1-6.6	13	26-424
1i-53	$2Br^-$	BK96700	0.48	0.1	0.06-0.1	0.2-6.6	13-424
1i-55	$2Br^-$	BK96031	0.53*	0.4	0.1-0.8	1.6-6.6	13-424
1i-56	$2.75Br^-$	BK96059	0.24	3.3	3.3-6.6		13-424
1i-58	$2Br^-$	BK96773	0.58	0.4	0.2-1.6	3.3-13	26-424
1i-60	$2Br^-$	BL00058	0.24	53	6.6-53		106-424
1i-62	$2Br^-$	BK98553	0.67*	0.1		0.06-0.8	1.6-13
1m-39	$2TsO^-$	BK70984	0.93	0.1	0.1-1.6	3.3-53	106-424
1m-61	$2Br^-$	BK73743	0.69	3.3	0.8-3.3	6.6-53[h]	106-424

1n-39	$2Br^-$	BK73761	0.64	1.6	0.8-1.6	3.3-53^{i}	106-424
1o-39	$2Br^-$	BK72844	0.67	0.8	0.4-1.6	3.3-26	53-424
1p-39	$2Br^-$	BL07039	0.92	0.2	0.2-0.8	1.6-212	424
1p-53	$2Br^-$	BL06989	0.94	0.1	0.1-0.8	1.6-106	424
1q-39	$2TsO^-$	BL07655	0.83	0.4	0.2-26	53-212^{j}	424
1q-53	$2Br^-$	BL07664	0.63	3.3	0.8-1.6	3.3-106	212-424
1s-39	$2TsO^-$	BK51952	0.87	0.4	0.2-0.4	0.8-26^{k}	53-424
1t-39	$2TsO^-$-	BK75167	0.79*	0.4	0.1-0.4	0.8-53	106-424
1u-39	$2Br^-$	BK47985	0.29	3.3	0.8-1.6	3.3-13	26-424
1u-40	$2Br^-$	BK47958	0.33	0.4		0.4-1.6^{l}	26-424
1u-51	$2Br^-$	BK50268	0.24	0.8	0.8-3.3		6.6-424
1u-61	$2Br^-$	BK57230	0.07	13	13	26-424	
1v-39	$2Br^-$	BK51907	0.32	1.6	1.6-6.6		13-424
1v-61	$2Br^-$	BK62786		3.3	3.3-13		
1w-39	$2Br^-$	BK96719	0.45*	0.2	0.1-0.2	0.4-6.6	13-424
1w-53	$2Br^-$	BL00076	0.47	0.2	0.1-0.2	0.4-6.6	13-424
1x-39	$2Br^-$	BK65349	0.43	0.4	0.2-0.4	0.8-3.3^{m}	6.6-424
1x-61	$2Br^-$	BK65367	0.44	0.4	0.2-0.8	1.6-3.3	13-424
2a-39	$2Br^-$	BK65009	0.47*	0.1	0.1-0.4	0.8-6.6	13-424
2a-51	$2Br^-$	BL03924	0.26	3.3	0.8-6.6		13-424
2a-53	$2Br^-$	BL00030	0.36	0.8	0.4-0.8	1.6-3.3	6.6-424
2a-58	$2Br^-$	BL05366	0.45	0.8	0.8	1.6-13	26-424
2a-59	$2Br^-$	BL03933	0.44	0.8	0.8-1.6	3.3-6.6	13-424
2a-60	$2Br^-$	BL05357	0.09		6.6-26		106-424
2a-61	$2Br^-$	BK69687	0.60	0.8	0.1-1.6	3.3-13	26-424
2a-62	$2Br^-$	BL00067	0.67	0.4	0.4-1.6	3.3-53	106-424
2g-39	$2Br^-$	BK40673	0.49	0.8	0.2-1.6	3.3-13	26-424
2g-41	$2Br^-$	BL22303					
2g-53	$2Br^-$	BL18541	0.75	0.4	0.2-1.6	3.3-6.6	13-424
2g-58	$2Br^-$	BL28056					
2g-61	$2Br^-$	BK40664	0.64	0.8	0.2-0.8	1.6-26	53-424
2g-62	$2Br^-$	BL18550	0.70	0.8	0.8-1.6	3.3-26	53-424
2h-39	$2Br^-$	BL06961	0.81		0.06-0.2	0.4-13	26-424
2h-41	$2Br^-$	BL12763	0.67		0.4-0.8	1.6-13	26-424
2h-53	$2Br^-$	BL06970	0.46	0.8	0.4-6.6		13-424
2h-59	$2Br^-$	BL35560		1.6			
2h-61	$2Br^-$	BL35579		0.8			
2h-62	$2Br^-$	BL31053		0.8			
2i-39	$2Br^-$	BL06952	0.52	0.2	0.06-0.1	0.2-6.6	13-424
2i-53	$2Br^-$	BL06934	0.32	0.4	0.2-1.6	3.3	6.6-424
2j-39	$2TsO^-$	BL12183	0.67	6.6	0.8-3.3	6.6-212^{n}	424
2j-53	$2Br^-$	BL31062					
2j-62	$2Br^-$	BL12754	0.64	1.6	0.4-3.3	6.6-26	53-424
3a-39	$2TsO^-$	BL09462	0.89	0.1	0.06-0.1	0.2-26	53-424
3a-41	$2Br^-$	BL24129					
3a-53	$2TsO^-$	BL12165	0.74	0.8	0.1-6.6	13-212	424
3a-59	$2Br^-$	BL22296					
3a-61	$2Br^-$	BL19824		0.21			
3a-62	$2Br^-$	BL11202	0.71	0.4		0.4-26	53-424
3g-39	$2TsO^-$	BK40655	0.85	0.4	0.2	0.4-53^{o}	106-424
3g-53	$2Br^-$	BL20685	0.90	0.42		0.4-106	212-424
3g-59	$2Br^-$	BL21566	0.65	0.4	0.4-0.8	1.6-13	26-424
3g-61	$2Br^-$	BL20710	0.86	0.4	0.4-0.8	1.6-106	212-424
3g-62	$2Br^-$	BL19806					

3h-39	2Br$^-$	BL28065					
3h-53	2Br$^-$	BL24147					
3h-62	2Br$^-$	BL28074					
4a-39	2TsO$^-$	BL07815	0.94	0.06	0.03-0.2	0.4-212	424
4a-53	2Br$^-$	BL18532	0.34	0.8	0.2-0.4	0.8-3.3	6.6-424
4a-59	2Br$^-$	BL21575	0.34	13	6.6-13	26	53-424
4a-62	2Br$^-$	BL07824	0.58*	0.06	0.06-0.1	0.2-13	26-424
5a-39	2TsO$^-$	BL09024	0.24	106	26-424		
5a-53	2Br$^-$	BL11195	0.06	106			106-424
5g-59	2Br$^-$	BL12156	0.00				106-424
5a-61	2Br$^-$	BL11186	0.01				424
5g-39	2TsO$^-$	BL10054			26-424		
5g-53	2TsO$^-$	BL10063		424			
5g-62	2Br$^-$	BL11177	0.00		424		424
6-39	2TsO$^-$	BK21909	0.65	0.4	0.4-0.8	3.3-13	26-424
6-40	2I$^-$	BK47967	0.52	0.4	0.1-0.2	0.4-6.6	13-424
6-46	3Br$^-$	BK69669	0.04				3.3-424
6-47	3Br$^-$	BK47912	0.00				6.6-424
6-49	3Br$^-$	BK57132	0.09		1.6-3.3		6.6-424
6-51	2I$^-$	BK47994	0.56	0.2	0.1-1.6	3.3-13^{p}	26-424
6-53	2Br$^-$	BL00021	0.54*	0.1	0.1-0.2	0.4-6.6	13-424
6-61	2Br$^-$	BK62820	0.44	0.8	0.8-6.6	13	26-424
6-62	2Br$^-$	BK98544	0.47*	0.2	0.1-0.2	0.4-6.6	13-424
8-39	2Br$^-$	BL12138	0.19	6.6	6.6-13		26-424
8-53	2Br$^-$	BL12772	0.23	6.6	3.3-26		53-424
8-59	2Br$^-$	BL11168	0.30	13	13		26-424
8-61	2Br$^-$	BL10036	0.19	3.3	3.3-13		53-424
8-62	2Br$^-$	BL11159	0.59	1.6	0.8-26	53	106-424
9-39	2Br$^-$	BL28029	0.16	6.6	1.6-3.3	6.6	13-424
9-41	2TsO$^-$	BL31017					
9-53	2TsO$^-$	BL24101					
9-59	2Br$^-$	BL28038	0.30	13	13		26-424
9-61	2Br$^-$	BL24085					
9-62	2Br$^-$	BL24110					
9-63	2Br$^-$	BL31026					
10-39	2Br$^-$	BL11131					
10-41	2Br$^-$	BL19780					
10-53	2TsO$^-$	BL12147	0.33	0.8	0.8-3.3		6.6-424
10-58	2Br$^-$	BL35542		3.3			
10-59	2Br$^-$	BL18523	0.29	6.6	0.8-6.6	13	26-424
10-61	2Br$^-$	BL10018	0.68	0.2	0.1-0.4	0.8-13	26-424
10-62	2Br$^-$	BL09471	0.52	1.6	0.8-6.6	13	26-424
11-53	2TsO$^-$	BL09480	0.16	13	3.3-13		26-424
11-61	2Br$^-$	BL08241	0.12	3.3	3.3-6.6		13-424
11-62	2Br$^-$	BL09015	0.00				53-424
12-39	2TsO$^-$	BL07002	0.07		1.6-3.3		13-424
12-41	2Br$^-$	BL20658	0.18	6.6	3.3-6.6		13-424
12-53	2Br$^-$	BL07637	0.19	0.1	0.03-0.1	0.2-0.4	0.8-424
12-59	2Br$^-$	BL08250	0.04		6.6		13-424
12-61	2Br$^-$	BL06998	0.04	13	6.6-13		26-424
12-62	2Br$^-$	BL07646	0.31	6.6	1.6-26		53-424
13-39	2TsO$^-$	BL09033	0.45	0.8	0.8-3.3	6.6	13-424
13-53	2Br$^-$	BL10027	0.47	0.8	0.4-1.6	3.3-13	26-424
13-61	2Br$^-$	BL08232	0.36	3.3	0.8-1.6	3.3-6.6	13-424

13-62	2Br$^-$	BL09051	0.45	0.8	0.8-3.3	6.6-13	26-424
14-53	2TsO$^-$	BL12727	0.47	0.8	1.6-3.3	6.6	26-424
14-61	2Br$^-$	BL12129	0.21	13		3.3-26	53-424
15-39	2TsO$^-$	BL21600					
15-41	2TsO$^-$	BL22278					
15-53	2TsO$^-$	BL22250		0.03			
15-59	2Br$^-$	BL22269					
15-61	2Br$^-$	BL21593	0.64	1.6	0.4-0.8	1.6-26	53-424
15-62	2Br$^-$	BL21584	0.54	0.8	0.8	1.6-26	53-424

* i.c.e. would increase if lower doses were included

isolated as mixed bromide-iodide salt

At dose rates noted there was one or more animal which was an exception within the range quoted.

a) 4/5 at 6.6 b) 4/5 at 13 c) 4/5 at 3.3 d) 1/10 toxic at 1.6 e) 8/10 at 26 f) 19/20 at 1.6 g) 4/5 at 3.3 h) 14/15 at 26 i) 14/15 at 26 j) 3/5 at 106 k) 13/15 at 26 l) 4/5 at 0.8 m) 9/10 at 1.6 n) 14/15 at 26 o) 9/10 at 0.8 p) 4/5 at 6.6

TABLE 7

Other Substituted Guanylhydrazones - Functional Groups 63-65

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
1a-63	$2TsO^-$	BK73752	0.70	0.8	0.8-1.6	3.3-26	53-424
1a-64	Br^-	BK95007					
1a-65	$2Br^-$	BK51890	0.22	0.8	0.8		1.6-424
1h-63	$2TsO^-$	BK73789	0.85	0.8	0.4-1.6	3.3-53	106-424
1h-64	Br^-	BK95016					
1h-65	$2Br^-$	BK96022	0.37	3.3	1.6	3.3-13	26-424
1i-63	$2Br^-$	BK75327	0.71*	0.2	0.2-0.4	0.8-13	26-424
1i-65	$2Br^-$	BL05348	0.31	0.8	0.8-3.3		6.6-424
1q-63	$2Br^-$	BL07673	0.84	0.8	0.8	1.6-212	424.TE
2a-63	$2Br^-$	BK75087	0.57	0.4	0.1-0.4	0.8-6.6	13-424
2g-63	$2Br^-$	BL18569	0.74	0.8	0.4-0.8	1.6-13	26-424
2h-63	$2Br^-$	BL06943	0.85	0.2	0.2-0.8	1.6-26	106-424
3a-63	$2Br^-$	BL22287					
3h-63	$2Br^-$	BL31044		1.6			
2j-63	$2Br^-$	BL39700					
5a-63	$2Br^-$	BL12718	0.01				53-424
5g-63	$2TsO^-$	BL12736	0.17	106	53		106-424
6-63	$2TsO^-$	BK75130	0.52	0.8	0.8-1.6	3.3-13	26-424
13-63	$2TsO^-$	BL10045	0.22	1.6	1.6-6.6		13-424
15-63	$2Br^-$	BL24094					

* i.c.e. would increase if lower doses were included.

TABLE 8

Heterocyclic Hydrazones and Related Structures - Functional Groups 66-78

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
1a-66	$2 Br^-$	BK64119	0.71	0.8	0.8-26	53	106-424
1a-67	$2Br^-$	BK75149	0.05				6.6-424
1a-68	$2Br^-$	BK75112	0.00				26-424
1a-69	$2Cl^-$	BK85663	0.12		26		53-424
1a-70	TsO^-	BK70742	0.00				53-424
1a-71	TsO^-	BK70966	0.18	212	53-106		212-424
1a-72	$2Br^-$	BK50295	0.26	6.6	1.6-6.6	13	26-424
1a-74	TsO^-	BK69678	0.47	6.6	3.3-106	212-424	
1a-76	$2Br^-$	BK50302					
1a-77	Br^-	BK51998	0.18	53	3.3-13		26-424
1a-78	$2Br^-$	BK73734	0.29	13	13		26-424
1b-66	$2Br^-$	BK24017	0.07				105-424
1h-66	$2Br^-$	BK51961	0.39	13	3.3-106		212-424
1h-68	$2Br^-$	BK75112	0.04		26		106-424
1h-69	$2Cl^-$	BK85654	0.05		6-26		53-424
1h-70	I^-	BK70948	0.00				106-424
1h-71	$2Br^-$	BK70957	0.48	0.8	0.4	0.8-6.6	13-424
1h-73	TsO^-	BK69972	0.00				13-424
1h-74	I^-	BK70724	0.71		0.8-1.6	3.3-53	212-424
1h-75	I^-	BK70975	0.00				13-424
1h-76	$2Br^-$	BL00049	0.28	106	26-106	212	424
1h-78	$2Br^-$	BK72853	0.29	26	13		26-424
1i-69	$2Cl^-$	BK85681	0.05		6-26		53-424
1m-73	TsO^-	BK72817	0.00				
1m-74	TsO^-	BK72826	0.71	1.6	0.8-6.6	13-212	424
1x-70	$2Br^-$	BK70797	0.00				
1x-74	I^-	BK70788	0.06		26		53-424
1x-76	$2I^-$	BK71007	0.00				
2-66	$2Br^-$	BK70715	0.23		13-26		53-212
2-68	$2Br^-$	BK94993	0.00				26-424
2-70	TsO^-	BK70733	0.00				
2-71	TsO^-	BK70939	0.23	53	26-53		106-424
2-73	TsO^-	BK70779	0.04		13-53		106-424
2-74	TsO^-	BK69696	0.00				
2-76	$2Br^-$	BL05320	0.27	53	13-53		106-424
2-78	$2Br^-$	BL75096	0.10	53	26-53		106-424
6-66	$2Br^-$	BK24035	0.50	13	1.6-53		424
6-68	$2Br^-$	BK75336	0.00				
6-69	$2Cl^-$	BK85707	0.02		13		26-424
6-72	$2Br^-$	BK62839	0.05		6.6-13		26
6-74	TsO^-	BK65312	0.00				106-424
6-76	$2Br^-$	BK03096	0.31	26	26-106	212	424
6-77	Br^-	BK63649	0.21	212	26-212		424

TABLE 9

Dimeric Compounds

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	100% Cures	Toxic
$(1a)_2$-1	$2Br^-$	BK47949	0.02				13-424
$(1a)_2$-2	$2TsO^-$	BK51943	0.03				1.6-424
$(1a)_2$-3	$2TsO^-$	BK51934	0.00				6.6-424
$(1a)_2$-4	$3Cl^-$	BK63630	0.21	13	1.6-13		26-424
$(1a)_2$-5	$2Br^-$	BK51970	0.41	6.6	0.8-13		26-424
$(1a)_2$-6	$4Br^-$	BK50213	0.26	0.8	0.8-1.6		3.3-424
$(1a)_2$-7	$4I^-$	BL07842					
$(1a)_2$-8	$2TsO^-$	BK75050	0.11	6.6	1.6		6.6-424
$(1a)_2$-9	$2TsO^-$	BK57178	0.50	26	6.6-26	53	106-424
$(1a)_2$-10	$3Br^-$	BK63676	0.31	53	13-53		106-424
$(1a)_2$-11	$2Br^-$	BK52002	0.00				13-424
$(1a)_2$-12	$2TsO^-$	BL08223	0.69	3.3	0.8-6.6	13-212	
$(1a)_2$-13	$2TsO^-$	BK72808	0.66	1.6	0.8-6.6	13-53	106-424
$(1a)_2$-14	$2Br^-$	BL21548	0.00				
$(1a)_2$-15	$2TsO^-$	BK75069	0.17	13	3.3-6.6		13-424
$(1a)_2$-16	$2TsO^-$	BK75103	0.18	212	26-53		106-424
$(1e)_2$-4	$3Cl^-$	BK64155	0.01				53-212
$(1h)_2$-4	$3Cl^-$	BK57141	0.13	26	6.6-424		
$(1h)_2$-13	$2TsO^-$	BK73681	0.45	3.3	0.8-13	26	53-424
$(1q)_2$-13	$2TsO^-$	BL07806	0.00				
$(2a)_2$-4	$3Cl^-$	BK70760	0.20	424	53		
$(2a)_2$-8	$2TsO^-$	BK72791	0.24	26	26-106		212-424
$(2a)_2$-9	$2TsO^-$	BK70751	0.18	212	13-424		
$(2a)_2$-10	$3Cl^-$	BK72773	0.04		106-212	424	
$(2a)_2$-13	$2TsO^-$	BK75318	0.27	106	26-212		424
$(2a)_2$-15	$2TsO^-$	BK73725	0.00				
$(2a)_2$-16	$2TsO^-$	BK75345	0.00				
$(3a)_2$-13	$2TsO^-$	BL20701	0.00				
$(4a)_2$-13	$2TsO^-$	BL07833	0.06	424	212-424		
$(5a)_2$-13	$2TsO^-$	BL12174	0.55	1.6	0.4-0.8	3.3-13	26-424
$(6)_2$-3	$2Br^-$	BK63612	0.00				13-424
$(6)_2$-4	$3Cl^-$	BK51925	0.05				0.8-424
$(6)_2$-5	$2Br^-$	BK57221	0.32	3.3	1.6-13		26-424
$(6)_2$-9	$2TsO^-$	BK62802	0.45	3.3	3.3-6.6		13-424
$(6)_2$-10	$2.7Br^-$	BK73707	0.04				26-424
$(6)_2$-11	$2Br^-$	BK63667	0.00				6.6-424
$(6)_2$-13	$2TsO^-$	BK73716	0.32	0.8	0.4-6.6		13-424

Selected compounds were also investigated by peritoneal dosing (PO). This data is reported in the same way as for subcutaneous administration. Many of the compounds were curative, although typically at higher doses than for SC administration. Toxic deaths were rare by the PO route of administration. The results are collected in Table 10.

A selective group of active compounds was assessed using T. rhodesiense strains that are resistant to the established trypanocides suramin, melarsoprol and pentamidine. Table 11 shows the qualitative degree of effectiveness of selected compounds against drug resistant strains of T. rhodesiense. The first column gives the ED_{50} for normal drug-sensitive T. rhodesiense. The right hand columns indicate if the drug was effective (+) or ineffective (-) toward the resistant strains.

Concomitant with the in vivo testing, a representative cross section of the compounds were subjected to an in vitro assay in which the inhibition of uptake radioactive of thymidine and leucine by T. rhodesiense cells growing in culture is measured. The results are reported in Table 12 as the concentration in μg/liter which effect 50% inhibition of uptake of thymidine and leucine. For comparison, the i.c.e. value as determined by SC administration in vivo is also given. The highly active trypanocides (i.c.e. > .70) all show I_{50} for thymidine uptake <5 μg/ml but there is some variability in the I_{50} for leucine. The moderately active trypanocides (.70>i.c.e.>.30) generally give positive responses in the in vitro screen also. The inactive compounds (i.c.e. = 0) show some "false positives" in the in vitro screen, but this may reflect the fact that many of these compounds are toxic.

B. Activity against T. cruzi (Chagas disease).

Many of the compounds were tested in a T. cruzi mouse in vivo screen. No significant activity was detected.

C. Activity Against Other Pathogenic Protozoa.

Screening against other pathogenic protozoa was done. The selection of compounds was not entirely systematic but a representative selection of active trypanocides were tested. Tables 13 and 14 give results, against leishmania (hamster) and malaria (mouse) models.

Some of these compounds exhibit weak antileishmanial activity. No significant activity was seen in the malaria screen.

A number of compounds were tested against filarius (B. phargi, D. viteae) in jirds. Compounds showing significant suppression are shown in Table 15.

D. Antileukemic Activity

The dimeric subclass of compounds showed some anti-leukemic activity. Table 16 gives the structure code, WRAIR bottle number, the National Cancer Institute number and the T/C (life extension) in the two standard antileukemic screens of the National Cancer Institute.

TABLE 10

Activity by PO Administration

Structure Code	Counter Ions	WRAIR Number	i.c.e.	50% Cures	Partial Cures	Complete Cures	Toxic
1a-1	I^-	BJ36718	0.24	106	106 424		
1a-10	TsO^-	BJ90712	0.00				
1a-11	TsO^-	BJ90721	0.01				
1a-12	TsO^-	BJ90730	0.03				
1a-39	$2TsO^-$	BJ90749	0.48	26	13	26-424	
1a-51	$2Br^-$	BL28083	0.65	6.6	3.3	6.6-424	
1a-53	$2Br^-$	BK50277	0.64	6.6	3.3-6.6	13-106(424)	
1a-61	$2Br^-$	BK50311	0.56	13	6.6-26	53-424	
1a-62	$2Br^-$	BK98571	0.75	6.6	3.3-13	26-424	
1a-65	$2Br^-$	BK51890	>0.5*			<53-424	
1a-76	$2Br^-$	BK50302	0.00				
1a-77	Br^-	BK51998	0.00				
1b-9	Br^-	BK02566	0.07	424	106-424		
1b-23	Br^-	BK02539	0.00				
1b-53	$2Br^-$	BL06989	0.31	53	26-212	424	
1bh-1	Br^-	BK02557	0.02		424		
1e-39	$2TsO^-$	BK13069	0.50	13	13	26-106(424)	
1h-39	$2TsO^-$	BK13078	0.56	6.6	6.6	13-212[a]	
1h-41	$2Br^-$	BL12763	0.35	26	13-424		
1h-62	$2Br^-$	BK98562	0.56	3.3	3.3-6.6	26-424[b]	
1h-63	$2Br^-$	BL06943	0.59	6.6	6.6	13-424	
1i-41	$2Br^-$	BK98599	0.57	13	6.6-13	26-424	
1i-42	$2Br^-$	BK98580	0.45	26	13-26	53-424	
1i-43	$2Br^-$	BK98526	0.32	26	26-424		
1i-53	$2Br^-$	BL06934	0.47	13	13	26-212	424
1i-62	$2Br^-$	BK98553	0.57	6.6	6.6-13	26-424	
1k-1	TsO^-	BJ90758	0.00				
1l-1	TsO^-	BJ90767	0.00				
1p-39	$2Br^-$	BL07039	0.27	26	26-212	424	
1q-39	$2TsO^-$	BL07655	0.28	106	26-106	212-424	
1q-53	$2Br^-$	BL07664	0.17	212	106-212	212-424	
1q-63	$2Br^-$	BL07673	0.40	26	26-53	106-424	
1s-66	Br^-	BK51961	0.07	424	106-424		
1u-51	$2Br^-$	BK50268	0.36	53	13-212	424	
1v-39	$2Br^-$	BK51907	0.43	26	13-26	53-212	
1w-53	$2Br^-$	BL00076	0.67	3.3	3.3	6.6-424	
1x-61	$2Br^-$	BK65367	0.60	6.6	3.3-13	26-106(424)	
2g-39	$2Br^-$	BK40673	0.48	13	13	26-212(424)	
2g-63	$2Br^-$	BL18569	0.48	13	6.6-26	53-424	
2h-39	$2Br^-$	BL06961	0.61	6.6		6.6-212	424
2h-53	$2Br^-$	BL06970	0.49	13	13	26-424	
2i-39	$2Br^-$	BL06952	0.57	6.6	3.3-6.6	13-106	424
2j-39	$2TsO^-$	BL12183	0.13	212	106-424		
2j-62	$2Br^-$	BL12754	0.19	106	26-424		
3a-62	$2Br^-$	BL11202	0.53	13	6.6-26	53-212	
3a-53	$2TsO^-$	BL12165	0.16	424	26-212	424	
3g-39	$2TsO^-$	BK40655	0.30	53	53-106	212(424)	
3g-53	$2Br^-$	BL20685	0.36	53	13-53	106-424	
3g-59	$2Br^-$	BL21566		53	53-106	212-424	
3g-61	$2Br^-$	BL20710	0.42	26	13-53	106-212(424)	

4a-39	2TsO$^-$	BL07815	0.63	6.6	3.3	6.6-424	
4a-53	2Br$^-$	BL18532	0.31	53	13-53	212-424	
4a-59	2Br$^-$	BL21575		53	26	53-212	
4a-62	2Br$^-$	BL07824	0.51	13	13	26-424	
5a-39	2TsO$^-$	BL09024	0.06	424	424		
5a-53	2Br$^-$	BL11195	0.01		424		
5a-59	2Br$^-$	BL12156	0.00				
5a-61	2Br$^-$	BL11186	0.00				
5a-63	2Br$^-$	BL12718	0.02		106-424		
5g-63	2Br$^-$	BL12736	0.03		424		
6-37	2Br$^-$	BK50231	0.06		106-424		
6-40	2I$^-$	BK47967	0.60	6.6	6.6	13-106(424)	
6-53	2Br$^-$	BL00021	0.70	3.3	3.3-6.6	13-424	
8-39	2Br$^-$	BL12138	0.06	424	212-424		
8-53	2Br$^-$	BL12772	0.12	424	106-424		
8-59	2Br$^-$	BL11168	0.15	424	106-424		
8-61	2Br$^-$	BL10036	0.10	424	106-424		
8-62	2Br$^-$	BL11159	0.23	106	26-212	424	
10-53	2TsO$^-$	BL12147	0.57	6.6	6.6-26	53-424	
10-59	2Br$^-$	BL18523		212	13-212		
10-61	2Br$^-$	BL10018	0.53	13	13	26-424	
10-62	2Br$^-$	BL09471	0.57	6.6	6.6-26	53-424[c]	
11-53	2TsO$^-$	BL09480	0.00				
11-61	2Br$^-$	BL08241	0.00				
11-62	2Br$^-$	BL09015	0.00				
12-39	2TsO$^-$	BL07002	0.00				
12-41	2Br$^-$	BL20658		53-212			
12-53	2Br$^-$	BL07637	0.17	106	26-424		
12-59	2Br$^-$	BL08250	0.00				
12-61	2Br$^-$	BL06998	0.27	106	26-53	106	424
12-62	2Br$^-$	BL07655	0.28	106	26-106	212-424	
13-39	2TsO$^-$	BL09033	0.42	26	26	53-424	
13-53	2Br$^-$	BL10027	0.40	26	26-53	106-424	
13-61	2Br$^-$	BL08232	0.45	13	6.6-424		
13-62	2Br$^-$	BL09051	0.24	53	26-53	106-424	
13-63	2TsO$^-$	BL10045	0.12	424	106-424		
14-53	2TsO$^-$	BL12727	0.04	424	424		
14-61	2Br$^-$	BL12129	0.12	424	106-212	424	
15-39	2TsO$^-$	BL21600	>0.5[d]			6.6-212[e]	
15-61	2Br$^-$	BL21593	0.69			3.3-212[f]	
15-62	2Br$^-$	BL21584	0.63	6.6	6.6	13-212	

* substantial discrepancy between two different test series.

a 13/15 at 26

b 4/5 at 53

c 9/10 at 106

d complete data are not available

e 8/10 at 106

f 8/10 at 6.6, 13/15 at 13

Table 11.

	ED_{50}	Suramin resistant	Melarsoprol resistant	Pentamidine resistant
BK65009	0.2	+	–	–
BK73752	0.3	+	–	–
BK96086	0.8	+	–	–
BK98553	0.06	+	–	–
BL00667	0.6	+	–	–
BL03899	0.2	+	–	–
BL05339	1.0	±	–	–
BL06934	0.3	+	–	–
BL07637	0.05	–	–	–

TABLE 12

In Vitro Activity Data

Structure Code	WRAIR Number	i.c.e.	Thymidine I_{50}	Leucine I_{50}
1a-1	BJ83315	0.14	>10	>10
1a-17	BK50222	0.00	3.9	>10
1a-18	BK51989	0.00	>10	>10
1a-24	BK21883	0.00	8.6	>10
1a-29	BK23001	0.01	1.3	1.4
1a-30	BK50259	0.12	0.9	2.6
1a-31	BK62795	0.00	4.9	>10
1a-33	BK63603	0.00	9.0	>10
1a-34	BK63621	0.00	11.9	>10
1a-36	BK21892	0.00	9.6	>10
1a-37	BK47921	0.55	3.8	5.8
1a-40	BK46200	0.40	0.5	0.7
1a-45	BK62777	0.45	2.3	11.7
1a-46	BK64100	0.00	5.8	
1a-47	BK46175	0.06	0.4	0.5
1a-52	BK50286	0.35	1.1	1.0
1a-53	BK50277	0.39	0.6	0.6
1a-61	BK50311	0.57	0.8	0.9
1a-65	BK51890	0.22	6.7	9.7
1a-66	BK64119		0.5	>10
1a-69	BK85654	0.12	10.9	>10
1b-66	BK24017	0.07	0.2	>10
1c-1	BJ83244	0.10	7.0	5.9
1d-1	BJ83235	0.17	3.2	5.2
1e-28	BK46148	0.00	5.7	>10
1h-37	BK62811	0.38	4.0	>10
1h-41	BL12763	0.67	0.4	0.5
1h-57	BL03915	0.39	>10	7.0
1h-63	BK73789	0.85	2.3	1.0
1h-66	BK51961	0.39	3.8	
1h-69	BK85681	0.05	4.9	>10
1h-74	BK70724	0.71	0.3	>10
1h-78	BK72853	0.29	>10	>10
1i-39	BK46219	0.55	1.0	
1i-42	BK98580	0.63	1.9	4.6
1i-62	BK98553	0.67	0.7	1.1
1i-63	BK75327	0.71	0.9	0.7
1i-69	BK85663	0.05	7.4	>10
1m-73	BK72817	0.00		
1m-74	BK72826	0.71	0.6	>10
1o-37	BK72835	0.00	1.2	>10
1s-39	BK51952	0.87	5.9	4.3
1t-39	BK75167	0.79	1.5	>10
1u-39	BK24026	0.29	2.7	1.7
1u-40	BK47958	0.36	5.4	3.4
1v-61	BK62786		0.7	0.7
1x-39	BK65349	0.43	0.5	
1x-61	BK65367	0.44	>10	
1x-70	BK70797	0.00	5.6	>10
1x-74	BK70788	0.06	1.3	>10
2a-28	BK65330	0.26	0.7	1.2

2a-37	BK65027	0.44	4.6	3.3
2a-39	BK65009	0.47	0.8	0.9
2a-66	BK70715	0.23	0.5	>10
2a-71	BK70939	0.23	7.9	10.1
2a-73	BK70779	0.04	0.4	>10
2j-62	BL12763	0.67	0.4	0.5
3a-39	BL09462	0.89	2.7	9.3
5a-39	BL09024	0.24	4.2	4.5
5a-53	BL11195	0.06	>10	>10
5a-61	BL11186		>10	>10
5a-63	BL12718	0.01	>10	13.1
6-20	BK63658	0.05	3.9	>10
6-21	BK64164		5.1	
6-26	BK24035	0.00	1.2	>10
6-28	BK21874	0.23	0.3	0.8
6-29	BK23010	0.04	2.3	2.3
6-39	BK21909	0.65	1.4	1.3
6-40	BK47967	0.52	1.5	1.2
6-51	BK47994	0.61	1.0	1.0
6-61	BK62820	0.44	0.6	0.8
6-63	BK75130	0.55	2.0	1.7
6-72	BK62839	0.05	9.5	>10
6-77	BK63649	0.21	2.4	4.6
7-12	BK23994	0.00	4.6	>10
7-29	BK42739	0.01	1.3	2.2
7-35	BK21865	0.02	>10	>10
8-53	BL12772	0.23	0.6	0.7
8-61	BL10036	0.19	11.1	>10
10-39	BL11131		1.9	6.1
10-62	BL09471	0.52	4.4	>10
11-22	BL1140	0.18	10.1	>10
11-53	BL09480	0.16	2.2	0.7
13-39	BL09033	0.45	1.8	>10
13-53	BL10027	0.47	0.3	0.8
13-62	BL09051	0.45	3.7	>10
13-63	BL10045		3.8	10.3
14-53	BL12727	0.47	9.3	13.6

Table 13. Compounds Screened Against Visceral Leishmania (Hamster)

Structure Code	WRAIR Number	% Max. Suppression (dose in mg/kg)
1a-1	BJ83315	44(416)
1a-2	BJ83262	20(52)
1a-7	BJ92645	15(416)
1a-13	BK11743	-
1a-16	BK47930	-
1a-27	BJ84965	~40(208)
1a-30	BK50259	51(52)
1a-33	BK63603	33(416)
1a-34	BK63621	34(52)
1a-35	BJ84974	55(832)
1a-48	BK63596	15(52)
1a-52	BK50286	31(52)
1a-53	BK50277	-
1a-61	BK50311	50(208)
1a-72	BK50295	32(52)
1a-76	BK50302	-
1b-7	BJ92627	22(52)
1b-39	BK11770	-
1be-1	BK11761	15(208)
1e-1	BJ83280	29(832)
1e-39	BK13069	16(52)
1f-1	BJ83306	-
1h-1	BJ84938	31(832)
1h-78	BK72853	-
1m-73	BK72817	-
1m-74	BK72826	-
1o-37	BK72835	-
1o-39	BK72844	-
1u-16	BK50240	66(208)
6-37	BK50231	44(52)

Table 14. Compounds Screened Against Malaria (plasmodium falciparum) in Mice

Structure Code	WRAIR Number	Activity
1a-24	BK21883	-
1a-33	BK63603	-
1a-34	BK63621	-
1a-35	BJ84974	-
1a-47	BK46175	-
1b-39	BK11770	-
1e-28	BK46148	
1e-35	BK46193	-
1e-36	BK46157	-
1h-28	BK46166	-
1i-39	BK46219	-
2a-39	BK65009	-
6-16	BK47903	-
6-28	BK21874	-
6-29	BK23010	-
6-36	BK22997	-
6-40	BK47967	-
7-29	BK42739	-
7-36	BK23029	-
1u-28	BK42757	-

Table 15. Compounds Showing Suppression of Filariasis

Structure Code	WRAIR Number	% Max. Suppression (dose)	
		B.phangi	D. viteae
1a-40	BK46200	27(6.25)	80(6.25)
1a-53	BK50277	-	73(6.5)
1a-62	BK98571	61(6.25)	17(17.5)
1a-76	BK50302	85(100)	30(100)
1b-1	BJ58296	60(100)	32(100)
1h-37	BK62811	34(100x2)	69(100x2)
1h-53	BK96746	34(1.56)	74(6.25)
1h-62	BK98562	38(12.5)	60(6.25)
1h-74	BK70724	58(100)	70(100)
1u-40	BK47958	89(12.5x5)	100(12.5x5)
2a-28	BK65330	-	49(12.5)
2a-39	BK65009	36(12.5)	62(12.5)

Table 16. Antileukemic Activity

Structure Code	WRAIR Number	NCS Number	3PS31		3LE31			
			dose	T/C	dose	T/C		
$(1a)_2$-3	BK51934	365173	inactive					
$(1a)_2$-7	BL07842	603172	inactive					
$(1a)_2$-9	BK57178	370656	6.25	123,142				
			12.5	149,155				
			25	131,142				
$(1a)_2$-10	BK63676	375166	15	131				
			30	150				
			60	144,88				
$(1a)_2$-12	BL08223	603173	25	159	6.2	168	5.4	200
			100	200,179	25	312	9.0	211
			200	202,141	50	126	15.0	352
			400	153	100	86	25.0	341
$(1a)_2$-13	BK72808	375161	7.5	150	12.5	45		
			15	164	25	162,224		
			30	169	50	142,306		
			60	200,205	100	307,306		
			100	207	200	329,153		
			200	261	400	329		
			400	252				
$(1a)_2$-15	BK75069	380479	inactive					
$(1a)_2$-16	BK75103	380481	inactive					
$(1q)_2$-13	BL07806	603176	inactive					
$(2a)_2$-4	BK70760	380534	inactive					
$(2a)_2$-8	BK72791	375164						
$(2a)_2$-10	BK72773	375163	inactive					

Table 16. Antileukemic Activity (Continued)

Structure Code	WRAIR Number	NCS Number	3PS31 dose	3PS31 T/C	3LE31 dose	3LE31 T/C
(2a)$_2$-13	BK75318	380477	inactive			
(2a)$_2$-15	BK73725	380480	inactive			
(4a)$_2$-13	BL078331	603169	30	127		
			60	128		
			120	122,127		
			240	122		
(6)$_2$-9	BK62802	365174	1.6	119,127	inactive	
			3.1	132,128		
			6.2	144		
(6$_2$)-10	BK73707	380482				
(6)$_2$-11	BK63667	603168				
(6)$_2$-13	BK75318	380477	inactive			

IV. Discussion of Activity in the In Vivo T. rhodesiense Screen

Activity will be discussed from two points of view. Potency can be discussed with reference to the "50% cures" entry in the table. We define the very potent compound with those with 50% cures at 0.4 mg/kg and less. All compounds which are considered potent are those with 50% cures at 1.6 mg/kg and less. By perusal of Tables 2-9 it is possible to identify compounds possessing these degrees of potency. There is a tendency for some of the most potent compounds to be highly toxic. For this reason the i.c.e. index may be more useful in identifying the most promising compounds. Table 17 lists all compounds which have i.c.e. values >0.7.

The use of the i.c.e. index focuses attention on the following classes of compounds: (a) 6- and 7-methyl guanylhydrazones and N-alkylguanylhydrazones as illustrated by 1h-39, 1h-62, and 1i-43; (b) functionally substituted guanylhydrazones, especially the 6-alkylthio-substituted group; 1m-39, 1p-39, 1p-53, 1q-39, 1s-39 and 1t-39; (c) the ether-stretched and vinyl stretched guanylhydrazones and N-alkylguanylhydrazones 2g-53, 2g-62, 2h-39, 3a-39, 3a-53, 3a-62, 3g-39, 3g-53, 3g-61 and 4a-39. (d) The N-hydroxyguanylhydrazones (1a-63, 1h-63, 1i-63, 1q-63, 2g-63 and 2h-63) of the same structural groups are also very effective.

Consideration of the range of activity and synthetic accessibility, I recommend the following derivatives for further evaluation: 1h-39, 1m-39, 2h-63, 3a-39, 3g-53 and 4a-39.

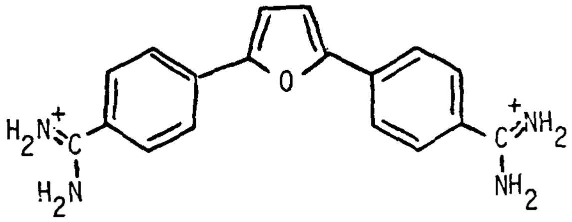
V. Structural Relationship to Other Trypanocides

The structural relationship of the current series of compounds to other types of cationic trypanocides is of interest. These include the bis-amidines berenil, pentamidine, 2,5-bis-(4'-carboxamidinylphenyl)furan(1), aminocarbilide(2) and 2-(4'-carboxamidinylphenyl)-6-carboxamidinylindole (DAPI)(3), as well as m-diacetylbenzene-bis-guanylhydrazone.(4) Bis-cyclic amidines (imidazolines such as iminocarb(3) and the terephthalanilide BW 458C(5) have also shown trypanocidal activity. These compounds can all adopt conformations which separate the cationic centers by 12-14 Å and it was proposed some years ago that this separation permitted interaction with phosphate sites along the DNA backbone. The 1-methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridine guanylhydrazones can correspond to this structural group if the heteroaromatic cation is considered to represent one of the centers of positive charge. The presence of this positive center is critical to the biological activity of the imidazo[1,2-a]pyridines as the non-quaternized guanylhydrazone is nearly inactive.

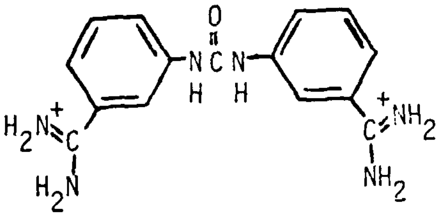
Definitive information on the mechanism of action of the broad class of bis-cationics is lacking, although there is some evidence that they are tightly bound by DNA and a connection with polyamine metabolism has been established.(6) As a working hypothesis, as yet untested by experiment, we propose that the imidazo[1,2-a]pyridinium salts prepared in the course of this work are related to the above named trypanocidal compounds.

Table 17. Compounds with i.c.e. >0.7

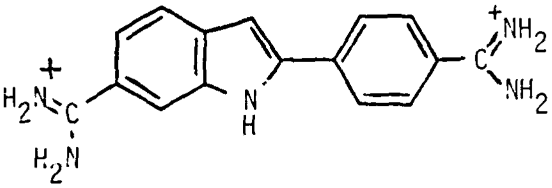
Structure Code	WRAIR Number	i.c.e	Structural Type
1h-39	BK13078	0.83	alkyl-substituted
1h-62	BK98562	0.76	
1i-43	BK98526	0.71	
1m-39	BK70984	0.93	alkylthio substituted
1p-39	BL07039	0.92	
1p-53	BL06989	0.94	
1q-39	BL07655	0.83	
1s-39	BK5195L	0.87	6-methoxy
1t-39	BK75167	0.79	6-acetamido
2g-53	BL18541	0.75	ether-spaced
2g-62	BL18550	0.70	
2h-39	BL06961	0.81	
3a-39	BL09462	0.89	vinyl-spaced
3a-53	BL12165	0.74	
3a-62	BL11202	0.71	
3g-39	BK40655	0.85	
3g-53	BL20685	0.90	
3g-61	BL20710	0.86	
4a-39	BL07815	0.94	ring structure 4
1a-63	BK72752	0.70	N-hydroxyguanylhydrazone
1h-63	BK73789	0.85	
1i-63	BK75327	0.71	
1q-63	BL07673	0.84	
2g-63	BL18569	0.74	
2h-63	BL06943	0.85	
1a-66	BK64119	0.71	heterocyclic hydrazones
1h-74	BK70724	0.71	



2,5-bis-(4'-carboxamidinyl-phenyl)furan



aminocarbilide



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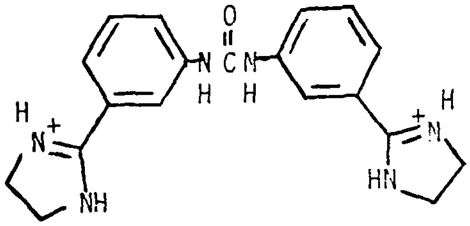
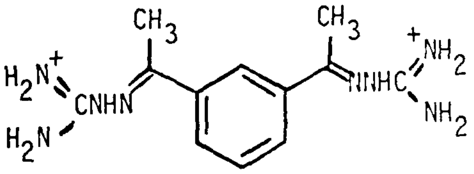
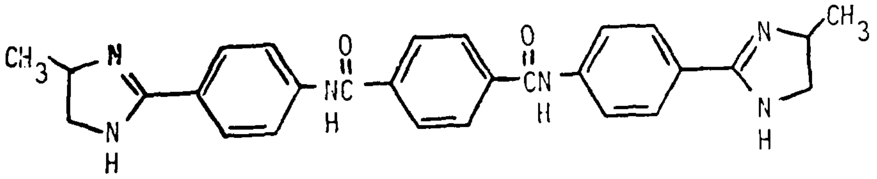


iminocarb





BW 458 C

VII . Experimental Section

General methods for the synthesis of imidazo[1,2-a]pyridines and for concersion of bromides to nitriles and nitriles to aldehydes were described in the Final report (dated February 1986) for the preceding contracts DAMD17-78-C-8016 and DAMD17-83-C-3127. That report also gives methods for synthesis of and N-allkylguanylhydrazones and heterocyclic hydrazones used in the final derivatization of the target compounds.

V-40-GM (BK96700)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

S-Methylthiosemicarbazide hydroiodide, 1.15 g (5.0 mmol) was refluxed with 2 mL of pyrrolidine in 50 ml of ethanol for 24 hours. The solvent was removed and the residue was washed with ether. 1,7-Dimethyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate 2.1 g (5.0 mmol) was added and the mixture was refluxed for 4 hours in 50 mL of ethanol. At room temp., 4 mL of conc HBr was added. After stirring about 1 hour ether was added to complete the precipitation. The product was collected and recrystallized from ethanol containing a few drops of conc HBr. Yield: 2.2 g (79%) MP: 297°C.

Anal. calcd for: $C_{21}H_{26}NBr_2 \cdot 2H_2O$
Calcd: C, 45.17; H, 5.43; N, 15.05; Br, 28.65
Found: C, 45.27; H, 5.41; N, 15.05; Br, 28.61

Procedure for 1,3-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium Derivatives

Step 1: 3-Methyl-2-(4'-bromophenyl)imidazo[1,2-a]pyridine

A mixture of 44.2 g (0.15) mole) of 1-bromoethyl 4-bromophenyl ketone and 14.2 g (0.15 mol) of 2-aminopyridine was refluxed in 500 mL acetone for 24 hours. The solid which formed was collected by filtration and the mother liquor were refluxed again for 24 hours. The solution was cooled and filtered to obtain a second crop. This process was repeated several times and the combined solid was taken up in 500 mL of 95% ethanol, acidified with 48% HBr and boiled for 15 minutes. After cooling the solution was basified with conc. ammonium hydroxide and filtered. The solid which was obtained was recrystallized from 95% ethanol. Yield: 17.5 g (31.8%) MP: 205-208°C.

Step 2: 3-Methyl-2-(4'-cyanophenyl)imidazo[1,2-a]pyridine

The bromide was converted to the nitrile by reaction with copper cyanide in DMF, following the standard procedure. MP: 185-187°C

Step 3: 3-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridine

The aldehyde was prepared by following the standard procedure, using Raney nickel, sodium hypophosphite, acetic acid and pyridine. Yield: 25% MP: 168-170°C.

Step 4: 1,3-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium Tosylate

1,3-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridine, 2.36 g (10 mmol), was refluxed with 2.23 g (12 mmol) of methyl tosylate in 50 mL of acetonitrile for 48 hours. After cooling, the reaction mixture was poured into 500 mL ether with stirring. The precipitated product was collected by filtration, washed with ether and dried. Yield: Quantitative. MP: 185-186°C.

III-88-MJB (BK96719)

1,3-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium Guanylhydrazone Dibromide

A mixture of 3.8 g (9.0 mmol) of 1,3-dimethyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate, 1.23 g (9.0 mmol) of aminoguanidine bicarbonate and 2 g (11.6 mmol) of p-toluenesulfonic acid was refluxed in 100 mL of abs. ethanol for 15 hours. The solution was concentrated, acidified with 48% HBr and precipitated by the addition of ether. The solid was collected by filtration and recrystallized twice from 95% ethanol with HBr. Yield: 3.4 g (79%) MP: 290-292°C.

Anal. calcd for: $C_{17}H_{20}N_6Br_2 \cdot 0.5\ H_2O$
Calcd: C, 42.79; H, 4.44; N, 17.61; Br, 33.49
Found: C, 42.70; H, 4.51; N, 17.53; Br, 33.43

V-32-GM (BK96728)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N'-Dimethylguanylhydrazone Diiodide.

A mixture of 2.55 g (7.0 mmol) of 1-methyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium iodide and 1.6 g (7.0 mmol) of N,N'-dimethyl-aminoguanidine hydroiodide in 100 mL of ethanol was refluxed for 2 hours. The solution was then concentrated to 50 mL and stirred again at room temperature. The precipitate which formed was collected and recrystallized from 95% ethanol. Yield: 3.4 g (81%) MP: 285°C.

Anal. calcd for: $C_{18}H_{22}N_6I_2 \cdot H_2O$
Calcd: C, 36.39; H, 4.07; N, 14.15; I, 42.71
Found: C, 36.34; H, 4.09; N, 14.10; I, 42.64

V-38-GM (BK96737)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Ethylguanylhydrazone Dibromide

A solution of S-methylthiosemicarbazide hydroiodide 1.6 g (7.0 mmol) in 50 mL of ethanol was refluxed with excess of aqueous ethylamine solution (5 mL of 70% aqueous solution) for 15 hours. The solvent was removed. The residue was mixed with 2.9 g (7.0 mmol) of 1-methyl-2-(4'-formylphenyl-imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol and was refluxed for 4 hours. At room temperature, 8 mL of conc. HBr was added and stirred. Ether was added to complete precipitation. The product was collected and recrystallized from ethanol-ether. Yield: 2.7 g (77%) MP: 285°C.

Anal. calcd for: $C_{18}H_{22}N_6Br_2 \cdot H_2O$
Calcd: C, 43.22; H, 4.83; N, 16.80; Br, 31.95
Found: C, 43.39; H, 4.78; N, 16.80; Br, 31.90

V-39-GM (BK96746)

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

S-Methylthiosemicarbazide hydroiodide 2.07 g (9.0 mmol) was refluxed for 24 hours with 5 mL of pyrrolidine in 50 mL of ethanol. The solvent was removed and the residue was washed with ether. 1,6-Dimethyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate 3.8 g (9.0 mmol) was added and the mixture was refluxed for 5 hours. After cooling to room temperature, 8 mL of conc. HBr was added with stirring. Ether was added to complete the precipitation of the product, which was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 3.6 g (74%) MP: 290°C.

Anal. calcd for: $C_{21}H_{26}N_6Br_2 \cdot 1.5\ H_2O$
Calcd: C, 45.91; H, 5.32; N, 15.30; Br, 29.09
Found: C, 45.88; H, 5.31; N, 15.28; Br, 29.00

V-43-GM (BK96755)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Propylguanylhydrazone Dibromide

S-Methylthiosemicarbazide hydroiodide 1.6 g (7.0 mmol) was refluxed with 3 mL n-propylamine in 50 mL of ethanol for 15 hours. The solvent was removed and the residue was mixed with 2.9 g (7.0 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol. The mixture was refluxed for 4 hours. About 8 mL of conc. HBr was then added, and the mixture was cooled. Ether was added to complete the precipitation. The product was collected and recrystallized from ethanol-ether. Yield: 3.0 g (82%) MP: 258°C.

Anal. calcd for: $C_{19}H_{24}N_6Br_2 \cdot H_2O$
Calcd: C, 44.37; H, 5.09; N, 16.34; Br, 31.08
Found: C, 44.15; H, 5.13; N, 16.32; Br, 30.99

V-42-GM (BK96764)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Allylguanylhydrazone Dibromide

A mixture of 1.6 g (7.0 mmol) of S-methylthiosemicarbazide hydroiodide in 50 mL of ethanol was refluxed for 15 hours with 3 mL of allylamine. The solution was evaporated to dryness. 1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]-pyridinium tosylate, 2.9 g (7.0 mmol), was added to the residue and the mixture was refluxed in 50 mL of ethanol for 4 hours. The solution was then acidified with HBr and the product was precipated with ether. The solid was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.9 g (79%) MP: 251°C.

Anal. calcd for: $C_{19}H_{22}N_6Br_2 \cdot H_2O$
Calcd C, 44.54; H, 4.73; N, 16.40; Br, 31.20
Found: C, 44.49; H, 4.75; N, 16.31; Br, 31.13

V-41-GM (BK96773)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N'-Dimethylguanylhydrazone Dibromide

A mixture of 2.95 g (7.0 mmol) of 1,7-dimethyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate and 1.6 g (7.0 mmol) of N,N'-dimethylaminoguanidine hydroiodide in 60 mL of ethanol was refluxed for 4 hours. The solution was then acidified with conc HBr (8 mL) and stirred for about 1 hour. Ether was added to complete the precipitation. The product was recrystallized from 95% ethanol. Yield: 2.65 g (78%) MP: 310°C.

Anal. calcd for: $C_{18}H_{24}N_6Br_2 \cdot 1.5\ H_2O$
Calcd: C, 43.60; H, 5.20; N, 16.06; Br, 30.54
Found: C, 43.67; H, 5.20; N, 16.03; Br, 30.45

V-56-GM (BK98526)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium
N-Butylguanylhydrazone Dibromide

A mixture of 1.15 g (5.0 mmol) of S-methylthiosemicarbazide hydroiodide in 50 mL of ethanol was refluxed for 15 hours with excess (2 mL) of n-butylamine. The solution was then evaporated to dryness. The residue was mixed with 2.0 g (5.0 mmol) of 1,7-dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol and refluxed for 4 hours. The solution was then acidified with HBr, and refrigerated after adding 5 mL of ether. The solid product was collected and recrystallized from ethanol-ether. Yield: 2.15 g (81%) MP: 163-165°C.

Anal. calcd for: $C_{21}H_{28}N_6Br_2 \cdot H_2O$
Calcd: C, 46.50; H, 5.57; N, 15.50; Br, 29.47
Found: C, 46.40; H, 5.58; N, 15.47; Br, 29.36

V-55-GM (BK98535)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Butylguanylhydrazone Dibromide

A mixture of 1.6 g (7.0 mmol) of S-methylthiosemicarbazide hydroiodide in 50 mL of ethanol was refluxed for 15 hours with excess (3 mL) of n-butylamine. The solution was then evaporated to dryness and the residue was mixed with 2.85 g (7.0 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol. The mixture was refluxed for 4 hours. Then conc. HBr, 8 mL , was added and the mixture stirred for about 1 hour. Addition of ether completed the precipitation of the product, which was collected and recrystallized from ethanol-ether. Yield: 2.9 g (78%) MP: 161-163°C.

Anal. calcd for: $C_{20}H_{26}N_6Br_2 \cdot H_2O$
Calcd: C, 45.47; H, 5.34; N, 15.91; Br, 30.25
Found: C, 45.41; H, 5.37; N, 15.81; Br, 30.23

V-52-GM (BK98544)

1-Methyl-2-(4'-formylphenyl)imidazo[2,1-b]thiazolium 3,4,5,6-Tetrahydropyrimidin-2-ylhydrazone Dibromide.

A mixture of 1.45 g (6.0 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidinium hydroiodide and 2.5 g (6.0 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo-[2,1-b]thiazolium tosylate in 50 mL of ethanol was refluxed for 4 hours. About 7 mL of conc HBr was added and the mixture was stirred at room temperature for 15 minutes. Ether was added and the precipitate was collected and recrystallized from 95% ethanol. Yield: 2.15 g (69%) MP: 287°C.

Anal. calcd for: $C_{17}H_{20}N_6SBr_2 \cdot H_2O$
Calcd: C, 39.39; H, 4.28; N, 16.22; S, 6.19; Br, 30.84
Found: C, 39.81; H, 4.22; N, 16.33; S, 6.26; Br, 31.13

V-51-GM (BK98553)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimidin-2-ylhydrazone Dibromide

A mixture of 2.95 g (7.0 mmol) of 1,7-dimethyl-2-(4'-formylphenyl)imidazo-[1,2-a]pyridinium tosylate and 0.7 g (7.0 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidinium hydroiodide in 50 mL of ethanol was refluxed for 4 hours. Then 8 mL of conc. HBr was added and the mixture was cooled. The precipitate was collected and recryallized from 90% ethanol. Yield: 3.0 g (82%). MP: 320°C.

Anal. calcd for: $C_{20}H_{24}N_6Br_2 \cdot 1.5\ H_2O$
Calcd: C, 44.87; H, 5.08; N, 15.70; Br, 29.86
Found: C, 45.03; H, 5.05; N, 15.74; Br, 29.73

V-50-GM (BK98562)

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimidin-2-yl Hydrazone Dibromide

A mixture of 2.95 g (7.0 mmol) of 1,6-dimethyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate and 1.7 g (7.0 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidinium hydroiodide in 50 mL ethanol was refluxed for 4 hours. Then 9 mL of conc. HBr was added and the mixture was cooled. The precipitate was collected and recrystallized from 90% ethanol. Yield: 2.9 g (79%). MP: 313°C.

Anal. calcd for: $C_{20}H_{24}N_6 \cdot Br_2 \cdot H_2O$
Calcd: C, 45.64; H, 4.98; N, 15.97; Br, 30.37
Found: C, 45.65; H, 5.01; N, 15.94; Br, 30.39

V-49-GM (BK98571)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimidin-2-ylhydrazone Dibromide

A solution of 2.85 g (7.0 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo-[1,2-a]pyridinium tosylate in 50 mL of ethanol was refluxed with 1.7 g (7.0 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidinium hydroiodide for 4 hours. The solution was then acidified with 8 mL of conc. HBr and refrigerated. The solid obtained by filtration was recrystallized from 90% ethanol. Yield: 3.0 g (83%). MP: 308°C.

Anal. calcd for: $C_{19}H_{22}N_6Br_2 \cdot H_2O$
Calcd: C, 44.54; H, 4.72; N, 16.40; Br, 31.20
Found: C, 44.51; H, 4.76; N, 16.39; Br, 31.13

V-47-GM (BK98580)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Propylguanylhydrazone Dibromide

S-Methylthiosemicarbazide, 1.6 g (7.0 mmol) was refluxed with 3 mL of n-propylamine in 50 mL of ethanol for 15 hours. The solvent was removed and the residue was mixed with 2.95 g (7.0 mmol) of 1,7-dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol. The mixture was refluxed for 4 hours. About 8 mL of conc. HBr was then added and the mixture was cooled. Ether was added to complete the precipitation. The product was collected and recrystallized from ethanol-ether. Yield: 3.0 g (83%). MP: 256-250°C.

Anal. calcd for: $C_{20}H_{26}N_6Br_2 \cdot H_2O$
Calcd: C, 45.47; H, 5.34; N, 15.91; Br, 30.25
Found: C, 45.28; H, 5.36; N, 15.87; Br, 30.14

V-46-GM (BK98599)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium
N-Ethylguanylhydrazone Dibromide

S-Methylthiosemicarbazide hydroiodide 1.6 g (7.0 mmol) in 50 mL of ethanol was refluxed with 4 mL of 70% aqueous ethylamine. After 15 hours, the solution was evaporated to dryness. 1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]-pyridinium tosylate, 2.95 g (7.0 mmol), was added and the mixture was refluxed in 50 mL of ethanol for 4 hours. About 6 mL of conc. HBr was added and after stirring for 30 minutes at room temperature, addition of ether completed the precipitation of the product. It was collected and recrystallized from ethanol-ether. Yield: 2.9 g (81%). MP: 255°C.

Anal. calcd for: $C_{19}H_{24}N_6Br_2 \cdot H_2O$
Calcd: C, 44.37; H, 5.09; N, 16.34; Br, 31.08
Found: C, 44.18; H, 5.10; N, 16.18; Br, 30.87

V-48-GM (BL00003)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N'-Dibutylguanylhydrazone Dibromide

A solution of 1.9 g (6.0 mmol) of N,N'-di-n-butylaminoguanidinium hydroiodide in 50 mL of ethanol was refluxed 4 hours with 2.5 g (6.0 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate. About 6 mL of conc. HBr was added and the mixture was allowed to stir at room temperature for 1 hour. After addition of ether and stirring, the product precipitated. The solid was redissolved in ethanol, followed by addition of ether and refrigerated. Yield: 3.0 g (82%). MP: 162°C.

Anal. calcd for: $C_{24}H_{34}N_6Br_2 \cdot 1.5\ H_2O$
Calcd: C, 48.57; H, 6.28; N, 14.16; Br, 26.93
Found: C, 48.70; H, 5.86; N, 14.25; Br, 26.74

V-54-GM (BL00012)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-(Methylenethiodimethylene)guanylhydrazone Ditosylate

A solution of 2.7 g (4.0 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo[1,2-a]-pyridinium S-methylsemicarbazone ditosylate in 60 mL of ethanol was refluxed for 80 hours with 0.48 g (5.0 mmol) of thiazolidine. The solvent was removed and the residue was washed with ether. The product was dried over the pump to yield a hygroscopic yellow glassy product. Yield: 2.5 g (87%).

Anal. calcd for: $C_{33}H_{36}N_6S_3O_6 \cdot 0.5\ H_2O$
Calcd: C, 55.20; H, 5.20; N, 11.71; S, 13.23
Found: C, 55.09; H, 5.23; N, 11.52; S, 13.59

V-57-GM (BL00021)

1-Methyl-2-(4'-formylphenyl)imidazo[2,1-b]thiazolium N,N-Tetramethylene *guanylhydrazone Dibromide.*

S-Methylthiosemicarbazide hydroiodide, 0.9 g (4.0 mmol), was refluxed with 2 mL of pyrrolidine in 50 mL of ethanol for 24 hours. The solvent was removed and the residue was washed with ether. 1-Methyl-2-(4'-formylphenyl)-imidazo[2,1-b]thiazolium tosylate 1.65 g (4.0 mmol) was added and the mixture was refluxed in 50 mL of ethanol for 5 hours. To the warm solution was added 5 mL of conc. HBr and it was stirred for 15 minutes. Ether was added to complete the precipitation and the product was collected and recrystallized from 95% ethanol containing a few drops of HBr. Yield: 1.6 g (74%). MP: 275°C.

Anal. calcd for: $C_{18}H_{22}N_6SBr_2 \cdot 1.5H_2O$
Calcd: C, 39.94; H, 4.66; N, 15.53; S, 5.92; Br, 29.52
Found: C, 40.05; H, 4.46; N, 15.58; S, 6.00; Br, 29.40

V-58-GM (BL00030)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

S-Methylthiosemicarbazide hydroiodide, 1.6 g (7.0 mmol), was refluxed with 4 mL of pyrrolidine in 50 mL of ethanol for 24 hours. The solvent was removed and the residue was washed with ether. 1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate 3.0 g (7.0 mmol), was added and the mixture was refluxed in 70 mL of ethanol for 24 hours. The solution was then acidified with HBr, concentrated and refrigerated. The solid obtained by filtration was recrystallized twice from 95% ethanol containing HBr. Yield: 3.0 g (76%). MP: 276°C.

Anal. calcd for: $C_{21}H_{26}N_6OBr_2 \cdot 2H_2O$
Calcd: C, 43.91; H, 5.27; N, 14.63; Br, 27.82
Found: C, 43.80; H, 5.30; N, 14.57; Br, 27.78

V-59-GM (BL00049)

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 2-Thiazolylhydrazone Dibromide

A mixture of 0.8 g (7.0 mmol) of 2-hydrazinothiazole and 2.95 g (7.0 mmol) of 1,6-dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol was refluxed for 4 hours. Then conc. HBr, 6 mL, was added and the mixture stirred for 1 hour at room temperature. Ether was added to complete precipitation and the product was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.9 g (83%). MP: 292°C.

Anal. calcd for: $C_{19}H_{19}N_5SBr_2$
Calcd: C, 44.80; H, 3.77; N, 13.75; S, 6.29; Br, 31.38
Found: C, 44.75; H, 3.80; N, 13.70; S, 6.36; Br, 31.33

V-60-GM (BL00058)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N'-Dibutylguanylhydrazone Dibromide

A solution of N,N'-di-n-butyl-aminoguanidinium hydroiodide, 1.9 g (6.0 mmol), in 60 mL of ethanol was refluxed 4 hours with 2.5 g (6.0 mmol) of 1,7-dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate. About 6 mL of conc. HBr was added and the mixture was allowed to stir at room temperature for 1 hour. Addition of ether, followed by stirring, made the product solidify. The solid product was redissolved in ethanol and stirred with ether. The solidified product was collected. Yield: 2.9 g (79%). MP: 173°C.

Anal. calcd for: $C_{25}H_{36}N_6Br_2 \cdot 2H_2O$
Calcd: C, 48.71; H, 6.55; N, 13.63; Br, 25.93
Found: C, 48.64; H, 6.40; N, 13.52; Br, 25.75

V-64-GM (BL00067)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimidin-2-ylhydrazone Dibromide

A mixture of 2.65 g (6.0 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)-imidazo[1,2-a]pyrimidinium tosylate and 1.45 g (6.0 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidinium hydroiodide was refluxed in 70 mL of ethanol for 24 hours. The solution was then acidified with HBr, concentrated and refrigerated. The solid obtained by filtration was recrystallized twice from 95% ethanol containing HBr. Yield: 2.7 g (81%). MP: 295°C.

Anal. calcd for: $C_{20}H_{24}N_6OBr_2 \cdot 2H_2O$
Calcd: C, 42.87; H, 5.03; N, 15.00; Br, 28.52
Found: C, 42.74; H, 5.05; N, 15.19; Br, 28.90

V-68-GM (BL00076)

1,3-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

A mixture of 1.6 g (7.0 mmol) of S-methylthiosemicarbazide hydroiodide and 4 mL of pyrrolidine in 50 mL of ethanol was refluxed for 24 hours. The solvent was removed and the residue was washed with ether. The residue was mixed with 2.95 g (7.0 mmol) of 1,3-dimethyl-2-(4'-formylphenyl)imidazo-[1,2-a]pyridinium tosylate in 50 mL ethanol and refluxed for 4 hours. At room temperature, 6 mL of conc. HBr was added and the mixture was stirred for 1 hour. Ether was added to complete the precipitation and the product was filtered and recrystallized from ethanol. Yield: 3.2 g (83%). MP: 305°C.

Anal. calcd for: $C_{21}H_{26}N_6Br_2 \cdot 1.5\ H_2O$
Calcd: C, 45.91; H, 5.32; N, 15.28; Br, 29.00
Found: C, 46.05; H, 5.32; N, 15.29; Br, 29.02

V-62-GM (BL03899)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate, 4.08 g (10.0 mmol) in 60 mL of ethanol was refluxed for 4 hours. with 2.85 g (11.0 mmol) of N,N'-diethylaminoguanidine hydroiodide. Then 8 mL of conc. HBr was added and the solution was stirred. Addition of ether completed the precipitation. The product was collected and recrystallized from ethanol containing a few drops of HBr by addition of ether. Yield: 4.6 g (89%); MP: 185-187°C.

Anal. calcd for: $C_{20}H_{26}N_6Br_2 \cdot 0.5H_2O$
Calcd: C, 46.25; H, 5.24; N, 16.19; Br, 30.78
Found: C, 46.11; H, 5.23; N, 16.16; Br, 30.70

V-63-GM (BL03906)

1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]thiazolium 2-Thiazolylhydrazone Dibromide

A mixture of 2.9 g (7.0 mmol) of 1-methyl-2-(4'-formylphenyl)-imidazo[1,2-a]thiazolium tosylate and 9.8 g (7.0 mmol) of 2-hydrazinothiazole in 60 mL of ethanol was refluxed for 4 hours. After cooling to room temperature, 8 mL of conc. HBr was added and the mixture was stirred until precipitation was complete. The precipitate was collected and recrystallized two times from ethanol containing a few drops of HBr. Yield: 2.1 g (59%); MP: 263-266°C.

Anal. calcd for: $C_{16}H_{15}N_5Br_2 \cdot H_2O$
Calcd: C, 37.00; H, 3.30; N, 13.49; S, 12.35; Br, 30.78
Found: C, 36.91; H, 3.36; N, 13.43; S, 12.40; Br, 30.70

V-70-GM (BL03915)

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-Dimethylenethiamethyleneguanylhydrazone Ditosylate

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium S-methylsemicarbazone ditosylate, 2.7 g (4.0 mmol) in 60 mL of ethanol was refluxed for 4 days with 0.48 g (5.0 mmol) of thiazolidine. The solvent was removed and the residue was washed with ether. It was dried over the pump to yield a hygroscopic yellow glassy product. Yield: 2.8 g (93%).

Anal. calcd for: $C_{34}H_{38}N_3O_6 \cdot 1.5H_2O$
Calcd: C, 54.45, H, 5.51; N, 11.21; S, 12.83
Found: C, 54.53; H, 5.54; N, 11.18; S, 12.92

V-75-GM (BL03924)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N,N-Dimethylguanylhydrazone Dibromide

S-Methyl thioisemicarbazide hydroiodide, 1.6 g (7.0 mmol), was refluxed with 4 mL of dimethylamine in 50 mL of ethanol for 15 hours. The solvent was removed and the residue was washed with ether. 1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate 2.6 g (6 mmol) was added and the mixture was refluxed for 18 hours in 60 mL of ethanol. Then 8 mL of conc. HBr was added and the mixture was stirred until precipitation was complete. The precipitate was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.3 g (71%); MP: 254°C.

Anal. calcd for: $C_{19}H_{24}N_6OBr_2 \cdot 2H_2O$
Calcd: C, 41.62; H, 5.14; N, 15.33; Br, 29.15
Found: C, 41.44; H, 4.74; N, 15.08; Br, 28.79

V-76-GM (BL03933)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N,N'-Diethylguanylhydrazone Dibromide.

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate, 3.05 g (7.0 mmol), in 60 mL of ethanol was refluxed for 12 hours with 1.8 g (7.0 mmol) of N,N'-diethylaminoguanidine hydroiodide. Then 8 mL of conc. HBr was added and the mixture stirred until precipitation was complete. The product was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 3.0 g (77%); MP: 250°C.

Anal. calcd for: $C_{21}H_{28}N_6OBr_2 \cdot 1.5H_2O$
Calcd: C, 44.46; H, 5.50; N, 14.82; Br, 28.17
Found C, 44.25; H, 5.55; N, 14.76; Br, 28.02

V-65-GM (BL05320)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N-Thiazolylhydrazone Dibromide

A mixture of 0.58 g (5.0 mmol) of 2-hydrazinothiazole and 2.2 g (5.0 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol was refluxed for 8 hours. Then conc. HBr, 6 mL, was added and the mixture was stirred and then chilled to complete precipitation. The precipitate was redissolved in 95% ethanol, reacidified and chilled. The product was recrystallized from ethanol containing a few drops of HBr. Yield: 2.1 g (75%); MP: 257°C.

Anal. calcd for: $C_{19}H_{19}N_5OSBr_2 \cdot 1.5H_2O$
Calcd: C, 41.32; H, 4.02; N, 12.68; S, 5.80; Br, 28.94
Found: C, 41.73; H, 3.96; N, 12.76; S, 5.66; Br, 28.56

V-66-GM (BL05339)

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide.

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate and 1.55 g (6.0 mmol) of N,N'-diethylaminoguanidine hydroiodide in 60 mL of ethanol were refluxed for 5 hours. After cooling to room temperature, 6 mL of conc. HBr was added and the mixture was stirred and chilled. The precipitate was collected, redissolved in ethanol and acidified again. The product was collected and recrystallized from ethanol and ether. Yield: 2.4 g (71%); MP: 255°C.

Anal. calcd for: $C_{21}H_{28}N_6Br_2 \cdot 2H_2O$
Calcd: C, 45.01; H, 5.76; N, 15.00; Br, 28.52
Found: C, 44.85; H, 5.79; N, 14.94; Br, 28.44

V-73-GM (BL05348)

1,7-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Morpholinoguanylhydrazone Dibromide.

S-Methyl thiosemicarbazide hydroiodide, 2.3 g (10.0 mmol) was refluxed with N-aminomorpholine 1.2 g (11.8 mmol), in 50 mL of dry ethanol for 24 hours. The reaction mixture was concentrated to about 15 mL and diluted with ether. The oily product which formed was separated and purified by reprecipitation from ethanol with ether. 1,7-Dimethyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate, 2.6 g (6.16 mmol), was added to the aminoguanidinium salt, 1.85 g (6.5 mmol), and the mixture was refluxed in 50 mL of absolute ethanol for 15 hours. The solution was cooled, acidified with HBr and stirred until precipitation was complete. The precipitate was collected and washed with a little ethanol. Yield: 2.3 g (67%); MP: 205-208°C.

Anal. calcd for: $C_{21}H_{27}N_7OBr_2 \cdot 1.5H_2O$
Calcd: C, 43.46; H, 5.21; N, 16.90; Br, 27.54
Found: C, 43.38; H, 5.18; N, 16.84; Br, 27.48

V-77-GM (BL05357)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N'-Dibutylguanylhydrazone Dibromide

A solution of N,N'-di-n-butylaminoguanidinium hydroiodide, 1.25 g (4.0 mmol), in 40 mL of ethanol was refluxed with 1.75 g (4.0 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate. After

15 hours, 6 mL of conc. HBr was added and the mixture was stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Y:ield: 1.6 g (64%); MP: 174°C.

Anal. calcd for: $C_{25}H_{36}N_6OBr_2 \cdot 1.5H_2O$
Calcd: C, 48.16; H, 6.30; N, 13.48; Br, 25.64
Found: C, 48.07; H, 6.31; N, 13.40; Br, 25.68

V-80-GM (BL05366)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N,N'-Dimethylguanylhydrazone Dibromide

A mixture of 1-methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate, 2.6 g (6.0 mmol), and 1.6 g (6.0 mmol) of N,N'-dimethylaminoguanidine hydroiodide in 70 mL of ethanol was refluxed for 15 hours. Then 8 mL of conc. HBr was added and the mixture stirred until precipitation was complete. The precipitate was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.4 g (76%); MP: 272°C.

Anal. calcd for: $C_{19}H_{24}N_6OBr_2 \cdot H_2O$
Calcd: C, 43.03; H, 4.94; N, 15.85; Br, 30.14
Found: C, 43.09; H, 4.99; N, 15.83; Br, 30.05

V-92-GM (BL06934)

1,7-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N,N-Tetramethyleneguanylhydrazone Dibromide

A mixture of 2.5 g (5.5 mol) of 1,7-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,-2a]pyridinium tosylate and 1.4 g (5.5 mmol) of N,N-tetramethylene-N'-aminoguanidinium hydroiodide in 60 mL of ethanol was refluxed for 5 hours. The product was acidified with 6 mL of conc. HBr and stirred. After refrigerating, the solid obtained by filtration was recrystallized twice from ethanol containing a few drops of conc. HBr, Yield: 2.75 g (88%); MP: 274°C.

Anal. calcd for: $C_{22}H_{28}N_6Br_2O \cdot H_2O$
Calcd: C, 46.33; H, 5.30; N, 14.74; Br, 28.02
Found: C, 46.39, H, 5.30; N, 14.72; Br, 27.94

V-91-GM (BL06943)

1,6-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N-Hydroxyguanylhydrazone Dibromide

A mixture of 2.25 g (5.0 mmol) of 1,6-dimethyl-2-[(4'-formylphenoxy)-

methyl]imidazo[1,2-a]pyridinium tosylate and 1.3 g (5.5 mmol) of N-hydroxy-N'-aminoguanidinium tosylate in 60 mL of ethanol was refluxed for 6 hours. Conc HBr (8 mL) was then added and the mixture was stirred for half an hour and refrigerated. The solid obtained by filtration was recrystallized twice from ethanol containing a few drops of conc HBr. Yield: 2.2 g (83%) MP: 202°C.

Anal. calcd for: $C_{18}H_{22}N_6Br_2O_2 \cdot H_2O$
Calcd: C, 40.62; H, 4.55; N, 15.79; Br, 30.02
Found: C, 40.89; H, 4.55; N, 15.75; Br, 30.19

1,7-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium Tosylate

Starting with 2-amino-4-methylpyridine, 7-methyl-2-(4'-formylphenoxymethyl)-imidazo[1,2-a]pyridine was prepared as described for the 6-methyl isomer. The yield of 2-chloromethyl-7-methylimidazo[1,2-]pyrildine was 23% and the yield in the second step was 24%, giving aldehyde, MP 150-153°C. Quaternization with methyl tosylate was carried out by the standard procedure.

V-90-GM (BL06952)

1,7-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
Guanylhydrazone Dibromide

A mixture of 2.25 g (5.0 mmol) of 1,7 dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate, and 0.75 g (5.5 mmol) of aminoguanidine bicarbonate in 50 mL of ethanol was refluxed for 4 hours. Conc HBr (8 mL) was added and stirred. After cooling, the solid obtained by filtration was recrystallized twice from ethanol containing a few drops of HBr. Yield: 2.1 g (81%); MP: 288°C.

Anal. calcd for: $C_{18}N_{22}N_6Br_2O \cdot H_2O$
Calcd: C, 41.87; H, 4.69; N, 16.28; Br, 30.95
Found: C, 41.79; H, 4.70; N, 16.23; Br, 30.81

Sequence for Preparation of 2-(4'-Formylphenoxymethyl)imidazo]1,2-a]pyridines

Step 1: 2-Chloromethyl-6-methylimidazo[1,2-a]pyridine

A mixture of 21.7 g (0.17 mole) of 1,3-dichloroacetone and 18.4 g (0.17 mole) of 2-amino-5-methylpyridine in 250 mL of acetone was refluxed for 15 hours. The mixture was cooled and the uncyclized intermediate was collected as the hydrochloride salt. It was dissolved in 40 mL of hot water, 40 mL of conc HCl was then added and this mixture was heated for 30 minutes. The solution was cooled and slowly basified with NH_4OH (throughout it should be kept below 0°C). This solution was extracted with chloroform, dried and evaporated. The crude product was chromotographed on a silica column using $CHCl_3$ and then $CHCl_3$/MeOH. Yield: 11.4 g (34%).

Step 2: 6-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridine

Sodium hydride (2.35 g, 97.9 mmol, 60% oil dispersion) was washed with hexane in a 250 mL 3-necked round bottomed flask. The flask was protected by a slow stream of nitrogen. A condenser and a 25 mL drying funnel were fitted to the flask. Dry DMF (50 mL) was added and with stirring a solution of 9.5 g (78.0 mmol) p-hydroxybenzaldehyde in 35 mL of DMF was added through the dropping funnel within 15 minutes. The mixture was allowed to stand for half an hour, after which 11.3 g (62.6 mmol) of 2-chloromethyl-6-methylimidazo[1,2-a]pyridine in 40 mL of dry DMF was added through the dropping funnel within 15 minutes. The flask was then heated on an oil bath at 95-100°C for 24 hours. The contents of the flask were poured into 1500 mL of cold water and stirred. The product was then filtered. The crude aldehyde was recrystallized 2-3 times using chloroform/hexane. Yield 8.0 g (48%); MP: 133-134°C.

1,6-Dimethyl-2-[(4'-formylphenoxy)methyl]imidazo[1,1-a]pyridinium Tosylate.

This compound was made by using the standard procedure for quaternization. Yield: 82%.

V-88-GM (BL06961)

1,6-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium Guanylhydrazone Dibromide

A mixture of 2.25 g (5.0 mmol) of 1,6-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate, 0.75 g (5.5 mmol) of aminoguanidine bicarbonate and 1.1 g (6.0 mmol) of p-toluenesulfonic acid monohydrate in 60 mL of ethanol was refluxed for 4 hours. The resulting solution was acidified with 8 mL of conc HBr and stirred for an hour. After cooling the precipitate was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.2 g (81%); MP: 266°C.

Anal. calcd for $C_{18}H_{22}N_6Br_2 \cdot 2.5H_2O$
Calcd: C, 39.79; H, 5.00; N, 15.47; Br, 29.41
Found: C, 39.75; H, 5.02; N, 15.46; Br, 29.33

V-89-GM (BL06970)

1,6-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

A solution of 1.4 g (5.5 mmol) of N,N-tetramethylene-N'-aminoguanidinium hydroiodide in 60 mL of ethanol was refluxed 5 hours with 2.5 g (5.5 mmol) 1,6-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate. The reaction solution was acidified with 6 mL of conc HBr and stirred. The mixture was chilled and the precipitate was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.8 g (86%), MP: 264°C.

Anal. Calcd for: $C_{22}H_{28}N_6Br_2 \cdot 2H_2O$
Calcd: C, 44.91; H, 5.47; N, 14.29; Br, 27.17
Found: C, 45.00; H, 5.49; N, 14.25; Br, 27.15

Sequence for Preparation of 1-Methyl-6-propylthio-2-(4'-formylphenyl)-imidazo[1,1-a]pyridinium Salts

Step 1: 2-Amino-5-(propylthio)pyridine

Sodium (1.0 g) was dissolved in 40 mL of absolute ethanol and 3.3 g (43.5 mmol) of propanethiol was then added and stirred for 10 minutes. The solution was then transferred to a pressure bottle containing 6.7 g (30.0 mmol) of 2-amino-5-iodopyridine and 0.6 g of copper powder. This mixture was heated at 110°C for 24 hours. The contents were transferred to a round bottomed flask and evaporated. About 100 mL of water was added and the mixture was extracted 3 times with 100 mL of ethyl acetate. The total organic layer was washed with water, dried and evaporated. The crude product was crystallized from hexane. It was not further characterized but used as such for further steps. Yield: 3.4 g.

Step 2: 6-(Propylthio)-2-(4'-bromophenyl)imidazo[1,2-a]pyridine

A mixture of 9.0 g (54.6 mmol) of 2-amino-5-(propylthio)pyridine and 15.0 g (53.9 mmol) of p-bromophenacyl bromide in 120 mL of acetone was refluxed for 5 hrs. The usual work up and recrystallization from ethanol yielded 14.5 g (75%) of the product. MP: 147-149°C.

Step 3: 6-(Propylthio)-2-(4'-cyanophenyl)imidazo[1,2-a]pyridine

6-(Propylthio)-2-(4'-cyanophenyl)imidazo[1,2-a]pyridine was prepared using the standard procedure starting with the corresponding bromide and reacting with cuprous cyanide. Yield: 74%; MP: 115°C.

Step 4: 6-(Propylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridine

This compound was prepared following the standard procedure for reduction of the nitrile to aldehyde using diisobutylaluminum hydride. Yield: 71%; MP: 120-122°C.

Step 5: 1-Methyl-6-(propylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium Tosylate

This compound was prepared using the standard quaternization procedure using methyl p-toluenesulfonate. Yield: 84%.

V-86-GM (BL06989)

1-Methyl-6-(propylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

S-Methylthiosemicarbazide hydroiodide, 1.25 g (5.5 mmol), was refluxed with 4 mL of pyrrolidine in 50 mL of ethanol for 24 hours. The solvent was removed and the residue was washed with ether. 1-Methyl-6-(propylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate 2.4 g (5.0 mmol) was added and the mixture was refluxed in 50 mL of ethanol for 5 hours. To the warm solution was added 6 mL of conc HBr and it was stirred for an hour. Ether was added to complete the precipitation and the product was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 2.1 g (68%); MP: 268°C.

Anal. calcd for: $C_{23}H_{30}N_6SBr_2 \cdot 2H_2O$
Calcd: C, 44.67; H, 5.54; N, 13.59; S, 5.18; Br, 25.84
Found: C, 44.42; H, 5.59; N, 13.51; S, 5.11; Br, 25.79

2-(4'-Formylphenoxymethyl)pyridine

p-Hydroxybenzaldehyde, 6.85 g, (56 mmol) and powdered KOH, 3.4 g (60 mmol) were added to 30 mL of DMSO and the mixture was stirred for 1 hour. A solution of 2-picolylchloride hydrochloride, 4.0 g, (24 mmol) in 20 mL of DMSO was added to the alkaline solution of p-hydroxybenzaldehyde. The reaction mixture was stirred overnight at room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed repeatedly with water and 5% aqueous NaOH solution until the washing appeared colorless. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid. It was recrystallized from ethyl acetate/hexane. Yield: 3.5 g (70%); MP: 93-95°C.

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium Tosylate

Methyl tosylate (1.9 g (10 mmol) was added to a solution of 2-(4'-formylphenoxymethyl)pyridine (1.7 g, 7.9 mmol) in 30 mL of acetonitrile. The reaction mixture was refluxed for 60 hrs. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 3.0 g (97%); MP: 193-195°C.

I-005-AB: (BL06998)

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 2.0 g (4.9 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate and 1.2 g (5.4 mmol) of 2-hydrazinoimidazoline hydroiodide in 50 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.95 g (78%); MP: >200°C decomp.

Anal. calcd for: $C_{17}H_{21}N_5Br_2 \cdot 1.5H_2O$
Calcd: C, 40.98; H, 4.85; N, 14.07; Br. 32.07
Found: C, 40.88; H, 4.79; N, 14.03; Br. 31.84

I-006-AB (BL07002)

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium Guanylhydrazone Ditosylate

A mixture of 2.0 g (4.9 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate, 0.75 g (5.5 mmol) of aminoguanidine bicarbonate and 1.5 g (8.72 mmol) of p-toluenesulfonic acid was refluxed in 50 mL of 95% ethanol for 4 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The pale yellowish solid was recrystallized from ethanol/ether. Yield: 2.1 g (65%); MP: 205-210°C.

Anal. calcd for: $C_{29}H_{33}N_5O_7S_2$
Calcd: C, 55.48; H, 5.29; N, 11.15; S, 10.21
Found: C, 55.31; H, 5.35; N, 11.25; S, 10.28

V-85-GM (BL07039)

1-Methyl-6-(propylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium Guanylhydrazone Dibromide

A mixture of 2.4 g (5.0 mmol) of 1-methyl-6-(propylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate and 0.75 g (5.5 mmol) of aminoguanidine bicarbonate in 60 mL ethanol was refluxed for 5 hours. At room temperature, 8 mL of conc HBr was added and the mixture was stirred for an hour and then cooled. The precipitate which was collected was recrystallized from ethanol containing a few drops of HBr. Yield: 2.1 g (76%); MP: 130-135°C.

Anal. calcd for: $C_{19}H_{24}N_6SBr_2 \cdot 1.5H_2O$
Calcd: C, 41.09; H, 4.90; N, 15.14; S, 5.77; Br, 28.78
Found: C, 41.15; H, 4.89; N, 15.11; S, 5.80; Br, 28.70

A-I-9 (BLO7646): Also resubmitted as BL09006

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

Excess of pyrrolidine (6 mL) was added to a solution of 1 g (4.5 mmol) of S-methyl thiosemicarbazide hydroiodide in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.7 g (4.2 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate in 35 mL of ethanol. The mixture was refluxed for 5 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacdified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (80%); MP: 250°C.

Anal. calcd for: $C_{19}H_{25}N_5Br_2O \cdot 1.5H_2O$
Calcd: C, 43.35; H, 5.36; N, 30.37; Br, 13.30
Found: C, 43.45; H, 5.40; N, 30.30; Br, 13.23

A-I-10 (BL07646): Also resubmitted as BL09042

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium
3,4,5,6-Tetrahydropyrimidyl-2-hydrazone Dibromide

A mixture of 1.7 g (4.2 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate and 1.1 g (4.6 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 9 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (80%); MP: 250°C decomp.

Anal. calcd for: $C_{18}H_{23}N_5Br_2O\cdot H_2O$
Calcd: C, 42.96; H, 5.0; N, 13.9; Br, 31.75
Found: C, 42.99; H, 5.03; N, 13.7; Br, 31.66

Sequence for Preparation of 1-Methyl-6-(butylthio)-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium Salts

Step 1: 6-(Butylthio)-2-(4'-bromophenyl)imidazo[1,2-a]pyridine

This compound was prepared using the procedure described above for the propylthio analog. MP: 130-131°C.

Step 2: 6-(Butylthio)-2-(4'-cyanophenyl)imidazo[1,2-a]pyridine

This compound was prepared using the standard procedure starting with the corresponding bromide and reacting with cuprous cyanide. Yield: 73% MP: 106°C.

Step 3: 6-(Butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridine

This compound was prepared following the standard procedure using the corresponding nitrile and diisobutylaluminum. Yield: 75%; MP: 120°C.

Step 4: 1-Methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate.

This salt was made by using the standard procedure. Yield: 82%.

V-93-GM (BL07655)

1-Methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium
Guanylhydrazone Ditosylate

A mixture of 2.0 g (4.0 mmol) of 1-methyl-6-butylthio-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate, 0.65 g (4.8 mmol) of aminoguanidine bicarbonate and 0.95 g (5.0 mmol) of p-toluenesulfonic acid monohydrate in 50 mL of ethanol was refluxed for 5 hours. The solution was cooled and ether was added to complete the precipitation. The precipitate was collected and recrystallized from ethanol-ether. Yield: 2.25 g; (77%) MP: 228°C.

Anal. calcd for: $C_{34}H_{40}N_6S_3O_6$
Calcd: C, 56.33; H, 5.56; N, 11.59; S, 13.27
Found: C, 56.23; H, 5.61; N, 11.54; S, 13.20

V-94-GM (BL07664)

1-Methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide.

A mixture of 2.0 g (4.0 mmol) of 1-methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate and 1.0 g (4.0 mmol) of N,N-tetramethylene-N'-aminoguanidinium hydroiodide in 40 mL of ethanol was refluxed for 5 hours. Conc HBr (6 mL) was added and the mixture was stirred for 1 hour. The mixture was then cooled and the precipitate was collected and recrystallized from ethanol containing a few drops of HBr. Yield: 1.95 g, 79%; MP: 245-247°C.

Anal. calcd for: $C_{24}H_{32}N_6SBr_2 \cdot H_2O$
Calcd: C, 46.91; H, 5.57; N, 13.68; S, 5.22; Br, 26.01
Found: C, 46.73; H, 5.59; N, 13.61; S, 5.13; Br, 25.92

V-95-GM (BL07673)

1-Methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Hydroxyguanylhydrazone Dibromide

A solution of 2.0 g (4.0 mmol) of 1-methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate in 50 mL of ethanol was refluxed for 4 hours with 1.05 g (4.0 mmol) of N-hydroxy-N'-aminoguanidinium tosylate. The product could not be crystallized as the ditosylate salt. Addition of HBr permitted isolation of the crude dibromide salt. This was purified by recrystallization using ethanol-ether. Yield: 1.5 g (65%); MP: 200-202°C.

Anal. calcd for: $C_{20}H_{26}N_6SBr_2O \cdot 0.5H_2O$
Calcd: C, 42.34; H, 4.80; N, 14.82; S, 5.65; Br, 28.17
Found: C, 42.44; H, 4.79; N, 14.79; S, 5.59; Br, 28.05

V-96-GM (BL07806)

bis-[1-Methyl-6-(butylthio)-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 1,4-Benzenecarbonyldihydrazone Ditosylate

A mixture of 4.0 g (8.0 mmol) of 1-methyl-6-butylthio-2-(4'-formylpheny)imidazo[1,2-a]pyridinium tosylate, 0.78 g (4.0 mmol) of terephthalic acid dihydrazide and 1.5 g (8.0 mmol) of p-toluenesulfonic acid monohydrate in 120 mL of 95% ethanol was refluxed for 24 hours. The product was collected and recrystallized using aqueous ethanol. Yield: 3.6 g (68%); MP: 295-298°C.

Anal. calcd for: $C_{60}H_{62}N_8S_4O_8 \cdot 1.5H_2O$
Calcd: C, 61.15; H, 5.56; N, 9.51; S, 10.87
Found: C, 60.80; H, 5.48; N, 9.68; S, 11.05

Sequence for Preparation and Methylation of 2-[4'-(3-Oxopropenyl)phenyl]imidazo[1,2-a]pyridine

Step 1: Preparation of 2-[4'-(β-carboethoxyvinyl)phenyl]imidazo[1,2-a]pyridine

Sodium (1.6 g) was dissolved in 80 mL of absolute ethanol. Triethyl phosphonoacetate (15.6 g) was added and stirred for 15 minutes. To this mixture 15.5 g (70 mmol) of 2-(4'-formylphenyl)imidazo[1,2-a]pyridine was added and the solution was heated in an oil bath at 90°C for 15 hours. The mixture was poured into water and the precipitated product was recrystallized from ethanol. Yield: 11.6 g (57%); MP: 207-209°C.

Anal. calcd for: $C_{18}H_{16}N_2O_2$
Calcd: C, 73.97; H, 5.48; N, 9.59
Found: C, 73.84; H, 5.58; N, 9.55

Step 2: 2-[4'-(3-oxo-1-propenyl)phenyl]imidazo[1,2-a]pyridine

The ester prepared in Step 1 (18.0 g) was dissolved in toluene (120 mL) and reduced using diisobutylaluminum hydride. After stirring it overnight, a few mL (~10 mL) of methanol was added carefully, followed by 10% H_2SO_4 (100 mL). The aqueous layer was carefully neutralized and basified slightly with NaOH. The product allylic alcohol was extracted with $CHCl_3$ and dried. To the same chloroform solution active MnO_2 (50 g) was added and the mixture was stirred for 20 hours. The precipitate was filtered off and the solvent was removed in vacuo. The residue was taken in hot ethanol, heated with saturated $NaHSO_3$ and the bisulfite adduct was collected. It was suspended in water and basified with NaOH. The crude aldehyde was collected and recrystallized in ethanol. Yield: 7.8 g (38%), MP: 206-208°C.

Anal. calcd for: $C_{16}H_{12}N_2O$
Calcd: C, 77.42; H, 4.84; N, 11.29
Found: C, 77.18; H, 4.93; N, 11.22

Step 3: 1-Methyl-2-[4'-(3-oxopropenyl)phenyl]imidazo[1,2-a]pyridinium Tosylate

The quaternization of the aldehyde was done following the usual procedure using methyl tosylate in CH_3CN. Yield: 86%, MP: 208-210°C.

V-98-GM (BL07815)

1-Methyl-2-[4'-(3-oxopropenyl)phenyl]imidazo[1,2-a]pyridinium Guanylhydrazone Ditosylate

A mixture of 2.0 g (4.6 mmol) of 1-methyl-2-[4'-(3-oxo-1-propenyl)phenyl]imidazo[1,2-a]pyridinium tosylate, 0.7 g (5.0 mmol) of aminoguanidine bicarbonate and 1.0 g (5.2 mmol) of p-toluenesulfonic acid monohydrate in 50 mL of ethanol was refluxed mildly for 5 hours. The reaction mixture was cooled and the precipitate was recrystallized in ethanol. Yield: 2.4 g (77%); MP: 265°C.

Anal. calcd for: $C_{32}H_{34}N_6S_2O_6 \cdot 0.5H_2O$
Calcd: C, 57.21; H, 5.25; N, 12.51; S, 9.54
Found: C, 57.30; H, 5.26; N, 12.49; S, 9.51

V-99-GM (BL07824)

1-Methyl-2-[4'-(3-oxopropenyl)phenyl]imidazo[1,2-a]pyridinium tosylate, 1.75 g (4.0 mmol), in 50 mL of ethanol was refluxed for 5 hours with 1.0 g (4.0 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide. The solution was then acidified with conc HBr, concentrated and refrigerated. The solid obtained by filtration was recrystallized from ethanol containing a few drops of HBr. Yield: 1.8 (82%); MP: 262°C.

Anal. calcd for: $C_{21}H_{24}N_6Br_2 \cdot H_2O$
Calcd: C, 46,85; H, 4.87; N, 15.61; Br, 29.69
Found: C, 46.72; H, 4.89; N, 15.59; Br, 29.68

V-101-GM (BL07833)

bis-1-Methyl-2-[4'-(3-oxopropenyl)phenyl]imidazo[1,2-a]pyridinium
1,4-Benzenedicarbonylhydrazone Ditosylate

A mixture of 3.5 g (8.0 mmol) of 1-methyl-2-[4'-(3-oxopropenyl)-phenyl]imidazo[1,2-a]pyridinium tosylate, 0.78 g (4.0 mmol) of terephthaloyl hydrazide and 1.5 g (8.0 mmol) of p-toluenesulfonic acid monohydrate in 120 mL ethanol was refluxed for 20 hours. The reaction mixture was cooled and the precipitate was recrystallized from aqueous ethanol. Yield: 2.5 g (61%); MP: 273°C.

Anal. calcd for: $C_{56}H_{50}N_8S_2O_8 \cdot H_2O$
Calcd: C, 64.35; H, 5.01; N, 10.72; S, 6.13
Found: C, 64.40; H, 5.04; N, 10.70; S, 6.05

V-103-GM (BL07842)

bis-1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium
N,N'-Hexamethyleneguanylhydrazone Tetraiodide

Step 1: Preparation Hexamethylene-N,N'-diaminoguanidine Dihydroiodide

A mixture of 1.4 g (12 mmol) of hexamethylenediamine and 4.6 g (20.0 mmol) of S-methylthiosemicarbazide hydroiodide in 60 mL of ethanol was refluxed for 20 hours. The solvent was removed and the residue was washed with ether and crystallized using ethanol. The crude product was recrystallized from ethanol. Yield: 2.2 g (45%); MP: 170°C.

Step 2: Reaction with 1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium Iodide

A mixture of 2.18 g (6.0 mmol) of 1-methyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium iodide and 1.46 g (3.0 mmol) of the hexamethylene-N,N'-diaminoguanidine salt from Step 1 in 70 mL of 95% ethanol was refluxed for 18 hours. A little ether was added and the resulting precipitate was collected. The crude product was carefully recrystallized using hot water, to give product as a yellow powder. Yield: 1.4 g (39%); MP: 196-199°C.

Anal. calcd for: $C_{38}H_{45}N_{12}I_4 \cdot 0.5H_2O$
Calcd: C, 38.43; H, 3.99; N, 14.15; Br, 42.75
Found: C, 38.62; H, 4.14; N, 14.18; Br, 42.94

V-104-GM (BL08223)

Step 1: bis-2-(4'-Aminophenyl)imidazo[1,2-a]pyridine 1,4-Benzenedicarboxamide

A mixture of 4.2 g (20 mmol) of 2-(4'-aminophenyl)imidazo[1,2-a]pyridine, 2.0 g (10 mmol) of terephthalyl chloride and 2.0 g (20 mmol) of triethylamine in 30 mL dry DMF was heated in an oil bath at 135°C for 18 hours under N_2. The mixture was poured into 90% ethanol. The precipitate is difficult to recrystallize. Hence it was boiled in ethanol and filtered. The crude precipitate was used as such for the next step. Yield: 2.1 g.

Step 2: bis-1-Methyl-2-(4'-aminophenyl)imidazo[1,2-a]pyridinium 1,4-Benzenedicarboxamide Ditosylate

The crude diamide (1.1 g) and 2.0 g of the methyl tosylate in 30 mL of nitrobenzene was heated in a pressure bottle at 135°C for 6 days. The mixture was cooled and poured into ether. The precipitate was collected and recrystallized in dilute ethanol. Yield 250 mg. MP: 345-347°C.

Anal. calcd. for: $C_{50}H_{44}N_6O_8S_2 \cdot H_2O$
Calcd: C, 63.94; H, 4.94; N, 8.95; S, 6.82
Found: C, 63.83; N, 4.98; N, 8.91; S, 6.79

Preparation of 3-Methyl-4-(4'-formylphenoxymethyl)thiazolium Tosylate

Step 1: Thioformamide

Phosphorus pentasulfide, 3 g (13.5 mmol) was added to a solution of 3 g (66 mmol) of formamide in 50 mL of dioxane. The mixture was heated over a steam bath for 4 hours. The clear liquid solution was decanted and evaporated under vacuum to give the product as a yellow oil. It was used for the next reaction without further purification.

Step 2: 4-Chloromethylthiazolium hydrochloride

Thioformamide, 3.1 g (50 mmol), and 1,3-dichloroacetone 6.3 g (50 mmol) were dissolved in 80 mL of dry acetone. The solution was stirred overnight, during which the product appeared as a white powdery precipitate. The mixture was further diluted with ether and filtered. The product was washed with ether and used for next reaction. Yield: 5.0 g (65%).

Step 3: 4-(4'-Formylphenoxymethyl)thiazole

p-Hydroxybenzaldehyde (7 g, 57 mmol) and powdered KOH (3.1 g, 47 mmol) were added to 50 mL of DMSO and the mixture was stirred for 1 hour. A solution of 4-chloromethylthiazolium chloride (4 g, 24 mmol) in 20 mL of DMSO was added to the mixture containing p-hydroxybenzaldehyde. The reaction mixture was stirred overnight at room temperature and was then extracted with ethyl acetate. The extracts were combined and washed with water and 5% aqueous NaOH solution until the aqueous washing appeared colorless. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid. It was used without further purification. Yield: 3.4 g (57%).

Step 4: 3-Methyl-4-(4'-formylphenoxymethyl)thiazolium Tosylate

Methyl tosylate (1.9 g, 10 mmol) was added to a solution of 4-(4'-formylphenoxymethyl)thiazole (2 g, 9 mmol) in 40 mL of acetonitrile. This reaction mixture was refluxed overnight. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 2.5 g (75%); MP: 236-239°C.

I-25-A (BL08232)

3-Methyl-4-(4'-formylphenoxymethyl)thiazolium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.6 g (4.0 mmol) of 3-methyl-4-(4'-formylphenoxymethyl)thiazolium tosylate and 1.1 g (5 mmol) of 2-hydrazinoimidazoline hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated the product. The product was redissolved and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (88%); MP: 236-239°.

Anal. calcd. for: $C_{15}H_{19}N_5SOBr_2 \cdot 1.5H_2O$
Calcd: C, 35.73; H, 4.36; N, 13.90: S, 6.34; Br, 31.70
Found: C, 35.83; H, 4.42; N, 13.87; S, 6.38; Br, 31.61

3-(4'-Formylphenoxymethyl)pyridine

p-Hydroxybenzaldehyde (6.85 g, 56 mmol) and powdered potassium hydroxide (3.4 g, 5.6 mmol) were added to 30 mL of DMSO and the mixture was stirred for 1 hour. A solution of 3-chloromethylpyridinium hydrochloride (4 g, 29.4 mmol) in 20 mL of DMSO was added to the mixture containing p-hydroxybenzaldehyde. The reaction mixture was stirred overnight at room temperature and was extracted with ethyl acetate. The ethyl acetate extracts were combined and washed with water and 5% aqueous NaOH solution until the washings appeared colorless. The organic layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give a yellow solid. It was decolorized with charcoal in hot ethyl acetate. After filtration and evaporation of solvent the product was obtained as a white solid. Yield: 3.0 g (60%).

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium Tosylate

Methyl tosylate (1.9 g, 10 mmol) was added to a solution of 3-(4'-formylphenoxymethyl)pyridine (1.7 g, 7.9 mmol) in 30 mL of acetonitrile. The reaction mixture was refluxed overnight. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 2.8 g (90%). MP: 150-152°C.

I-29-A (BL08241)

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.9 g (4.7 mmol) of 1-methyl-3-(4'-formylphenoxymethyl)pyridinium tosylate and 1.1 g (5 mmole) of 2-hydrazinoimidazoline hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (75%); MP 250°C decomp.

Anal. calcd. for: $C_{17}H_{21}N_5OBr_2 \cdot 1.5H_2O$
Calcd: C, 40.98; H, 4.85; N, 14.06; Br, 32.07
Found: C, 41.14; H, 4.81; N, 13.97; Br, 32.01

I-12-A (BL08250)

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 1.8 g (4.4 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate and 1.3 g (5 mmol) of N,N'-diethyl-N''-aminoguanidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of concentrated HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol reacidified, and reprecipitated. Finally it was recrystallized from ethanol/ether. Yield: 1.9 g (83%); MP: 195-200°C.

Anal. calcd. for: $C_{19}H_{27}N_5Br_2O \cdot 2H_2O$
Calcd: C, 42.47; H, 5.81; N, 13.03; Br, 29.74
Found: C, 42.35; H, 5.84; N, 12.99; Br, 29.67

I-39-A (BL09015)

3-Methyl-4-(4'-formylphenoxymethyl)thiazolium 3,4,5,6-Tetrahydropyrimidyl-2-hydrozone Dibromide

A mixture of 1.6 g (3.9 mmol) of 3-methyl-4-(4'-formylphenoxymethyl)thiazolium tosylate and 1.0 g (4.1 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 9 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.6 g (78%); MP: 230-233°C.

Anal. calcd. for: $C_{16}H_{21}N_5SBr_2O \cdot 2H_2O$
Calcd: C, 36.45; H, 4.78; N, 13.27; S, 6.06; Br, 30.31
Found: C, 36.58; H, 4.76; N, 13.29; S, 6.10; Br, 30.26

Preparation of 1-Methyl-2-formylimidazo[1,2-a]pyridinium Salts

Step 1: Ethyl Imidazo[1,2-a]pyridine-2-carboxylate

2-Aminopyridine (8.4 g, 0.09 mol) and ethyl bromopyruvate (17.6 g, 0.09 mol) in 100 mL of absolute ethanol were stirred under reflux for 5 hours. The reaction mixture was cooled and evaporated. The residue was dissolved in 10% HCl and basified to pH 8 with saturated $NaHCO_3$ solution. The precipitated solid was filtered, dried and recrystallized from CCl_4. Yield: 12.5 g (73%).

Step 2: 2-Hydroxymethylimidazo[1,2-a]pyridine

Ethyl imidazo[1,2-a]pyridine-2-carboxylate, 11.0 g (57.8 mmol) was dissolved in a minimum amount of anhydrous dichloromethane, 100 mL of anhydrous ether was added and the solution was kept stirring at room temperature in a nitrogen atmosphere. Lithium aluminum hydride, 2.2 g (58 mmol) was added in portions over a period of an hour, maintaining a gentle reflux. After the addition of the LAH was complete, the reaction mixture was gently refluxed for an hour. The reaction mixture was cooled and treated with 2.5 mL of water, 2.5 mL of 15% NaOH, and 7.5 mL of water in sequence and stirred for half an hour. The precipitated lithium and aluminum salts were filtered off and thoroughly washed with hot ethyl acetate. The combined organic filtrates were evaporated and the solid obtained was recrystallized from ethyl acetate and hexane. Yield: 7.3 g (85%).

Step 3: 2-Formylimidazo[1,2-a]pyridine

2-Hydroxymethylimidazo[1,2-a]pyridine, 6.0 g (40.5 mmol) and 30.0 g of activated manganese dioxide were stirred in 200 mL of anhydrous chloroform at room temperature for 2 days. At the end of the reaction period, the reaction mixture was filtered and the solvent was removed in a rotary evaporator. The product obtained was recrystallized from CCl_4. Yield: 3.55 g (60%); MP: 126-128°C.

Step 4: 1-Methyl-2-formylimidazo[1,2-a]]pyridinium Tosylate

This compound was prepared using the standard quaternization procedure using methyl p-toluenesulfonate. Yield: 85%; MP: 207-210°C.

II-20-VS (BL09024)

1-Methyl-2-formylimidazo[1,2-a]pyridinium Guanylhydrazone Ditosylate

A mixture of 2.1 g (6.3 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate, 1.03 g (7.5 mmol) of aminoguanidine bicarbonate and 2.4 g (12.6 mmol) of p-toluenesulfonic acid monohydrate in 30 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled and the precipitated solid was recrystallized from ethanol and water. Yield: 3.5 g (86%); MP: 235-37°C.

Anal. calcd. for: $C_{24}H_{28}N_6O_6S_2\cdot 1H_2O$
Calcd: C, 49.83; H, 5.23; N, 14.52; S, 11.06
Found: C, 49.76; H, 5.26; N, 14.46; S, 11.04

I-31-A (BL09033)

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium Guanylhydrazone Ditosylate

A mixture of 2.0 g (4.9 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate, 0.75 g (5.5) mmol) of aminoguanidine bicarbonate, and 1.5 g (8.7 mmol) of p-toluenesulfonic acid was refluxed in 50 mL of 95% ethanol for 4 hours. On cooling, the product crystallized out. The solution was further diluted with ether and filtered. The pale yellowish solid was recrystallized from ethanol-ether. Yield: 2.5 g (80%); MP: 228-230°C.

Anal. calcd. for: $C_{29}H_{34}N_5S_2O\cdot 0.5H_2O$
Calcd: C, 54.7; H, 5.34; N, 10.99; S, 10.07
Found: C, 54.59; H, 5.43; N, 10.98; S, 10.02

I-34-A (BL09051)

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium 3,4,5,6-Tetrahydropyrimid-2-yl-hydrazone Dibromide.

A mixture of 1.7 g (4.2 mmol) of 1-methyl-3-(4'-formylphenoxymethyl)pyridinium tosylate and 1.1 g (4.6 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 9 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (82%); MP: 250-255°C decomp.

Anal. calcd. for: $C_{18}H_{23}N_5Br_2O\cdot 2H_2O$
Calcd: C, 41.60; H, 5.22; N, 13.43; Br, 30.66
Found: C, 41.31; H, 5.23; N, 13.36; Br, 30.64

II-33-VS (BL09453)

1-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Ditosylate

A mixture of 3.0 g (7.1 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)-imidazo[1,2-a]pyridinium tosylate and 2.75 g (9.2 mmol) of N,N-tetramethylene-N'-aminoguanidinium hydroiodide in 40 mL of ethanol was refluxed for 5 hours. The reaction mixture was cooled and the precipitated solid was recrystallized from ethanol and water. Yield: 4.4 g (86%); MP: 278-80°C.

Anal. calcd. for: $C_{35}H_{40}N_6S_2O_7$
Calcd: C, 58.31; H, 5.59; N, 11.66; S, 8.90
Found: C, 58.45; H, 5.65; N, 11.62; S, 8.81

Sequence for Preparation and Methylation of 2-(4'-Formylphenylethenyl)-imidazo[1,2-a]pyridine

Step 1: Preparation of 2-(4'-Cyanophenylethenyl)imidazo[1,2-a]pyridine

Diethyl 4-cyanobenzylphosphonate[7], 6.0 g (24 mmol), and 960 mg (24 mmol) of sodium hydride were stirred in 60 mL of dry dimethoxyethene in a N_2 atmosphere and 3.6 g (24 mmol) of 2-formylimidazo[1,2-a]pyridine in 50 mL of dimethoxyethane was added slowly using an addition funnel. The reaction mixture was gradually heated to 85°C in an oil bath and was maintained at that temperature for an hour. The reaction mixture was cooled and poured into excess water. The precipitated solid was filtered, dried and recrystallized from ethanol. Yield: 4.2 g (71%); MP: 232-34°C.

Step 2: 2-(4'-Formylphenylethenyl)imidazo[1,2-a]pyridine

The nitrile prepared in Step 1 (3 g, 12 mmol) was suspended in 50 mL of anhydrous toluene, in a nitrogen atmosphere, and 12 mL of diisobutyl aluminum hydride (1.5M solution) was syringed in. The reaction mixture was stirred overnight at room temperature, a few mL (~5 mL) of methanol was added carefully, followed by 10% H_2SO_4 (25 mL). The precipitated solid was filtered, redissolved in warm water and basified with 10% NaOH solution. The precipitated aldehyde was dissolved in hot ethanol, treated with saturated $NaHSO_3$ and the bisulfite adduct was collected. The bisulfite adduct was suspended in water and basified with NaOH. The precipitated aldehyde was filtered and dried. Yield: 2.2 g (73%); MP: 207-10°C (decomp).

Step 3: 1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium Tosylate

The quaternization of the aldehyde was done following the standard procedure by using methyl p-toluenesulfonate in acetonitrile. Yield: 86%; MP: 230-32°C (decomp).

II-36A-VS (BL09462)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium Guanylhydrazone Ditosylate

A mixture of 1.8 g (4.2 mmol) of 1-methyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate, 0.7 g (5.1 mmol) aminoguanidine bicarbonate and 1.8 g (9.4 mmol) of p-toluenesulfonic acid monohydrate in 40 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled and the precipitated product was recrystallized from ethanol and water. Yield: 2.2 g (76%) MP: 254-56°C.

Anal. calcd. for: $C_{32}H_{34}N_6S_2O_6 \cdot 1H_2O$
Calcd: C, 56.45; H, 5.33; N, 12.34; S, 9.42
Found: C, 56.53; H, 5.35; N, 12.31; S, 9.36

Sequence for Preparation of 1,3-Dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium Salts

Step 1: 2-(4'-Formylphenoxymethyl)benzimidazole

p-Hydroxybenzaldehyde, 8.4 g (69 mmol) and powdered potassium hydroxide 4.1 g (63 mmol) were added to 30 mL of DMSO and the mixture was stirred for 1 hour. A solution of 2-chloromethylbenzimidazole, 5 g (30 mmol) in 20 mL of DMSO was added to the alkaline solution of p-hydroxybenzaldehyde. The reaction mixture was stirred for 5 hours, poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed repeatedly with water and 5% aqueous NaOH solution until the washing appeared colorless. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid. It was used for next reaction without further purification. Yield: 5 g (66%); MP: 195-198°C.

Step 2: 1-Methyl-2-(4'-formylphenoxymethyl)benzimidazole

A solution of 2-(4'-formylphenoxymethyl)benzimidazole 3.6 g (14.3 mmol) in 20 mL of dry DMF was added to a mixture of 700 mg (17.4 mmol) of NaH in 10 mL of dry DMF. The mixture was stirred under nitrogen atmosphere at room temperature for 30 min. and 1.1 mL of methyl iodide (17.4 mmol) was added to the reaction mixture. The mixture was stirred under a nitrogen atmosphere for 6 hours at room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed with water to remove DMF. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid, which was recrystallized from ethyl acetate-hexane. Yield: 3 g (80%); MP 192-195°C.

Step 3: 1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium Tosylate

Methyl tosylate, 4.6 g (24 mmol), was added to a solution of 1-methyl-2-(4'-formylphenoxymethyl)benzimidazole 5.3 g (20 mmol), in 30 mL of acetonitrile. The reaction mixture was refluxed for 60 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 8.3 g (95%); MP: 185-200°C.

I-38-A (BL09471)

1,3-Dimethyl-N-(4'-formylphenoxymethyl)benzimidazolium N-(3,4,5,6-Tetrahydropyrimid-2-yl)hydrazone Dibromide

A mixture of 2 g (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium tosylate and 1.3 g (5.5 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol/ether. Yield: 1.8 g (75%); MP: 245-247°C.

Anal. calcd. for: $C_{21}H_{26}N_6Br_2O\cdot 1.5H_2O$
Calcd: C, 44.62; H, 5.16; N, 14.86; Br, 28.27
Found: C, 44.67; H, 5.20; N, 14.80; Br, 28.31

I-43-A (BL09480)

3-Methyl-4-(4'-formylphenoxymethyl)thiazolium N,N-Tetramethyleneguanylhydrazone Ditosylate.

Excess of pyrrolidine (6 mL) was added to a solution of 1.1 g (4 mmol) of S-methyl thiosemicarbazide tosylate in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.4 g (3.2 mmol) of 3-methyl-4-(4'-formylphenoxymethyl)thiazolium tosylate in 35 mL of 95% ethanol. The mixture was refluxed for 5 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The pale yellowish solid was recrystallized from ethanol-ether. Yield: 2 g (85%); MP: 190-192°C.

Anal. calcd. for: $C_{31}H_{37}N_5S_3O_7\cdot H_2O$
Calcd: C, 52.75; H, 5.56; N, 9.91; S, 13.62
Found: C, 52.88; H, 5.56, N, 9.90; S, 13.58

II-21A-VS (BL09499)

1-Methyl-2-formylimidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 2.5 g (7.5 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 2.2 g (9 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 30 mL of absolute ethanol was refluxed overnight. The solution was then acidified with conc. HBr, concentrated and cooled. The solid product obtained was filtered and recrystallized from ethanol and water. Yield: 2.90 g (87%); MP: 256-58°C (decomp).

Anal. calcd. for: $C_{13}H_{18}N_6Br_2\cdot 1.5H_2O$
Calcd: C, 35.08; H, 4.75; N, 18.87; Br, 35.92
Found: C, 35.26; H, 4.76; N, 18.87; Br, 36.02

I-50-A (BL10018)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium
N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 2 g (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium tosylate and 1.2 g (5.3 mmol) of 2-hydrazinoimidazoline hydroiodide in 50 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 2 g (80%); MP: 239-241°C.

Anal. calcd. for: $C_{20}H_{23}N_6Br_2O \cdot H_2O$
Calcd: C, 44.38; H, 4.61; N, 15.52; Br, 29.52
Found: C, 44.23; H, 4.83; N, 15.51; Br, 29.38

I-51-A (BL10027)

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium
N,N-Tetramethyleneguanylhydrazone Dibromide

Excess of pyrrolidine (6 mL) was added to a solution of 1 g (4.5 mmol) of S-methyl thiosemicarbazide hydroiodide in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.7 g (4.2 mmol) of 1-methyl-3-(4'-formylphenoxymethyl)pyridinium tosylate in 30 mL of ethanol. The mixture was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.5 g (70%); MP: 260-63°C.

Anal. calcd. for: $C_{19}H_{25}N_5Br_2O \cdot H_2O$
Calcd: C, 44.12; H, 5.26; N, 13.54; Br, 30.90
Found: C, 44.39; H, 5.18; N, 13.60; Br, 31.02

Sequence for Preparation of 1-Methyl-3-(4'-formylbenzyl)benzimidazolium Salts

Step 1: 1-(4'-Cyanobenzyl)benzimidazole

A solution of benzimidazole 4 g (33.8 mmol), in 20 mL of dry DMF was added to a suspension of 1.66 g (41.5 mmol) of NaH in 20 mL of dry DMF. The mixture was stirred for 30 minutes at room temperature under a N_2 atmosphere at room temperature. A solution of p-cyanobenzyl bromide 7.4 g (37.6 mmol) in 10 mL of dry DMF was added to the benzimidazole/NaH solution in DMF. The reaction mixture was warmed at 50°C for 2 hours, poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed repeatedly with water. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow oil, which solidified on standing. Yield: 6.8 g (85%).

Step 2: 1-(4'-Formylbenzyl)benzimidazole

1-(4'-Cyanobenzyl)benzimidazole 5.0 g (21 mmol) was dissolved in 75 mL of 75% formic acid and 5 g of Raney Ni alloy was added to this solution[8]. The reaction mixture was refluxed for 1.5 hour. The Raney Ni was filtered out and the filtrate was basified with NaOH solution to pH 9. This mixture was extracted with ethyl acetate. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid. The crude product was further purified by $NaHSO_3$ adduct formation to give the pure aldehyde. Yield: 3 g (60%).

Step 3: 1-(4'-Formylbenzyl)-3-methylbenzimidazolium Tosylate

Methyl tosylate 2.01 g (10.7 mmol) was added to a solution of 1-(4'-formylbenzyl)benzimidazole, 2.1 g (8.9 mmol), in 30 mL of acetonitrile. The reaction mixture was refluxed for 60 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 3.2 g (86%); MP: 160-180°C.

I-57-A (BL10036)

1-(4'-Formylbenzyl)-3-methylbenzimidazolium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.9 g (4.5 mmol) of 1-(4'-formylbenzyl)-3-methylbenzimidazolium tosylate and 1.20 g (5.2 mmol) of 2-hydrazimoimidazoline hydroiodide in 30 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr, stirred for 30 minutes and refrigerated. The solid obtained by filtration was recrystallized twice from ethanol containing a few drops of conc. HBr. Yield: 2.2 g (81 %); MP: 185-200°C.

Anal. calcd. for: $C_{19}H_{22}N_6Br_2 \cdot 2H_2O$
Calcd: C, 43.04; H, 4.94; N, 15.84; Br, 30.14
Found: C, 42.99; H, 4.96; N, 15.72; Br, 30.01

I-58-A (BL10045)

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium N-Hydroxyguanylhydrazone Dibromide

A mixture of 1.9 g (4.7 mmol) of 1-methyl-3-(4'-formylphenoxymethyl)pyridinium tosylate and 1.5 g (5.7 mmol) of N-hydroxy-N'-aminoguanidinium tosylate in 50 mL of ethanol was refluxed for 6 hours. Conc. HBr (9 mL) was then added and the mixture was stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 2.5 g (80%); MP:207-210°C.

Anal. calcd. for: $C_{29}H_{33}N_5S_2O_8 \cdot 0.5H_2O$
Calcd: C, 53.36; H, 5.25; N, 10.72; S, 9.82
Found: C, 53.38; H, 5.28; N, 10.69; S, 9.76

Sequence for Preparation of 1,5-Dimethyl-2-formylimidazo[1,2-a]pyridinium Salts

Step 1: Ethyl 5-Methylimidazo[1,2-a]pyridine-2-carboxylate

A solution of 10.8 g (0.1 mole) of 2-amino-6-methylpyridine and 19.5 g (0.1 mole) of ethyl bromopyruvate in 200 mL of absolute ethanol was refluxed for 5 hours and then evaporated in vacuo to dryness. The residue was dissolved in 10% aqueous HCl and the acid solution was carefully neutralized with a saturated solution of $NaHCO_3$ to pH 8, obtaining a precipitate which was collected and washed with water. After drying, the crude product was recrystallized from carbon tetrachloride to afford 12.3 g (61%) of colorless crystals. MP: 140-42°C.

Step 2: 2-Hydroxymethyl-5-methylimidazo[1,2-a]pyridine

Ethyl 5-methylimidazo[1,2-a]pyridine-2-carboxylate, 10.5 g (52 mmole) was dissolved in a minimum amount of anhydrous dichloromethane and 100 mL of anhydrous ether was added to the solution and the system was kept stirring under a nitrogen atmosphere. Lithium aluminum hydride, 1.98 g (52 mmole), was added in portions, over a period of an hour, maintaining a gentle reflux. After the addition of all of the LAH was complete, the reaction mixture was gently refluxed for an hour. The reaction mixture was cooled and treated with 2 mL of water, 2 mL of 15% NaOH solution and 6 mL of water in sequence and stirred for half hour. The precipitated lithium and aluminum salts were filtered off and thoroughly washed with hot ethyl acetate. The combined organic filtrates were evaporated and the solid obtained was recrystallized from ethyl acetate and hexane. Yield: 7.2 g (85%); MP: 142-44°C.

Step 3: 2-Formyl-5-methylimidazo[1,2-a]pyridine

2-Hydroxymethyl-5-methylimidazo[1,2-a]pyridine, 6.5 g (.04 mole), and 30 g of activated manganese dioxide were stirred in 200 mL of anhydrous chloroform at room temperature for 2 days. At the end of the reaction period, the reaction mixture was filtered off and the solvent was evaporated. The solid product obtained was recrystallized from carbon tetrachloride. Yield: 3.52 g (55%); MP: 118-120°C.

Step 4: 1,5-Dimethyl-2-formylimidazo[1,2-a]pyridinium Tosylate

This compound was prepared using the standard quaternization procedure using methyl p-toluenesulfonate. Yield: 82%

II-38-VS (BL10054)

1,5-Dimethyl-2-formylimidazo[1,2-a]pyridinium Guanylhydrazone Ditosylate.

A mixture of 1,5-dimethyl-2-formylimidazo[1,2-a]pyridinium tosylate (2.0 g, 5.8

mmol), 1.0 g (7.4 mmol) of aminoguanidine bicarbonate and 2.5 g (12.6 mmol) of p-toluenesulfonic acid monohydrate in 40 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled and the precipitated solid was recrystallized from ethanol and water. Yield: 3.3 g (97.8%); MP: 246°C.

Anal. calcd. for: $C_{25}H_{30}N_6S_2 \cdot 0.5H_2O$
Calcd: C, 51.44; H, 5.35; N, 14.40; S, 10.99
Found: C, 51.32; H, 5.40; N, 14.37; S, 10.93

II-39-VS (BL10063)

1,5-Dimethyl-2-formylimidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Ditosylate

A mixture of 2.0 g (5.8 mmol) of 1,5-dimethyl-2-formylimidazo[1,2-a]pyridinium tosylate and 2.3 g (7.6 mmol) of N,N-tetramethylene-N'-aminoguanidinium tosylate in 40 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled and the precipitated solid was recrystallized from ethanol and water. Yield: 3.45 g (92%); MP: 244-46°C.

Anal. calcd. for: $C_{29}H_{36}N_6O_6S_2 \cdot H_2O$
Calcd: C, 53.85; H, 5.92; N, 12.99; S, 9.92
Found: C, 53.74; H, 5.93; N, 12.96; S, 9.86

II-41-VS (BL10072)

1-Methyl-2-formylimidazo[1,2-a]pyridinium N-(4-Aminobenzoyl)hydrazone Tosylate

A mixture of 2.5 g (7.5 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 1.2 g (7.5 mmol) of p-aminobenzoylhydrazide in 30 mL of absolute ethanol was stirred under reflux overnight. The reaction mixture was cooled and the precipitated product was recrystallized from ethanol and water. Yield: 3.2 g (85%); MP: 240-42°C (decomp).

Anal. calcd. for: $C_{23}H_{23}N_5SO_4 \cdot 2H_2O$
Calcd: C, 55.08; H, 5.43; N, 13.96; S, 6.39
Found: C, 54.98; H, 5.46; N, 13.94; S, 6.40

I-49-A (BL11131)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium Guanylhydrazone Dibromide

A mixture of 2.0 g (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium tosylate and 0.6 g (4.6 mmol) of aminoguanidine bicarbonate in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of concentrated HBr and stirred. Addition of ether precipitated the product. The product was redissolved in ethanol, reacidified, and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.8 g (80% yield); MP 258-260°C.

Anal. calcd. for: $C_{18}H_{22}N_6Br_2O \cdot 1H_2O$
Calcd: C, 41.88; H, 4.7; N, 16.26; Br, 30.95
Found: C, 42.01; H, 4.7; N, 16.26; Br, 30.99

I-54-A (BL11140)

3-Methyl-4-(4'-formylphenoxymethyl)thiazolium N-(4-Aminobenzoyl)hydrazone Tosylate

A mixture of 1.6 g (4.0 mmol) of 3-methyl-4-(4'-formylphenoxymethyl)thiazolium tosylate and 0.76 g (5 mmol) of 4-aminobenzoylhydrazide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then diluted with ether to give a precipitate, which was filtered and recrystallized from ethanol-ether to give the final product. Yield: 1.5 g (70% yield); MP: 218-220°C dec.

Anal. Calcd. for: $C_{26}H_{26}N_4S_2O_5 \cdot 1.5H_2O$
Calcd: C, 55.21; H, 5.12; N, 9.9; S, 11.34
Found: C, 55.08; H, 5.20; N, 9.85; S, 11.28

I-62-A (BL11159)

1-(4'-Formylbenzyl)-3-methylbenzimidazolium
N-(3,4,5,6-Tetrahydropyrmid-2-yl)hydrazone Dibromide

A mixture of 1.9 g (4.5 mmol) of 1-(4'-formylbenzyl)-3-methylbenzimidazolium tosylate and 1.3 g (5.5 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol ether. Yield: 1.8 g (75% yield); MP: 230°C dec.

Anal. calcd. for: $C_{20}H_{24}N_6Br_2 \cdot 1.5H_2O$
Calcd: C, 44.14; H, 5.18; N, 15.43; Br. 29.36
Found: C, 44.48; H, 5.08; N, 15.49; Br, 29.49

I-67-A (BL11168)

1-(4'-Formylbenzyl)-3-methylbenzimidazolium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 1.9 g (4.4 mmol) of 1-(4'-formylbenzyl)-3-methylbenzimidazolium tosylate and 1.3 g (5 mmol) of N,N'-diethylaminoguanidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated the product. The product was redissolved in ethanol reacidified, and reprecipitated.

Finally it was recrystallized from ethanol-ether. Yield: 2.3 g (93%); MP: 150-158°C.

Anal. calcd. for: $C_{21}H_{28}N_6Br_2{\cdot}2H_2O$
Calcd: C, 45.0; H, 5.76; N, 15.0; Br, 28.52
Found: C, 45.05; H, 5.79; N, 14.95; Br, 28.45

II-39A-VS (BL11177)

1,5-Dimethyl-2-formylimidazo[1,2-a]pyridinium N-(3,4,5,6-Tetrahydropyrimid-2-yl)hydrazone Dibromide

A mixture of 2.0 g (5.8 mmol) of 1,5-dimethyl-2-formylimidazo[1,2-a]pyridinium tosylate and 1.9 g (7.8 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 30 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 2.2 g (83%); MP: 292-95°C (decomp).

Anal. Calcd. for: $C_4H_{20}N_6Br_2{\cdot}1.5H_2O$
Calcd: C, 36.62; H, 5.05; N, 18.30; Br, 34.81
Found: C, 36.64; H, 5.01; N, 18.26; Br, 34.74

I-44-VS (BL11186)

1-Methyl-2-formylimidazo[1,2-a]pyridinium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 2.2 g (6.0 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 1.5 g (6.5 mmol) of 2-hydrazinoimidazoline hydroiodide in 40 mL of absolute ethanol was refluxed overnight. The solution was then acidified with conc. HBr, concentrated and cooled. The solid product obtained was filtered and recrystallized from ethanol and water. Yield: 1.8 g (71%); MP: 284-86°C (decomp).

Anal. calcd. for: $C_{12}H_{16}N_6Br_2{\cdot}1H_2O$
Calcd: C, 34.14; H, 4.30; N, 19.91; Br, 37.86
Found: C, 33.93; H, 4.38; N, 19.84; Br, 37.77

II-49B-VS (BL11195)

1-Methyl-2-formylimidazo[1,2-a]pyridinium N,N-tetramethyleneguanylhydrazone Dibromide

A mixture of 2.0 g (6.0 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 2.3 g (7.6 mmol) of N,N-tetramethylene-N'-aminoguanidinium tosylate in 40 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 2.0 g (74%); MP: 282-84°C.

Anal. calcd. for: $C_{14}H_{20}N_6Br_2 \cdot 1.H_2O$
Calcd: C, 37.35; H, 4.93; N, 18.67; Br, 35.50
Found: C, 37.41; H, 4.93; N, 18.62; Br, 35.53

II-54-VS (BL11202)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N-(3,4,5,6-Tetrahydropyrimid-2-yl)hydrazone Dibromide

A mixture of 1.8 g (4.2 mmol) of 1-methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium tosylate and 1.1 g (4.6 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of absolute ethanol was stirred under reflux overnight. The solution was acidified with conc. HBr, and cooled. The precipitated product was filtered and recrystallized from ethanol and water. Yield: 1.8 g (78%); MP: 280-82°C.

Anal. calcd. for: $C_{21}H_{24}N_6Br_2 \cdot 1.5H_2O$
Calcd: C, 46.08; H, 4.97; N, 15.36; Br, 29.21
Found: C, 46.10; H, 5.01; N, 15.26; Br, 29.11

4-(4'-Formylphenoxymethyl)pyridine

p-Hydroxybenzaldehyde, 1.7 g (14 mmol) and powdered KOH, 0.85 g (13 mmol) were added to 25 mL of DMSO and the mixture was stirred for 1 hour. A solution of 4-picolylchloride hydrochloride, 1.0 g (6.0 mmol) in 4 mL of DMSO, was added to the alkaline solution of p-hydroxybenzaldehyde. The reaction mixture was stirred overnight at room temperature, poured into water and extracted with ethyl acetate. The extracts were combined and washed repeatedly with water and 5% aqueous NaOH solution until the washing was almost colorless. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid. It was decolorized and recrystallized from ethyl acetate/hexane. Yield: 8.3 3 (68%).

1-Methyl-4-(4'-formylphenoxymethyl)pyridinium Tosylate

Methyl tosylate (1.9 g, 10 mmol) was added to a solution of 4-(4'-formylphenoxymethyl)pyridine (1.7 g, 7.9 mmol) in 30 mL of acetonitrile. The reaction mixture was refluxed overnight. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 2.9 g (91% yield); MP: 155-165°C.

I-32-A (BL12110)

1-Methyl-4-(4'-formylphenoxymethyl)pyridinium Guanylhydrazone Ditosylate

A mixture of 2.0 g (4.9 mmol) of 1-methyl-4-(4'-formylphenoxymethyl)pyridinium tosylate, 0.75 g (5.5 mmol) of aminoguanidine bicarbonate, and 1.5 g (8.7 mmol) of p-toluenesulfonic acid was refluxed in 50 mL of 95% ethanol for 4 hours. On cooling, the product crystallized out. The solution was further diluted with ether and filtered. The pale yellowish solid was recrystallized from ethanol-ether. Yield: 2.0 g (62% yield); MP: 200°C dec.

Anal. calcd. for: $C_{29}H_{33}N_5S_2O_7 \cdot 1.5H_2O$
Calcd: C, 53.2; H, 5.54; N, 10.69; S, 9.79
Found: C, 53.48; H, 5.51; N, 10.92; S, 9.73

I-33-A (BL12129)

1-Methyl-4-(4'-formylphenoxymethyl)pyridinium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.9 g (4.7 mmol) of 1-methyl-4-(4'-formylphenoxymethyl)pyridinium tosylate and 1.1 g (5.0 mmol) of 2-hydrazinoimidazoline hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.6 g (70% yield); MP: 245-248°C.

Anal. calcd. for: $C_{17}H_{21}N_5OBr_2 \cdot 0.5H_2O$
Calcd: C, 42.43; H, 4.61; N, 14.56; Br, 33.24
Found: C, 42.48; H, 4.64; N, 14.56; Br, 33.22

I-60-A ((BL12138)

1-(4'-Formylbenzyl)-3-methylbenzimidazolium Guanylhydrazone Dibromide

A mixture of 1.9 g (4.5 mmol) of 1-(4'-formylbenzyl)-3-methylbenzimidazolium tosylate and 0.7 g (5.2 mmol) of aminoguanidine bicarbonate in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol ether. Yield: 2.3 g (98% yield); MP: 263-265°C.

Anal. calcd. for: $C_{17}H_{20}N_6Br_2 \cdot 2H_2O$
Calcd: C, 40.58; H, 4.79; M. 16.63; Br, 31.64
Found: C, 40.75; H, 4.75; N, 16.60; Br. 31.56

I-79-A (BL12146)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium
N,N-Tetramethyleneguanylghydrazone Ditosylate

Excess of pyrrolidine (6 mL) was added to a solution of 1.1 g (4 mmol) of S-methyl thiosemicarbazide tosylate in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.3 g (3.4 mmol) of

1,3-dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium tosylate in 35 mL of 95% ethanol. The mixture was refluxed for 5 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid was recrystallized from ethanol-ether. Yield: 1.8 g (70% yield); MP: 266-268°C.

Anal. calcd. for: $C_{36}H_{42}N_6S_2O_7 \cdot 0.5H_2O$
Calcd: C, 58.13; H, 5.82; N, 11.3; S, 8.62
Found: C, 58.16; H, 5.87; N, 11.3; S, 8.61

II-46-VS (BL12156)

1-Methyl-2-formylimidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 0.60 g (1.7 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 0.59 g (1.9 mmol) of N,N'-diethylaminoguanidine hydroiodide in 15 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 0.7 g (91%); MP: 255-57°C.

Anal. calcd. for: $C_{14}H_{22}N_6Br_2 \cdot 1H_2O$
Calcd: C, 37.18; H, 5.35; N, 18.58; Br, 35.34
Found: C, 37.33; H, 5.34; N, 18.61; Br, 35.40

II-57-VS (BL12165)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Ditosylate

A solution of 0.5 g (1.2 mmol) of 1-methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium tosylate and 0.4 g (1.3 mmol) of N,N-tetramethylene-N'-aminoguanidinium tosylate in 20 mL of absolute ethanol was stirred under reflux overnight. The reaction mixture was cooled and the precipitated solid was recrystallized from ethanol and water. Yield: 0.8 g (88%); MP: >300°C (decomp).

Anal. calcd. for: $C_{36}H_{40}N_6S_2O_6 \cdot 2H_2O$
Calcd: C, 57.42; H, 5.89; N, 11.16; S, 8.52
Found: C, 57.26; H, 5.93; N, 11.08; S, 8.45

II-78-VS (BL12174)

bis-1-Methyl-2-formylimidazo[1,2-a]pyridinium 1,4-Benzenedicarbonylhydrazone Ditosylate

A mixture of 2.0 g (6.0 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 0.60 g (3.0 mmol) of terephthalic acid hydrazide in 40 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled;

the product was filtered and recrystallized from aqueous dimethylformamide. Yield: 1.8 g(70%); MP: >300°C.

Anal. calcd. for: $C_{40}H_{38}N_8S_2O_8 \cdot 2H_2O$
Calcd: C, 55.93; H, 4.93; N, 13.04; S, 7.47
Found: C, 56.10; H, 4.87; N, 13.22; S, 7.43

Sequence for the Preparation of 1-Methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium Salts

Step 1: 2-Chloromethyl-6-trifluoromethylimidazo[1,2-a]pyridine

A mixture of 2.5 g (15 mmol) of 2-amino-5-trifluoromethylpyridine and 2.0 g (16 mmol) of 1,3-dichloroacetone was stirred under reflux in 40 mL of acetone overnight. The precipitated solid was dissolved in 30 mL of 5% aqueous HCl and refluxed for 2 hours. The reaction mixture was cooled and basified with saturated sodium bicarbonate solution. The precipitated product was filtered, dried and recrystallized from ethyl acetate and hexane. Yield: 1.9 g (55%).

Step 2:

6-Trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridine

p-Hydroxybenzaldehyde, 4.1 g (34 mmol) and powdered KOH, 2.5 g (38 mmol) were added to 30 mL of DMSO and the mixture was stirred for 1 hour. A solution of 4.0 g (17 mmol) of 6-trifluoromethyl-2-chloromethy-imidazo[1,2-a]pyridine in 20 mL of DMSO was added and the reaction mixture was stirred overnight at room temperature, poured into water (200 mL) and the aqueous solution of the reaction mixture was extracted with ethyl acetate. The extracts were combined and washed repeatedly with water, and 5% NaOH solution until the washing appeared colorless. The ethyl acetate layer was washed with satured sodium chloride solution, dried over anhydrous sodium sulfate and evaporated under vacuum to give the roduct. The product was recrystallized from ethyl acetate and hexane. Yield: 4.0 g (74%); MP: 166-68°C.

Step 3:

1-Methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate

The quaternization of the aldehyde was done following the usual procedure using methyl-p-toluenesulfonate in acetonitrite. Yield: 87%; MP: 218-20°C.

II-79-VS (BL12183)

1-Methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium Guanylhydrazone Ditosylate

A mixture of 1.8 g (3.6 mmol) of 1-methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate, 0.60 g (4.4 mmol) of aminoguanidine bicarbonate and 1.3 g (7.0 mmol) of p-toluenesulfonic acid monohydrate in 40 mL of absolute ethanol was refluxed overnight, cooled and the precipitated product was filtered and recrystallized from ethanol and water. Yield: 2.1 g (78%); MP: 228-30°C.

Anal. calcd. for: $C_{32}H_{33}N_6O_7F_3S_2 \cdot 0.5H_2O$
Calcd: C, 51.54; H, 4.48; N, 11.31; S, 8.63
Found: C, 51,72; H, 4.62; N, 11.27; S, 8.58

II-22C-VS (BL12718)

1-Methyl-2-formylimidazo[1,2-a]pyridinium N-Hydroxyguanylhydrazone Dibromide

A mixture of 2.5 g (7.5 mmol) of 1-methyl-2-formylimidazo[1,2-a]pyridinium tosylate and 2.4 g (9.2 mmol) of N-hydroxy-N'-aminoguanidinium tosylate in 40 mL of absolute ethanol was stirred under reflux overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 2.2 g (70%); MP: 236-38°C.

Anal. calcd. for: $C_{10}H_{14}N_6Br_2O \cdot 1H_2O$
Calcd: C, 29.15; H, 3.91; N, 20.39; Br, 38.78
Found: C, 30.13; H, 3.89; N, 20.23; Br, 38.30

I-87-A (BL12727)

1-Methyl-4-(4'-formylphenoxymethyl)pyridinium N,N-Tetramethyleneguanylhydrazone Ditosylate

Excess pyrrolidine (6 mL) was added to a solution of 1.1 g (4 mmol) of S-methyl thiosemicarbazide tosylate in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.3 g (3.2 mmol) of 1-methyl-4-(4'-formylphenoxymethyl)pyridinium tosylate in 35 mL of 95% ethanol. The mixture was refluxed for 5 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The pale yellowish solid was recrystallized from ethanol-ether. Yield: 1.8 g (78% yield); MP: 225-232°C.

Anal. Calcd. for: $C_{33}H_{39}N_5S_2O_7 \cdot 1.5H_2O$
Calcd: C, 55.92; H, 5.96; N, 9.87; S, 9.05
Found: C, 55.88, H, 5.96; N, 9.82; S, 8.97

II-94-V (BL12736)

1,5-Dimethyl-2-formylimidazo[1,2-a]pyridinium N-Hydroxyguanylhydrazone Ditosylate

A mixture of 2.5 g (7.3 mmol) of 1,5-dimethyl-2-formylimidazo[1,2-a]-

pyridinium tosylate and 1.9 g (7.3 mmol) of N-hydroxy-N'-aminoguanidinium tosylate was refluxed in 40 mL of absolute ethanol overnight. The reaction mixture was cooled, concentrated and ether was added. The precipitated product was filtered and recrystallized from ethanol. Yield: 2.8 g (64%); MP: 225-27°C.

Anal. Calcd. for: $C_{25}H_{30}N_6S_2O_7$
Calcd: C, 50.83; H, 5.12; N, 14.23; S, 10.86
Found: C, 50.74; H, 5.12; N, 14.45; S, 10.99

I-86-A (BL12745)

1-Methyl-4-(4'-formylphenoxymethyl)pyridinium 3,4,5,6-Tetrahydropyrimidyl-2-hydrazone Dibromide

A mixture of 1.7 g (4.2 mmol) of 1-methyl-4-(4'-formylphenoxymethyl)-pyridinium tosylate and 1.1 g (4.6 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 9 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (80% yield); MP: 260-265°C.

Anal. calcd. for: $C_{18}H_{23}N_5Br_2O \cdot 1.5H_2O$
Calcd: C, 42.2; H, 5.1; N, 13.7; Br. 31.2
Found: C, 42.36; H, 5.1; N, 13.65; Br, 31.26

II-80A-VS (BL12754)

1-Methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 1.6 g (3.2 mmol) of 1-methyl-6-trifluoromethyl-2-4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.9 g (3.7 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 30 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized twice from ethanol and water. Yield: 1.7 g (84%); MP: 258-62°C.

Anal. calcd. for: $C_{21}H_{23}N_6F_3Br_2O \cdot 2H_2O$
Calcd: C, 39.95; H, 4.31; N, 13.31; Br, 25.32
Found: C, 39.97; H, 4.46; N, 13.25; Br, 25.21

II-95-VS (BL12763)

1,6-Dimethyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium N-Ethylguanylhydrazone Dibromide

A mixture of 3.0 g (7.1 mmol) of 1,6-dimethyl-2-(4'-formylphenyl)imidazo-1,2-a]pyridinium tosylate and 2.0 g (7.3 mmol) of N-ethyl-N'-aminoguanidinium iodide in 40 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 2.0 g (55%); MP: 238-40°C.

Anal. calcd. for: $C_{19}H_{24}N_6Br_2 \cdot 1H_2O$
Calcd: C, 44.37; H, 5.10; N, 16.34; Br, 31.07
Found: C, 44.53; H, 5.10; N, 16.37; Br, 31.15

I-61-A (BL12772)

1-(4'-Formylbenzyl)-3-methylbenzimidazolium
N,N-Tetramethyleneguanylhydrazone Dibromide

Excess of pyrrolidine (6 mL) was added to a solution of 1.1 g (4 mmol) of S-methyl thiosemicarbazide tosylate in 30 mL of ethanol. The mixture was refluxed for 24 hour. The solvent was removed and the residue was washed 6 times with ether. The solid was then mixed with 1.4 g (3.3 mmol) of 1-(4'-formylbenzyl)-3-methylbenzimidazolium tosylate in 35 mL of ethanol and the mixture was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred for 3 hours. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.8 g (96% yield); MP 263-265°C.

Anal. calcd. for: $C_{21}H_{26}N_6Br_2 \cdot 2H_2O$
Calcd: C, 45.18; H, 5.4; N, 15.04; Br, 28.62
Found: C, 45.09; H, 5.5; N, 14.93; Br, 28.57

I-90-A (BL18514)

1-Methyl-4-(4'-formylphenoxymethyl)pyridinium N-(4-Aminobenzoyl)hydrazone Tosylate

A mixture of 2.0 g (4.9 mmol) of 1-methyl-4-(4'-formylphenoxymethyl)-pyridinium tosylate and 770 mg (5.1 mmol) of 4-aminobenzoylhydrazide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then diluted with ether to give a precipitate, which was filtered and recrystallized from ethanol-ether to give the final product. Yield: 2.3 g (89%); MP: 260-265°C.

Anal. calcd. for: $C_{28}H_{28}N_4SO_5$
Calcd: C, 63.14; H, 5.30; N, 10.51; S, 6.02
Found: C, 63.14; H, 5.34; N, 10.51, S, 5.98

I-92-A (BL18532)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium
N,N'-Diethylguanylhydrazone Dibromide

A mixture of 2.0 (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium tosylate and 1.3 g (5 mmol) of N,N'-diethylaminoguanidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of concentrated HBr and stirred at room temperature for 2 hours. Addition of ether precipitated out the product. The product was redissolved in ethanol reacidified, and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.6 g (65%); MP: 215-217°C.

Anal. calcd. for: $C_{22}H_{30}N_6Br_2O{\cdot}1H_2O$
Calcd: C, 46.17; H, 5.63; N, 14.70; Br, 27.92
Found: C, 46.08; H, 5.65; N, 14.65; Br, 27.85

II-99-VS (BL18532)

1-Methyl-2-[4'-(3-oxopropenyl)phenyl]imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

A mixture of 0.8 g (1.8 mmol) of 1-methyl-2-[4'-(3-oxopropenyl)-phenyl]-imidazo[1,2-a]pyridinium tosylate and 0.6 g (1.8 mmol) of N,N-tetramethylene-N'-aminoguanidinium tosylate in 20 mL of absolute ethanol was refluxed for 5 hours. The resulting solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.9 g (90%); MP: 265-67°C.

Anal. calcd. for: $C_{22}H_{26}N_6Br_2{\cdot}1H_2O$
Calcd: C, 47.84; H, 5.11; N, 15.22; Br, 28.94
Found: C, 47.91; H, 5.16; N, 15.25; Br, 28.87

Sequence for the Preparation and Methylation of 5-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridine

Step 1: 2-Chloromethyl-5-methylimidazo[1,2-a]pyridine

A mixture of 5.0 g (46 mmol) of 2-amino-6-picoline and 5.9 g (46 mmol) of 1,3-dichloroacetone in 150 mL of reagent grade acetone was refluxed for 6 hours. The reaction mixture was cooled and the precipitated solid obtained was collected, redissolved in water, acidified with dilute HCl and refluxed for an hour. The solution was cooled and basified with saturated $NaHCO_3$ solution. The precipitated solid was collected, dried and recrystallized from ethanol. Yield: 7.1 g (86%); MP: 132-5°C.

Step 2: 5-Methyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridine

p-Hydroxybenzaldehyde 2.7 g (22 mmol) and powdered KOH, 1.5 g (24 mmol) were added to 30 mL of DMSO and the mixture was stirred for 1 hour. A solution of 2-chloromethyl-5-methylimidazo[1,2-a]pyridine 2.0 g (11 mmol) in 10 mL of DMSO was added to the alkaline solution of p-hydroxybenzaldehyde. The reaction mixture was stirred overnight at room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed repeatedly with water, and 5% NaOH solution until the washings were colorless. The ethyl acetate layer was shaken with brine, dried over anhydrous sodium sulfate and evaporated under vacuum to give the product. The product was recrystallized from ethyl acetate-hexane. Yield: 2.2 g (75%); MP: 102-4°C.

Anal. calcd. for: $C_{16}H_{14}N_2O_2$
Calcd: C, 72.15; H, 5.30; N, 10.52
Found: C, 71.86; H, 5.37; N, 10.43

Step 3: 1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium Tosylate

The quaternization of the aldehyde was done using methyl p-toluenesulfonate in acetonitrile under standard conditions. Yield: 90%; MP: 228-30°C.

III-15-VS (BL18541)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

A solution of 0.35 g (1.2 mmol) of N,N-tetramethylene-N'-aminoguanidinium tosylate in 20 mL of absolute ethanol was refluxed 5 hours with 0.5 g (1.1 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate. The reaction solution was acidified with 2 mL of conc. HBr and stirred for an hour. The precipitated product was collected and recrystallized from ethanol and water. Yield: 0.5 g (86%); MP: 264-66°C.

Anal. calcd. for: $C_{22}H_{28}N_6Br_2O \cdot 2H_2O$
Calcd: C, 44.91; H, 5.48; N, 14.28; Br, 27.16
Found: C, 44.69; H, 5.51; N, 14.24; Br, 27.22

III-18-VS (BL18550)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 0.26 g (0.58 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.15 g (0.60 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 20 mL of ethanol was refluxed for 5 hours. The solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.6 g (90%); MP: 268-70°C.

Anal. calcd. for: $C_{21}H_{26}N_6Br_2O \cdot 2.5H_2O$
Calcd: C, 43.24; H, 5.36; N, 14.41; Br, 27.40
Found: C, 43.27; H, 5.35; N, 14.41; Br, 27.36

III-19-VS (BL18569)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N-Hydroxyguanylhydrazone Dibromide

A mixture of 0.25 g (0.55 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.16 g (0.59 mmol) of N-hydroxy-N'-aminoguanidinium tosylate in 15 mL of absolute ethanol was refluxed for 5 hours. The hot solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.24 g (81%); MP: 230-32°C.

Anal. calcd. for: $C_{18}H_{22}N_6Br_2O_2 \cdot 1H_2O$
Calcd: C, 40.62; H, 4.55; N, 15.79; Br, 30.03
Found: C, 40.42; H, 4.60; N, 15.74; Br, 30.01

III-11B-VS (BK40673)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium Guanylhydrazone Dibromide

A mixture of 0.5 g (1.1 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate, 0.15 g (1.1 mmol) of aminoguanidine bicarbonate and 0.25 g (1.3 mmol) of p-toluenesulfonic acid monohydrate in 15 mL of absolute ethanol was stirred under reflux for 5 hours. The resulting solution was acidified with 2 mL of conc HBr and stirred for an hour. After cooling the precipitate was collected and recrystallized from ethanol and water. Yield: 0.47 g (83%); MP: 262-65°C.

Anal. calcd. for: $C_{18}H_{22}N_6Br_2O \cdot 1H_2O$
Calcd: C, 41.88; H, 4.69; N, 16.28; Br, 30.96
Found: C, 42.04; H, 4.73; N, 16.26; Br, 30.87

III-25-VS (BK40664)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 0.5 g (1.1 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.35 g (1.5 mmol) of 2-hydrazinoimidazoline hydroiodide in 15 mL of absolute ethanol was refluxed for 5 hours. The solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.48 g (80%); MP 260-62°C.

Anal. calcd. for: $C_{20}H_{24}N_6Br_2O \cdot 1.5H_2O$
Calcd: C, 43.57; H, 4.94; N, 15.24; Br, 28.99
Found: C, 43.67; H, 4.99; N, 15.18; Br, 28.88

Sequence for Preparation and Methylation of 5-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridine

Step 1: Preparation of 2-(4'-Cyanophenylethenyl)-5-methylimidazo[1,2-a]pyridine

Diethyl 4-cyanobenzylphosphonate, 16 g (63 mmol) and 2.8 g (70 mmol) of NaH were stirred in 100 mL of dry dimethoxyethane in a N_2 atmosphere and 9 g (56 mmol) of 5-methyl-2-formylimidazo[1,2-a]pyridine in 50 mL of dimethoxyethane was added slowly using an addition funnel. The reaction mixture was gradually heated to 85°C in an oil bath and was maintained at that temperature for an hour. The reaction mixture was cooled and poured into excess water. The precipitated solid was filtered, dried and recrystallized from ethanol. Yield: 11 g (75%); MP: 295-98°C.

Step 2: 5-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridine

The nitrile prepared in Step 1 (5 g, 19 mmol) was suspended in 50 mL of anhydrous toluene in a nitrogen atmosphere, and 12 mL of diisobutylaluminum hydride (1.5 M solution) was syringed in. The reaction mixture was stirred overnight at room temerature, a few mL (~5 mL) of methanol was added carefully, followed by 10% H_2SO_4 (25 mL). The precipitated solid was filtered, redissolved in warm water and basified with 10% NaOH solution. The precipitated aldehyde was dissolved in hot ethanol, treated with saturated $NaHSO_3$ and the bisulfite adduct was collected. The bisulfite adduct was suspended in water and basified with NaOH. The precipitated aldehyde was filtered and dried. Yield: 4 g (81%); MP: 210-12°C.

Step 3: 1,5-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium Tosylate

The quaternization of the aldehyde was done following the standard procedure by using methyl p-toluenesulfonate in acetonitrile. Yield: 4.5 g (87%); MP: 245-48°C.

III-27-VS (BK40655)

1,5-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium Guanylhydrazone Ditosylate

A mixture of 0.5 g (1.1 mmol) of aminoguanidine bicarbonate and 0.25 g (1.3 mmol) of p-toluenesulfonic acid monohydrate in 15 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.9 g (83%); MP: 258-60°C.

Anal. calcd. for: $C_{33}H_{36}N_6S_2O_6 1.5H_2O$
Calcd: C, 56.31; H, 5.58; N, 11.94; S, 9.11
Found: C, 56.94; H, 5.56; N, 12.05; S, 9.19

I-91-A (BK40726)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium N-(4-Aminobenzoyl)-hydrazone tosylate

A mixture of 2.0 g (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium tosylate and 0.76 g (5 mmol) of 4-aminobenzoylhydrazide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then diluted with ether to give a precipitate, which was filtered and recrystallized from ethanol-ether to give a final product. Yield: 2.2 g (85%), MP: 255-259°C.

Anal. calcd. for: $C_{31}H_{31}N_5SO_5$
Calcd: C, 63.57; H, 5.33; N, 11.95; S, 5.5
Found: C, 63.08; H, 5.40; N, 11.87; S, 5.41

Sequence for Preparation of 1-(ω-Aminoalkyl)-4-Nitroimidazolium Salts

4-Nitroimidazole

Imidazole (8.0 g) were dissolved in 16 mL of conc. nitric acid, cooled to 0°C, and 16 mL of sulfuric acid cautiously added. A vigorous reaction ensued and when this had subsided the mixture was boiled gently for 2 hours, allowed to cool, and then poured into ice water, when 7.00 g of 4-nitroiomidazole separated. The mother liquors yielded a further 400 mg of 4-nitroimidazole. Yield: 7.4 g (56%); MP: 311-313°C.

Sodium Salt of 4-nitroimidazole(8)

4-Nitroimidazole (11.3 g, 100 mmol) was added to 16.7 mL of 20% NaOH solution. The reaction mixture was warmed to give a bright yellow colored homogeneous solution. Upon cooling, the product was obtained as a yellow precipitate. The solid was filtered, washed with 95% ethanol and dried. Yield: 6.8 g (50%).

1-(2-Phthalamidoethyl)-4-nitroimidazole

Sodium salt of 4-nitroimidazole 3.37 g (25 mmol) and 6.35 g (25 mmol) of N-(2-bromoethyl)phthalimide was added to 15 mL of DMF. The mixture was heated at 100°C for 2 hours (until all the starting materials were consumed) and poured into 60 mL of ice cold water. The product which precipitated as a white solid was filtered and dried. Yield: 5.8 g (85%).

1-(3-Phthalimidopropyl)-4-nitroimidazole

Sodium salt of 4-nitroimidazole 3.37 g (25 mmol) and 6.7 g (25 mmol) of N-(3-bromopropyl)phthalimide was added to 15 mL of DMF. The mixture was heated at 100°C for 2 hours (until all the starting materials were consumed) and poured into 60 mL of ice cold water. The product which precipitated as a white solid was filtered and dried. Yield: 6.4 g (88%).

1-(4-Phthalimidobutyl)-4-nitroimidazole

Sodium salt of 4-nitroimidazole 3.37 g (25 mmol) and 7.0 g (25 mmol) of N-(4-bromobutyl)phthalimide was added to 15 mL of DMF. The mixture was heated at 100°C for 2 hours (until all the starting materials were consumed) and poured into 60 mL of ice cold water. The product which precipitated as a white solid was filtered and dried. Yield: 6.9 g (91%).

II-10-A (BK40691)

1-(2-Phthalimidoethyl)-4-nitroiomidazole 6.9 g (25 mmol) and 1.2 g (25 mmol) of hydrazine hydrate was added to 80 mL of 95% ethyl alcohol. The reaction mixture was refluxed overnight and the alcohol was evaporated under vacuum. Conc HCl (30 mL of 6 N) was added to the residue and phthalhydrazide was separated by filtration. The acidic filtrate was evaporated to dryness to give the product as a white solid, which was recrystallized from 95% ethyl alcohol. Yield: 2.9 g (60%); MP: 240-243°C.

Anal. calcd. for: $C_5H_9N_4ClO_2$
Calcd: C, 31.16; H, 4.71; N, 29.08; Cl, 18.41
Found: C, 31.25; H, 4.72; N, 29.02; Cl, 18.36

I-97-A (BK40717)

1-(3-Aminopropyl)-4-nitroiomidazole Hydrochloride

1-(3-Phthalimidopropyl)-4-nitroimidazole 7.25 g (25 mmol) and 1.2 g (25 mmol) of hydrazine monohydrate was added to 80 mL of 95% ethyl alcohol. The reaction mixture was refluxed overnight and the alcohol was evaporated. Conc hydrochloric acid (30 mL, 6 N) was added to the residue and phthalhydrazide was separated by filtration. The acidic filtrate was evaporated to dryness to give the product as a white solid, which was recrystallized from 95% ethyl alcohol. Yield: 5.1 g (71%); MP: 225-230°C.

Anal. calcd. for: $C_6H_{11}N_4ClO_2$
Calcd: C, 34.85; H, 5.37; N, 27.10; Cl, 17.16
Found: C, 34.90; H, 5.39; N, 27.05; Cl, 17.07

II-6-A (BK40708)

1-(4-Phthalimidobutyl)-4-nitroimidazole 7.6 g (25 mmol) and 1.2 g (25 mmol) of hydrazine monohydrate was added to 80 mL of 95% ethyl alcohol. The reaction mixture was refluxed overnight and the alcohol was evaporated. Conc hydrochloric acid (30 mL, 6 N) was added to the residue and phthalhydrazide was separated by filtration. The acidic filtrate was evaporated to dryness to give the product as a white solid, which was recrystallized from 95% ethyl alcohol. Yield: 2.7 g (50%); MP: 155-165°C.

Anal. calcd. for: $C_7H_{13}N_4ClO_2$
Calcd: C, 38.09; H, 5.93; N, 25.40; Cl, 16.06
Found: C, 38.12; H, 5.96; N, 25.31; Cl, 16.01

II-69D-VS (BK40682)

bis-1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 2,3-Dihydroxy-1,4-benzenedicarboxylhydrazone Dibromide

A mixture of 2.5 g (6.13 mmol) of 1-methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium tosylate and 0.69 g (3.06 mmol) of 2,3-dihydroxybenzene-1,4-dicarboxylhydrazide in 15 mL of absolute ethanol was refluxed overnight. The reaction mixture was acidified with conc HBr, cooled and the precipitated product was recrystallized from aqueous dimethylsulfoxide. Yield: 2.1 g (80%); MP: >300°C (decomp).

Anal. calcd. for: $C_{38}H_{32}N_8Br_2O_4 \cdot 1.5H_2O$
Calcd: C, 53.59; H, 4.14; N, 13.16; Br, 18.77
Found: C, 53.48; H, 4.19; N, 13.12; Br, 18.67

II-15-A (BL19771)

1-(4'-Formylbenzyl)-3-methylbenzimidazolium N-Ethylguanylhydrazone Dibromide

A mixture of 1.9 g (4.5 mmol) of 1-(4'-formylbenzyl)-3-methylbenzimidazolium tosylate and 1.4 g (5mmol) of N-ethyl-N'-aminoguanidium tosylate in 30 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 1.8 g (78%); MP: 190-200°C.

Anal. calcd. for: $C_{19}H_{24}N_6Br_2 \cdot H_2O$
Calcd: C, 44.38; H, 5.09; N, 16.33; Br, 31.07
Found: C, 44.31; H, 5.14; N, 16.28; Br, 31.12

II-16-A (BL19780)

1,3-Dimethyl-N-(4'-Formylphenoxymethyl)benzimidazolium
N-Ethylguanylhydrazone Ditosylate

A mixture of 2.0 g (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium tosylate and 1.4 g (5 mmol) of N-ethyl-N'-aminoguanidinium tosylate was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 1.9 g (60%); MP: 193-195°C.

Anal. calcd. for: $C_{34}H_{40}N_6S_2O_7 \cdot H_2O$
Calcd: C, 56.18; H, 5.82; N, 11.55; S, 8.82
Found: C, 56.13; H, 5.84; N, 11.50; S, 8.76

II-17-A (BL19799)

1-Methyl-3-(4'-formylphenoxymethyl)pyridinium N-Ethylguanylhydrazone Dibromide

A mixture of 1.8 g (4.4 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate and 1.4 g (5 mmol) of N-ethyl-N'-aminoguanidinium tosylate in 25 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 1.4 g (62%); MP: 212-215°C.

Anal. calcd. for: $C_{17}N_{23}Br_2O \cdot 0.5H_2O$
Calcd: C, 42.34; H, 5.01; N, 14.50; Br, 33.14
Found: C, 42.24; H, 5.12; N, 14.48; Br, 33.06

III-28-VS (BL19806)

1,5-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 0.5 g (1.2 mmol) of 1,5-Dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.25 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 20 mL of absolute ethanol was refluxed for 6 hours. The mixture was then acidified with 2 mL of conc. HBr and stirred at room temperature for 2 hours. The precipitated product was recrystallized from ethanol and water. Yield: 0.5 g (83%); MP: >300°C.

Anal. calcd. for: $C_{22}H_{26}N_6Br_2 \cdot 2H_2O$
Calcd: C, 46.33; H, 5.30; N, 14.73; Br, 28.02
Found: C, 46.29; H, 5.34; N, 14.74; Br, 28.07

III-32-VS (BL19815)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 0.5 g (1.1 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)-imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.2 mmol) of N,N'-diethylaminoguanidine hydroiodide in 15 mL of absolute ethanol was refluxed for 5 hours. The reaction mixture was acidified with conc. HBr and stirred for an hour. After cooling, the precipitate was collected and recrystallized from ethanol and water. Yield: 0.6 g (92%); MP: 240-242°C.

Anal. calcd. for: $C_{22}H_{30}N_6Br_2O \cdot 2.5H_2O$
Calcd: C, 44.08; H, 5.88; N, 14.02; Br, 26.66
Found: C, 44.03; H, 5.87; N, 14.01; Br, 26.65

III-33-VS (BL19824)

1-Methyl-2-(4'-formylphenylethenyl)midazo[1,2-a]pyridinium N-(2-Imidazolinyl) hydrazone Dibromide

A mixture of 0.5 g (1.2 mmol) of 1-methyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.3 mmol) of 2-hydrazinoimidazoline hydroiodide in 15 mL of absolute ethanol was refluxed for 5 hours. The reaction mixture was cooled, acidified with conc. HBr, and the precipitated product was recrystallized from ethanol and water. Yield: 0.45 g (68%); MP: >300°C.

Anal. calcd. for: $C_{20}H_{22}N_6Br_2 \cdot 2.5H_2O$
Calcd: C, 43.57; H, 4.93; N, 15.24; Br, 28.99
Found: C, 43.71; H, 4.76; N, 15.22; Br, 29.00

II-18-A (BL20658)

1-Methyl-2-(4'-formylphenoxymethyl)pyridinium N-Ethylguanylhydrazone Dibromide

A mixture of 1.8 g (4.4 mmol) of 1-methyl-2-(4'-formylphenoxymethyl)pyridinium tosylate and 1.4 g (5 mmol) of N-ethyl-N'-aminoguanidinium tosylate in 30 mL of absolute ethanol was refluxed overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 1.6 g (75%); MP: 225-230°C.

Anal. calcd. for: $C_{17}H_{23}N_5Br_2O \cdot 0.5H_2O$
Calcd: C, 42.34; H, 5.01; N, 14.50; Br, 33.14
Found: C, 42.45; H, 5.01; N, 14.50; Br, 33.19

II-19-A (BL20667)

Bis-2-(4-nitroimidazol-1-yl)ethyl ether

The sodium salt of 4-nitroimidazole(8) (3.37 g, 25 mmol) and 1.4 mL (12 mmol) of bis-2-chloroethyl ether were added to 15 mL of DMF. The mixture was heated at 100°C for 3 hours and poured into 60 mL of ice cold water. The product, which precipitated as light brown solid, was filtered and crystallized from an ethanol-DMF mixture. Yield: 2.1 g (60%); MP: 178-180°C.

Anal. calcd. for: $C_{10}H_{12}N_6O_5$
Calcd: C, 40.55; H, 4.08; N, 28.36
Found: C, 40.50; H, 4.10; N, 28.34

II-20-A (BL20676)

4,4'-Dinitro-1,1'-(1,3-propanediyl)-bis-imidazole

The sodium salt of 4-nitroimidazole(8) (3.37 g, 25 mmol) and 1.13 mL (12 mmol) of 1,3 dibromopropane were added to 10 mL of DMF. The mixture was refluxed at 100°C for 4 hours and poured into 60 mL of ice cold water. The product, which precipitated as light brown solid, was filtered and crystallized from ethanol-DMF mixture. Yield: 2.0 g (65%); MP: 235-240°C.

Anal. calcd. for: $C_9H_{10}N_6O_4$
Calcd: C, 40.61; H, 3.78; N, 31.55
Found: C, 40.50; H, 3.80; N, 31.44

III-31A-VS (BL20685)

1,5-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium
N,N-Tetramethyleneguanylhydrazone Dibromide

A mixture of 0.45 g (10 mmol) of 1,5-dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.3 g (10 mmol) of N,N-tetramethylene-N'-aminoguanidine tosylate in 20 mL of absolute ethanol was refluxed for 5 hours. The resulting solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.48 g (85%); MP: >300°C.

Anal. calcd. for: $C_{23}H_{48}N_6Br_2\cdot 1H_2O$
Calcd: C, 48.77; H, 5.34; N, 14.84; Br, 28.22
Found: C, 48.50; H, 5.29; N, 14.60; Br, 28.32

III-37-VS (BL20694)

1,5-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium
N-(4-Aminobenzoyl)hydrazone Tosylate

A mixture of 1.0 g (2.4 mmol) of 1,5-dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.37 g (2.5 mmol) of 4-aminobenzoylhydrazide in 20 mL of absolute ethanol was stirred for 5 hours under reflux. The reaction mixture was cooled and the precipitated product was filtered, dried and recrystallized from ethanol and water. Yield: 1.36 g (92%); MP: 282-285°C.

Anal. calcd. for: $C_{32}H_{31}N_5O_4S\cdot 2H_2O$
Calcd: C, 62.22; H, 5.74; N, 11.32; S, 5.17
Found: C, 61.97; H, 5.71; N, 11.34; S, 5.19

III-38-VS (BL20701)

<u>bis</u>-1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium
1,4-Benzenedicarbonylhydrazone Ditosylate

A mixture of 1.0 g (2.4 mmol) of 1-methyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.23 g (1.2 mmol) of terephthaloyl hydrazide in 20 mL of absolute ethanol was refluxed overnight. The precipitated product was filtered, dried and recrystallized from ethanol and water. Yield: 1.9 g (75%); MP: >300 °C.

Anal. calcd. for: $C_{56}H_{50}N_8S_2O \cdot 2.5H_2O$
Calcd: C, 62.73; H, 4.99; N, 10.45; S, 5.98
Found: C, 62.80; H, 5.26; N, 10.26; S, 6.02

III-41-VS (BL20710)

1,5-Dimethyl-2-(4'-formylphenylethenylimidazo[1,2-a]pyridinium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.0 g (2.4 mmol) of 1,5-dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.6 g (2.6 mmol) of 2-hydrazinoimidazoline hydroiodide in 15 mL of absolute ethanol was refluxed for 5 hours. The solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 1.1 g (84%); MP: >300°C.

Anal. calcd. for: $C_{21}H_{24}N_6Br_2 \cdot 1.5H_2O$
Calcd: C, 46.08; H, 4.97; N, 15.36; Br, 29.20
Found: C, 45.93; H, 4.99; N, 15.31; Br, 29.10

III-35C-VS (BL21548)

<u>bis</u>-1-Methyl-2-(4'-formylphenyl)imidazo[1,2-a]pyridinium 1,4-(2,5-Dihyroxybenzenedicarbonyl)hydrazone Dibromide

A mixture of 1.5 g (4 mmol) of 1-methyl-2-(4'-formylphenyl)-imidazo[1,2-a]pyridinium tosylate and 0.45 g (2 mmol) of 2,5-dihydroxybenzene-1,4-dicarbonylhydrazide in 20 mL of absolute ethanol was refluxed overnight. The reaction mixture was acidified with conc. HBr, cooled and the precipitated product was recrystallized from aqueous dimethylsulfoxide. Yield: 3.1 g (88%); MP: >300°C.

Anal. calcd. for: $C_{38}H_{32}N_8Br_2O_4 \cdot 3H_2O$
Calcd: C, 51.94; H, 4.36; N, 12.75; Br. 18.19
Found: C, 51.79; H, 4.37; N, 12.70; Br, 18.09

III-45-VS (BL21557)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N-(4-Amino benzoyl)hydrazone Tosylate

A mixture of 0.5 g (10 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)-imidazo[1,2-a]pyridinium tosylate and 0.15 g (10 mmol) of 4-aminobenzoyl hydrazide in 20 mL of absolute ethanol was refluxed for 5 hours. The precipitated product was filtered, dried and recrystallized from ethanol and water. Yield: 0.55 g (92%); MP: 232-234°C.

Anal. calcd. for: $C_{31}H_{31}N_5O_5S \cdot 0.5H_2O$
Calcd: C, 62.61; H, 5.42; N, 11.78; S, 5.39
Found: C, 62.71; H, 5.43; N, 11.75; S, 5.35

III-46-VS (BL21566)

1,5-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 0.5 g (1.2 mmol) of 1,5-dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.31 g (1.2 mmol) of N,N'-diethylaminoguanidine hydroiodide in 20 mL of absolute ethanol was refluxed for 5 hours. The mixture was then acidified with 2 mL of conc. HBr and stirred at room temperature for 2 hours. The precipitated product was recrystallized from ethanol/water. Yield: 0.65 g (90%); MP: 285-287°C.

Anal. calcd. for: $C_{23}H_{30}N_6Br_2 \cdot 2.5H_2O$
Calcd: C, 46.40; H, 5.92; N, 14.11; Br, 26.84
Found: C, 46.09; H, 5.68; N, 14.08; Br, 26.79

II-98-VS (BL21575)

1-Methyl-2-[4'-(3-oxopropenyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 1.0 g (2.4 mmol) of 1-methyl-2-[4'-(3-oxopropenyl)phenyl]-imidazo[1,2-a]pyridinium tosylate in 20 mL of absolute ethanol and 0.6 g (2.4 mmol) of N,N'-diethylaminoguanidine hydroiodide was refluxed for 5 hours. *The resulting solution was acidified with conc. HBr,* cooled and the precipitated product was recrystallized from ethanol and water. Yield: 1.1 g (83%); MP: 238-240°C.

Anal. calcd. for: $C_{22}N_{28}N_6Br_2 \cdot 1H_2O$
Calcd: C, 47.67; H, 5.46; N, 15.16; Br, 28.83
Found: C, 47.75; H, 5.50; N, 15.08; Br, 28.73

Sequence for Preparation of Derivatives of 1-Methyl-2-(4'-formylphenylethenyl)imidazole

Step 1: 1-Methyl-2-hydroxymethylimidazole[9]

1-Methylimidazole (2.8 g, 3.4 mmol) and 40% formaldehyde solution (4.6 mL, 3.5 mmol) were heated for 5 hours. at 140°C in a pressure bottle. Most of the unreacted formaldehyde was then evaporated in a rotovap. The residual thick liquid was distilled under vacuum to give the product as a white solid with a trace of oily impurity. The product was recrystallized from hot ethyl acetate to give white crystals. Yield: 1.5 g (40%); MP: 133-115°C.

Step 2: 1-Methyl-2-formylimidazole[10]

1-Methyl-2-hydroxymethylimidazole (3.0 g) was dissolved in 150 mL of chloroform and 12 g of MnO_2 was added. The mixture was stirred at room temperature for 72 hr and filtered. The filtrate was concentrated and gave 2.7 g of aldehyde (100% yield) as a white solid. MP: 39-41°C.

Step 3: Preparation of 1-Methyl-2-(4'-cyanophenylethenyl)imidazole

Diethyl 4-cyanobenzylphosphonate, 6.0 g (24 mmol), and 960 mg (24 mmol) of sodium hydride were stirred in 60 mL of dry dimethoxyethane in a nitrogen atmosphere and 2.6 g (24 mmol) of 1-methyl-2-formylimidazole in 20 mL of dimethoxyethane was added slowly using an addition funnel. The reaction mixture was gradually heated to 85°C in an oil bath and was maintained at that temperature for an hour. The reaction mixture was cooled and poured into excess water. The precipitated solid was filtered, dried and recrystallized from ethyl acetate. Yield: 3.2 g (63%).

Step 4: 1-Methyl-2-(4'-formylphenylethenyl)imidazole

1-Methyl-2-(4'-cyanophenylethenyl)imidazole (3.0 g) was dissolved in 50 mL of 75% formic acid and 3 g of Raney Ni alloy was added to this solution. The reaction mixture was refluxed for 1.5 hours. The Raney Ni was filtered out and the filtrate was basified with NaOH solution to pH 9. The mixture was extracted with ethyl acetate. The ethyl acetate layer was shaken with brine, dried over $MgSO_4$ and evaporated under vacuum to give the product as a pale yellow solid. The crude product was further purified by $NaHSO_3$ adduct formation to give the pure aldehyde. Yield: 2 g (67%).

Step 5: 1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium Tosylate

Methyl tosylate 2.01 g (10.7 mmol) was added to a solution of 1-methyl-2-(4'-formylphenylethenyl)imidazole 1.9 g (8.9 mmol) in 30 mL of acetonitrile. The reaction mixture was refluxed for 60 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid obtained was washed with ether and dried. Yield: 3.9 g (86%).

II-28-A (BL21584)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium
3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)-imidazolium tosylate and 1.2 g (5 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 30 mL of absolute ethanol were refluxed overnight. The solution was then acidified with conc. HBr, concentrated and cooled. The solid product obtained was filtered and recrystallized from ethanol and water. Yield: 1.5 g (65%); MP: 300-305°C.

Anal. calcd. for: $C_{18}H_{24}N_6Br_2 \cdot 1.5H_2O$
Calcd: C, 42.29; H, 5.32; N, 16.43; Br, 31.25
Found: C, 42.14; H, 5.34; N, 16.41; Br, 31.19

II-27-A (BL21593)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)imidazolium tosylate and 1.20 g (5.2 mmol) of 2-hydrazinoimidazoline hydroiodide in 30 mL of absolute ethanol was refluxed for 6 hours. The mixture was then acidified with 10 mL of conc. HBr, stirred for 30 minutes and refrigerated. The solid obtained by filtration was recrystallized twice from ethanol containing a few drops of conc. HBr. Yield: 1.5 g (68%); MP: >310°C.

Anal. calcd. for: $C_{17}H_{22}N_6Br_2 \cdot 1H_2O$
Calcd: C, 41.82; H, 4.95; N, 17.20 Br, 32.73
Found: C, 41.58; H, 5.03; N, 17.07; Br, 32.55

II-26-A (BL21600)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium Guanylhydrazone Ditosylate

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)-imidazolium tosylate, 700 mg (5.2 mmol) of aminoguanidine bicarbonate and 1.7 g (9.0 mmol) of p-toulenesulfonic acid monohydrate in 30 mL of absolute ethanol was refluxed overnight. The reaction mixture was cooled and the precipitated solid was recrystallized from ethanol and water. Yield: 1.9 g (64%); MP: 230-235°C.

Anal. calcd. for: $C_{29}H_{34}N_6S_2O_6 \cdot 2H_2O$
Calcd: C, 52.56; H, 5.78; N, 12.67; S, 9.65
Found: C, 52.52; H, 5.75; N, 12.66; S, 9.71

II-31-A (BL22250)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium
N,N-Tetramethyleguanylhydrazone Ditosylate

Excess pyrrolidine (6 mL) was added to a solution of 1.1 g (4 mmol) of S-methyl thiosemicarbazide tosylate in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.6 g (4 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)imidazolium tosylate in 3.5 mL of 95% ethanol. The mixture was refluxed for 5 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The solid was recrystallized from ethanol-ether. Yield: 2.3 g (85%); MP: 255-258°C.

Anal. calcd. for: $C_{33}H_{40}N_6S_2O_6 \cdot 1H_2O$
Calcd: C, 56.72; H, 6.10; N, 12.02; Br, 9.10
Found: C, 56.70; H, 6.23; N, 11.90; Br, 9.09

II-32-A (BL22269)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)imidazolium tosylate and 1.20 g (4.8 mmol) of N,N'-diethylaminoguanidine hydroiodide in 20 mL of absolute ethanol was refluxed for 5 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred at room temperature for 2 hours. The precipitated product was recrystallized from ethanol-ether. Yield: 1.80 g (76%); MP: 265-270°C.

Anal. calcd. for: $C_{33}H_{42}N_6S_2O_6 \cdot 1.5H_2O$
Calcd: C, 43.27; H, 5.93; N, 15.93; Br, 30.30
Found: C, 43.15; H, 5.96; N, 15.94; Br, 30.16

II-34-A (BL22278)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium N-Ethylguanylhydrazone Ditosyate

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)imidazolium tosylate and 1.4 g (5 mmol) of N-ethyl-N'-aminoguanidinium tosylate in 30 mL of absolute ethanol was refluxed overnight. The solution was cooled and diluted with ether. The precipitated product was recrystallized from ethanol and ether. Yield: 2.5 g (82%); M. P. 207-210°C.

Anal. calcd. for: $C_{31}H_{38}N_6S_2O_6 \cdot 1.5H_2O$
Calcd: C, 54.62; H, 6.06; N, 12.32; S, 9.30
Found: C, 54.61; H, 6.08; N, 12.32; S, 9.39

II-96D-VS (BL22287)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium
N-Hydroxyguanylhydrazone Dibromide

A solution of 2.5 g (5.8 mmol) of 1-methyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate in 40 mL of absolute ethanol was refluxed for 4 hours with 1.5 g (6.0 mmol) of N-hydroxy-N'-aminoguanidinium tosylate. The reaction mixture was acidified with conc. HBr and stirred at room temperature for 2 hours. The precipitated product was recrystallized from ethanol containing a few drops of HBr. Yield: 2.2 g (88%); MP: 258-60°C.

Anal. calcd. for: $C_{18}H_{20}N_6Br_2O \cdot 1H_2O$
Calcd: C, 42.04; H, 4.31; N, 16.34; Br, 31.08
Found: C, 42.09; H, 4.33; N, 16.31; Br, 31.12

III-74A-VS (BL22296)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 0.5 g (1.2 mmol) of 1-methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium tosylate and 0.31 g (1.2 mmol) of N,N'-diethylaminoguanidine hydroiodide in 20 mL of absolute ethanol was refluxed for 5 hours. The resulting solution was acidified with conc. HBr, cooled and the precipitate was recrystallized from ethanol and water. Yield: 0.55 g (85%); MP: 262-64°C.

Anal. calcd. for: $C_{22}H_{28}N_6Br_2 \cdot 2H_2O$
Calcd: C, 46.17; H, 5.63; N, 14.68; Br. 27.92
Found: C, 45.95; H, 5.60; N, 14.61; Br, 27.82

III-55A-VS (BL22303)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N-Ethylguanylhydrazone Dibromie

A mixture of 0.5 g (1.1 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.1 mmol) of N-ethyl-N'-aminoguanidinium tosylate in 20 mL of absolute ethanol was refluxed for 5 hours. The resulting solution was acidified with concentrated HBr and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 0.48 g (78%); MP: 232-235°C.

Anal. calcd. for: $C_{20}H_{26}N_6Br_2O$
Calcd: C, 42.72; H, 5.38; N, 14.95; Br, 28.42
Found: C, 42.71; H, 5.41; N, 14.88; Br, 28.49

Sequence for the Preparation and Methylation of 1-Methyl-2-(4'-formylphenoxymethyl)imidazole

Step 1: 2-Chloromethyl-1-methylimidazole Hydrochloride.

This compound was prepared as described by Jocelyn.[11] 2-Hydroxymethyl-1-methylimidazole[9] (4.0 g) was added during 15 minutes to thionyl chloride (4.0 g) with stirring and cooling. The solution was refluxed for 15 minutes. The excess of thionyl chloride was evaporated and the residue was dissolved in hot ethanol (5 mL). The product (2.5 g) MP: 158°C crystallized on cooling.

Step 2: 1-Methyl-2-(4'-formylphenoxymethyl)imidazole

2-Chloromethyl-1-(4'-methylimidazolium chloride 4.6 (30 mmol) was taken in 20 mL of absolute alcohol and 2.0 g (32 mmol) of powdered KOH was added. The mixture was stirred for 30 minutes. p-Hydroxybenzaldehyde 2.8 g (32 mmol) and sodium hydride 1.6 g (31 mmol) were added and the reaction mixture was stirred overnight at room temperature, under an inert atmosphere.

The ethanol was evaporated under vacuum and 250 mL of ethyl acetate was poured into the residue. The ethyl acetate solution was washed repeatedly with 5% NaOH solution until the washings were colorless. The ethyl acetate layer was shaken with brine, dried over anhydrous $MgSO_4$ and evaporated under vacuum to give the product. The product was recrystallized from ethyl acetate-hexane. Yield: 4.1 g (65%); MP: 113-115°C.

Step 3: 1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium Tosyate

The quaternization of the aldehyde was done using methyl p-toluenesulfonate in acetonitrile under standard conditions. Yield: 90%; MP: 195-200°C.

II-24-A (BL24085)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium N-(2-Imidazolinyl)hydrazone Dibromide

A mixture of 1.7 g (4.2 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)imidazolium tosylate and 1.1 g (4.6 mmol) of 2-hydrazinoimidazoline hydroiodide in 15 mL of absolute ethanol was refluxed for 5 hours. The solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and ether. Yield: 1.6 g (81%); MP: 253-255°C.

Anal calcd. for: $C_{16}H_{22}N_6Br_2O$
Calcd: C, 40.53; H, 4.67; N, 17.71; Br, 33.70
Found: C, 40.39; H, 4.71; N, 17.62; Br, 33.52

II-33-A (24094)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium N-Hydroxyguanylhydrazone Ditosylate

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenylethenyl)imidazolium tosylate and 1.2 g (4.6 mmol) of N-hydroxy-N'-aminoguanidinium tosylate in 30 mL of absolute ethanol was stirred under reflux overnight. The mixture was cooled and the precipitated product was recrystallized from ethanol and ether. Yield: 1.75 g (80%); MP: 273-275°C.

Anal. calcd. for $C_{15}H_{20}N_6Br_2O \cdot 1.5H_2O$
Calcd: C, 36.98; H, 4.75; N, 17.24; Br, 32.80
Found: C, 37.12; H, 4.77; N, 17.19; Br, 32.86

II-36-A (BL24101)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium N,N-Tetramethyleneguanylhydrazone Ditosylate

Excess pyrrolidine (6 mL) was added to a solution of 1.1 g (4 mmol) of S-methyl thiosemicarbazide tosylate in 30 mL of ethanol. The mixture was refluxed for 24 hours. The solvent was removed and the residue was washed six times with ether. The solid was then mixed with 1.6 (4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)imidazolium tosylate in 35 mL of 95% ethanol. The mixture was refluxed for 5 hours. On cooling the product crystallized out. The solution was further diluted with ether and filtered. The white solid was recrystallized from ethanol-ether. Yield: 2.2 g (85%); MP: 206-208°C.

Anal. calcd. for: $C_{32}H_{40}N_6S_2O_7 \cdot 2H_2O$
Calcd: C, 53.32; H, 6.15; N, 11.65; S, 8.90
Found: C, 53.48; H, 6.10; N, 11.65; S, 8.95

II-41-A (BL24110)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium 3,4,5,6-tetrahydropyrimidyl-2-hydrazone Dibromide

A mixture of 1.7 g (4.2 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)imidazolium tosylate and 1.15 g (4.6 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 40 mL of 95% ethanol was refluxed for 6 hours. The mixture was then acidified with 9 mL of conc. HBr and stirred at room temperature. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 1.7 g (80%); MP: 215-217°C.

Anal. calcd. for: $C_{17}H_{24}N_6O \cdot 1H_2O$
Calcd: C, 39.63; H, 5.28; N, 16.30; Br, 31.01
Found: C, 39.78; H, 5.11; N, 16.37; Br, 30.93

III-57A-VS (BL24129)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N-Ethylguanylhydrazone Dibromide

A mixture of 0.5 g (1.2 mmol) of 1-methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.2 mmol) of N-ethyl-N'-aminoguanidinium tosylate in 15 mL of absolute ethanol was refluxed for 3 hours. The resulting solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 0.55 g (84%); MP: 260-263°C.

Anal. calcd. for: $C_{20}H_{24}N_6Br_2 \cdot 2H_2O$
Calcd: C, 44.13; H, 5.19; N, 15.44; Br, 29.36
Found: C, 44.06; H, 5.21; N, 15.39; Br, 29.35

III-64-VS (BL24138)

1-Methyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N-(4-Aminobenzoyl)hydrazone Tosylate

A mixture of 0.5 g (1.1 mmol) of 1-methyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.18 g (1.2 mmol) of 4-aminobenzoylhydrazide in 20 mL of absolute ethanol was refluxed for 5 hours. The reaction mixture was cooled and the precipitated product was filtered, dried and recrystallized from ethanol and water. Yield: 0.60 g (90%); MP: 258-260°C.

Anal. calcd. for: $C_{31}H_{29}N_5O_4S \cdot 2H_2O$
Calcd: C, 61.68; H, 5.51; N, 11.60; S, 5.31
Found: C, 61.46; H, 5.58; N, 11.52; S, 5.26

III-71-VS (BL24147)

1,6-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

A mixture of 0.5 g (1.0 mmol) of 1,6-dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.0 mmol) of N,N-tetramethylene-N'-aminoguanidine tosylate in 20 mL of absolute ethanol was refluxed for 5 hours. The resulting solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.48 g (82%); MP: >300°C.

Anal. calcd. for: $C_{23}H_{28}N_6Br_2 \cdot 2H_2O$
Calcd: C, 47.27; H, 5.52; N, 14.38; Br, 27.35
Found: C, 47.40; H, 5.55; N, 14.28; Br, 27.25

II-37-A (BL28029)

1,2-Dimethyl-2-(4'-formylphenylethenyl)imidazolium Guanylhydrazone Dibromide

A mixture of 1.8 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)imidazolium tosylate, 680 mg (5.0 mmol) and 1.3 g (7.5 mmol) of p-toluensulfonic acid were refluxed in 50 mL of 85% ethanol for 4 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred. Addition of ether precipitated out the product. The product was redissolved in ethanol, reacidified and reprecipitated. Finally it was recrystallized from ethanol-ether. Yield: 2.6 g (85%); MP: 245-250°C.

Anal. calcd. for: $C_{14}H_{20}N_6Br_2 \cdot 0.5H_2O$
Calcd: C, 36.80; H, 4.63; N, 18.4; Br, 34.95
Found: C, 36.89; H, 4.67; N, 18.32; Br, 35.03

II-40-A (BL28038)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium N,N'-Diethylguanylhydrazone Dibromide

A mixture of 1.82 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)imidazolium tosylate and 1.20 g (4.8 mmol) of N,N'-diethylaminoguanidine hydroiodide in 20 mL of absolute ethanol was refluxed for 5 hours. The mixture was then acidified with 10 mL of conc. HBr and stirred at room temperature for 2 hours. The precipitated product was recrystallized from ethanol-ether. Yield: 1.85% (78%); MP: 180-185°C.

Anal. calcd for: $C_{18}H_{28}N_6BrO \cdot 1.5H_2O$
Calcd: C, 40.68; H, 5.88; N, 15.81; Br, 30.08
Found: C, 40.24; H, 5.80; N, 15.72; Br, 29.98

II-42-A (BL28047)

1,3-Dimethyl-2-(4'-formylphenylethenyl)imidazolium N-(4-Aminobenzoyl)hydrazone Tosylate

A mixture of 1.8 g (4.5 mole) of 1,3-dimethyl-2-(4'-formylphenylethenyl)-imidazolium tosylate and 780 mg (4.8 mmol) of 4-aminobenzoylhydrazide in 20 mL of absolute ethanol was refluxed for 5 hours. The reaction mixture was cooled and the precipitated product was filtered, dried and recrystallized from ethanol and water. Yield: 2.0 g (85%); MP: 290-295°C.

Anal. calcd. for: $C_{28}dH_{29}N_5SO_4 \cdot 0.5H_2O$
Calcd: C, 62.20; H, 5.55; N, 12.94; S, 5.93
Found: C, 62.37; H, 5.62; N, 12.95; S, 5.97

III-66B-VS (BL28056)

1,5-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium
N,N'-Dimethylguanylhydrazone Dibromide

A mixture of 0.5 g (1.1 mmol) of 1,5-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.3 mmol) of N,N'-dimethylaminoguanidine hydroiodide in 20 mL of absolute ethanol was stirred under reflux for 6 hours. The reaction mixture was acidified with conc. HBr and stirred for an additional 3 hours. The precipitated product was recrystaliized from ethanol and water. Yield: 0.46g (79%); MP: 252-54°C.

Anal. calcd. for: $C_{20}H_{26}N_6Br_2O \cdot 1H_2O$
Calcd: C, 44.13; H, 5.19; N, 15.44; Br, 29.36
Found: C, 44.07; H, 5.21; N, 15.43; Br, 28.88

III-70B-VS (BL28065)

1,6-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium Guanylhydrazone Dibromide

A mixture of 0.5 g (1 mmol) of 1,6-dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium tosylate, 0.14 g (1 mmol) of aminoguanidine bicarbonate and 0.25 g (1.3 mmol) of p-toluenesulfonic acid monohydrate in 20 mL of absolute ethanol was stirred under reflux overnight. The solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 0.45 g (88%); mp: >300°c.

Anal. calcd. for: $C_{19}H_{22}N_6Br_2.1H_2O$
Calcd: C, 44.55; H, 4.72; N, 16.41; Br, 31.20
Found: C, 44.51; H, 4.78; N, 16.21; Br, 31.07

III-72A-VS (BL28074)

1,6-Dimethyl-2-(4'-formylphenylethenyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 0.5 g (1 mmol) of 1,6-dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.30 g (1.2 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 20 mL of absolute ethanol was refluxed for 5 hours. The mixture was then acidified with conc. HBr and stirred at room temperature. The precipitated product was recrystallized from ethanol and ether. Yield: 0.52 g (91%); MP: >300°C.

Anal. calcd. for: $C_{22}H_{26}N_6Br_2\cdot 2H_2O$
Calcd: C, 46.33; H, 5.30; N, 14.73; Br, 28.02
Found: C, 46.42; H, 5.21; N, 14.59; Br, 27.92

II-38-A (BL3017)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium N-Ethylguanylhydrazone Ditosylate

A mixture of 1.82 g (4.5 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-imidazolium tosylate and 1.4 g (5 mmol) of N-ethyl-N'-aminoguanidinium tosylate in 30 mL of absolute ethanol was refluxed overnight. The solution was cooled and diluted with ether. The precipitated product was recrystallized from ethanol and ether. Yield: 2.2 g (72%); MP: 220-227°C.

Anal. calcd. for: $C_{30}H_{38}N_6S_2O_7\cdot 1H_2O$
Calcd. C, 53.24; H, 5.95; N, 12.41; S, 9.47
Found: C, 53.01; H, 6.00; N, 12.35; S, 9.46

II-39-A (BL31026)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium N-Hydroxyguanylhydrazone Dibromide.

A solution of 1.8 g (4.5 mmol) 1,3-dimethyl-2-(4'-formylphenoxymethyl)imidazolium tosylate and 1.2 g (4.8 mmol) of N-hydroxy-N'-aminoguanidium tosylate in 20 mL of absolute ethanol was refluxed for 4 hours. The reaction mixture was acidified with conc. HBr and stirred at room temperature for 2 hours. The precipitated product was recrystallized from ethanol containing a few drops of HBr. Yield: 1.7 g (80%); MP: 217-219°C.

Anal. calcd. for: $C_{14}H_{20}N_6Br_2O_2.1H_2O$
Calcd: C, 34.87; H, 4.6; N, 17.42; Br, 33.14
Found: C, 35.03; H, 4.39; N, 17.24; Br, 32.9

II-43-A (BL31035)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)imidazolium N-(4-Aminobenzoyl)hydraone Tosylate

A mixture of 1.44 g (3.6 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-imidazolium tosylate and 620 mg (3.8 mmol) of 4-aminobenzoylhydrazide in 20 mL of absolute ethanol was refluxed for 5 hours. The reaction mixture was cooled and the precipitated product was filtered, dried and recrystallized from ethanol and water. Yield: 1.70 (85%); MP: 210-212°C.

Anal. calcd. for: $C_{27}H_{29}N_5SO_5\cdot 0.5H_2O$
Calcd: C, 59.53; H, 5.54; N, 12.85; S, 5.88
Found: C, 59.79; H, 5.56; N, 12.93; S, 5.97

II-74C-VS (BL31044)

1,6-Dimethyl-2-(4-formylphenylethenyl)imidazo[1,2-a]pyridinium N-Hydroxyguanylhydrazone Dibromide

A mixture of 0.5 g (1 mmol) of 1,6-dimethyl-2-(4'-formylphenylethenyl)-imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.2 mmol) of N-hydroxy-N'-aminoguanidinium tosylate in 20 mL of absolute ethanol was stirred under reflux for 5 hours. The resulting solution was acidified with conc. HBr, concentrated and cooled. The precipitated product was recrystallized from ethanol and water. Yield: 0.46 g (87%); MP: 245-247°C.

Anal. calcd. for: $C_{19}H_{22}N_6Br_2O\cdot 2H_2O$
Calcd: C, 43.20; H, 4.58; N, 15.91; Br, 30.25
Found: C, 43.12; H, 4.62; N, 15.83; Br, 30.19

III-87A-VS (BL31053)

1,6-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium 3,4,5,6-Tetrahydropyrimid-2-ylhydrazone Dibromide

A mixture of 0.5 g (1.1 mmol) of 1,6-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.3 g (1.2 mmol) of 2-hydrazino-3,4,5,6-tetrahydropyrimidine hydroiodide in 20 mL of ethanol was refluxed for 5 hours. The solution was acidified with conc. HBr, cooled and the precipitated product was recrystallized from ethanol and water. Yield: 0.58 g (92%); MP: 244-246°C.

Anal. calcd. for: $C_{21}H_{26}N_6Br_2O \cdot 2H_2O$
Calcd: C, 43.92; H, 5.27; N, 14.63; Br, 27.83
Found: C, 44.03; H, 5.28; N, 14.59; Br, 27.89

III-89-VS (BL31062)

1-Methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N-Tetramethyleneguanylhydrazone Dibromide

A mixture of 0.5 g (1.0 mmol) of 1-methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium tosylate and 0.35 g (1.2 mmol) of N,N-tetramethylene-N'-aminoguanidinium tosylate in 15 mL of absolute ethanol was refluxed for 5 hours. The resulting solution was acidified with conc. HBr and stirred for 4 hours at room temperature. The precipitated product was recrystallized from ethanol and water. Yield: 0.55 g (88%); MP: 247-249°C.

Anal. calcd for: $C_{22}H_{25}N_6Br_2F_3O \cdot 1H_2O$
Calcd: C, 42.32; H, 4.36; N, 13.47; Br, 25.60
Found: C, 42.16; H, 4.41; N, 13.41; Br, 25.50

II-47A (BL35542)

1,3-Dimethyl-2-(4'-formylphenoxymethyl)benzimidazolium N,N'-Dimethylguanylhydrazone Dibromide

A mixture of 2 g (4.4 mmol) of 1,3-dimethyl-2-(4'-formylphenoxymethyl)-benzimidazolium tosylate and 1.1 g (4.7 mmol) of N,N'-dimethylaminoguanidine hydroiodide in 20 mL of absolute ethanol was stirred under reflux for 6 hours. The reaction mixture was acidified with conc. HBr and stirred for an additional 3 hours. the precipitated product was recrystallized from ethanol and water. Yield: 1.8 g (80%), MP 280-285°C.

Anal. calcd for: $C_{20}H_{26}N_6OBr_2 \cdot 1.5H_2O$
Calcd: C, 43.42; H, 5.24; N, 15.18
Found: C, 43.34; H, 5.19; N, 15.18

III-94-VS (BL35579)

1,6-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium 2-Imidazolinylhydrazone Dibromide

A solution of 1,6-dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]-pyridinium and 2-imidazolinylhydrazine hydroiodide were refluxed in ethanol for 16 hours. The solution was cooled and acidified with conc. HBr. The product precipitated after several hours and was recrystallized from ethanol-water, MP 258-260°C.

Anal. calcd. for: $C_{20}H_{24}N_6OBr_2 \cdot H_2O$
Calcd: C, 44.30; H, 4.83; N, 15.50
Found: C, 44.38; H, 4.83; N, 15.48

III-90A-VS (BL35560)

1,6-Dimethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N,N'-Diethylguanylhydrazone Dibromide

A solution of 1,6-dimethyl-2-(4'-formylphenoxymethylimidazo[1,2-a]-pyridinium bromide (1.0 g) and N,N'-diethylguanylhydrazine (0.60 g) were refluxed together in ethanol for 5 hours. The solution was cooled to room temperature and acidfied with conc. HBr. The product was recrystallized from ethanol-water, MP 248-260°.

Calcd: C,44.76; H, 5.81; N, 14.24; Br, 27.07
Found: C,44.96; H, 5.77; N, 14.19; Br, 27.16

III-92-VS (BL39700)

1-Methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)imidazo[1,2-a]pyridinium N-Hydroxyguanylhydrazone Dibromide

A solution of 1-methyl-6-trifluoromethyl-2-(4'-formylphenoxymethyl)-imidazo[1,2-a]pyridinium tosylate (0.6 g) 0.4 of N-hydroxyguanylhydrazine tosylate in ethanol (20 mL) were refluxed together for several hours. The solution was cooled and acidified with conc. HBr. Recrystallization of the precipitate from ethanol water gave the roduct. MP 225-227°.

Anl. calcd. for: $C_{18}H_{19}N_6F_3O_2Br_2 \cdot 0.5H_2O$
Calcd: C, 43.42; H, 5.24; N, 15.18
Found: C, 43.34; H, 5.19; N, 15.18

VII. REFERENCES

(1) E. A. Steck, K. E. Kinnamon, D. S. Rane and W. L. Hanson, "Leishmania donovani, Plasmodium berghei, Trypanosoma rhodesiense: Antiprotozoal Effects of Some Amidine Types," Exp. Partasitol., 52, 404 (1981); B. P. Das and D. W. Boykin, "Synthesis and Antiprotozool Activity of 2,5-Bis(4-guanylphenyl) furans," J. Med. Chem., 20 531 (1977).

(2) H. C. Nathan, K. V. M. Soto, R. Moreiro, L. Chunosoff, S. H. Hutner and C. J. Bacchi, "Curative Effects of the Antipiroplasmas Amicarbalide and Imidocarb on Trypanosoma brucei Infections in Mice," J. Protozool, 26, 657 (1979).

(3) O. Dann, G. Bergen, E. Demant and G. Volz, "Trypanocide Diamidine des 2-Phenylbenzofurans, 2-Phenylindens und 2-Phenylindols," Liebig's Ann. Chem., 749, 68 (1982).

(4) P. C. Ulrich, R. W. Grady and A. Cerami "The Trypanocidal Activity of Various Aromatic bis-Guanyhydrazones in Vivo," Drug Develop. Res., 2, 219 (1982).

(5) H. C. Nathan, C. J. Bacchi, C. A. Nichol, D. S. Duch, E. A. Mulloney and S. H. Hutner, "Anti-tumor phthalanilides active in acute and chronic Trypanosoma brucei brucei murine infections," Am. J. Trop. Med. Hyg., 33, 845 (1984).

(6) (a) C. J. Bacchi, "Content, Synthesis, and Function of Polyamines in Trypanosomatides: Relationship to Chemotherapy," J. Protozool., 28, 20 (1981); C. J. Bacchi, P. P. McCann, M. C. Nathan, S. H. Hutner and A. Sjoerdsma, (b) "Antagonism of Polyamine Metabolism - A Critical Factor in Chemotherapy of African Trypanosomiasis,"Adv. Polyamine Res., 4, 221 (1983); S. L. Marcus, R. Kopelman, B. Koll and C. J. Bacchi, (c) "Effects of Exogenous Polyamine and Trypanocides on the Dna Polymerase Activities from Trypanosoma brucei brucei, Mouse Thymus and Murine Leukema Virus," Mol. Biochem. Parasitol., 5, 231 (1982).

(7) F. Kagan, R. D. Birkenmeyer and R. E. Stube, "Nitrogen Mustard Containing the Phosphonate Group," J. Am. Chem. Soc., 81, 3026 (1959).

(8) (a) R. G. Fargher and F. L. Pyman, "Nitro- Arylazo- and Amino-glyoxalines," J. Chem. Soc., 115, 217 (1919); (b) K. Lehnstedt, "Uber Kohlenstoffsalze des Tetranitro-biimidazols und dse Methylierung des Nitro-imidazols," Liebig's Ann. Chem., 507, 213 (1933);

(9) R. Grindley and F. L. Pyman, "Condensation of Glyoxalines with Formaldehyde," J. Chem. Soc., 3128 (1927).

(10) H. J. J. Loozen and E. F. Godefroi, "Benzimidazoles from Preformed Imidazoles - A Novel Approach," J. Org. Chem., 38, 3495 (1973).

(11) P. C. Jocelyn, "Some Derivatives of 2,2'-Aminoethylslyoxaline," J. Chem. Soc., 3305 (1957).

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