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SYNTHESIS LABORATORY FOR THE U. S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES SELECTION PANEL

FINAL PROGRESS REPORT

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JUNE 26, 1991
(For the period 1 December 1985 - 28 February 1991)

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SOUTHERN RESEARCH INSTITUTE
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13. ABSTRACT *(Maximum 200 words)*

A synthesis laboratory has been established for the preparation of compounds to be evaluated against viruses of interest to U.S. Army Medical Research Institute of Infectious Diseases. The synthesis of known compounds as well as new compounds has been undertaken, and all compounds are being made in sufficient quantity to allow for full evaluation. Among the compounds prepared thus far are 1-benzyloxy-adenosines, 9-substituted 1-benzyloxyadenines, 1,2,4,5,3,6-tetraazadiphosphorines, substituted imidazoles, selenadiazoles, triazoles, triazolotriazoles, guanidines, pyrazoles, adamantane derivatives, chloroquines, N^1-aminonucleosides, allopurinol acyclonucleosides, nucleotides of ribavirin and tiazofurin, and various other heterocyclic compounds.

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FOREWORD

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

I. Introduction

This report summarizes activities performed under Contract No. DAMD17-86-C-6011 from 1 December 1985 through 28 February 1991. The purpose of this contract was to support the synthesis of a wide variety of compounds for evaluation in the U. S. Army Medical Research Institute of Infectious Diseases (USAMRIID) viral testing program. Compounds that were synthesized included: (1) known compounds that were needed in larger quantities to allow further evaluation; and (2) new compounds whose structures were determined by rational processes.

In the early stages of this project, our strategy was to select potential lead compounds from the USAMRIID list of active antiviral compounds or from the literature, and then to propose and synthesize analogs of these compounds. In the later stages, our target compounds were selected by USAMRIID via Major Ussery and Dr. Gabrielsen, using the screening data for submitted compounds as well as other compounds reported in the literature. We also submitted compounds from one other source, our compound archives. We selected a number of previously synthesized compounds that had been shown to have bioactivities compatible with goals of this project, and these were submitted for screening.

By following this strategy, we were able to provide over 250 compounds selected from a wide range of compound classes. Among the compounds pursued during the course of this project are the following: substituted 1-benzyloxyadenosines, 9-substituted 1-benzyloxyadenines, N^1-aminoadenosines, tetraazadiphosphorines, guanidines, substituted triazoles, triazolotriazoles, triazolothiadiazoles, diazoloselenadiazoles, pyrazole carboxylates and carboxamides, adamantane derivatives, chloroquine derivatives, allopurinol acyclonucleosides, pyrazolopyrimidine nucleosides, ribavirin nucleotides and analogs, 6-alkylmercaptopurine ribosides, benzothiazin-2-one oximes, methanesulfonic acid derivatives, 6-benzyl-1,3-dioxole derivatives, 9-phosphonylmethyloxyethyl-substituted purines, as well a number of nucleosides of substituted purine and purine analogs (such as imidazo[1,2-*b*]pyrazole-7-carbonitrile, 6-carboxamidopurine and the corresponding nucleosides, and 5-chlorotriazolopyrimidin-7-one).

II. Personnel

The following personnel comprised the synthesis laboratory for this contract/project. Dr. John A. Secrist III was the principal investigator. Dr. Cecil D. Kwong was the project coordinator (principal assistant). Dr. Kwong, Mr. Charles A. Krauth, Ms. Angela G. Ford, Dr. Yajnanarayana H. R. Jois, Ms. Deborah A. Carter, Ms. Lisa K. Hanna, and Mr. George S. McCaleb performed the syntheses.

The time charges made by these as well as other SRI support personnel are listed below and are divided into various categories.

III. Compounds Submitted

The compounds that we submitted during the contract years are shown in Tables 1-6. The compounds are presented in approximate chronological order of submission, and our SRI numbers and the USAMRIID numbers are listed for each compound along with the amounts submitted. In some cases, the same compound

Table 1

Compounds Submitted from December 1, 1985 to November 30, 1986

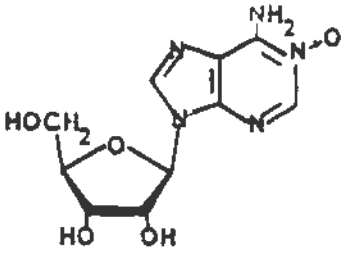
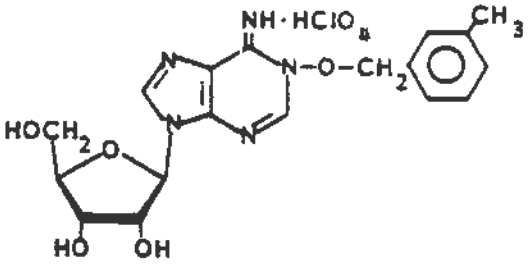
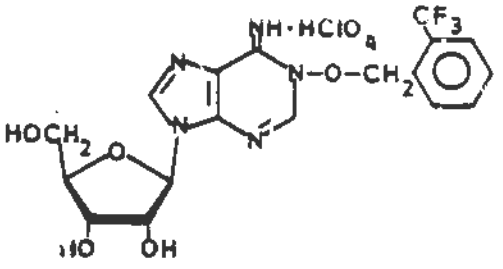
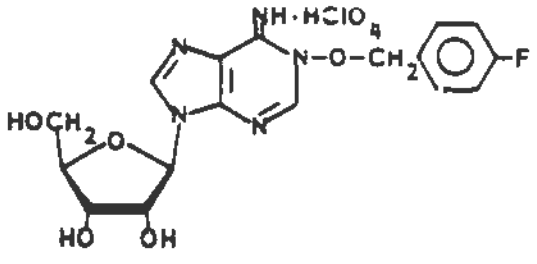
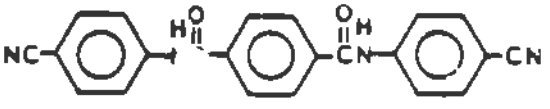
Compound	USAMRIID	SoRI Number	Amount Prepared
	AVS-001985	4544	2.0 g
	AVS-001986	6767	2.0 g
	AVS-001987	6768	2.0 g
	AVS-001988	6769	2.0 g
	AVS-001989	6770	1.7 g

Table 1 (Continued)

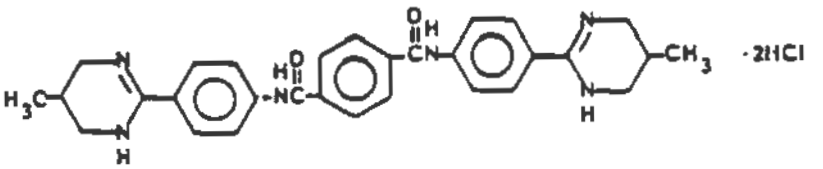
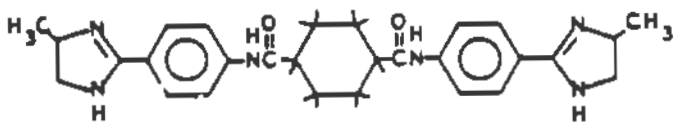
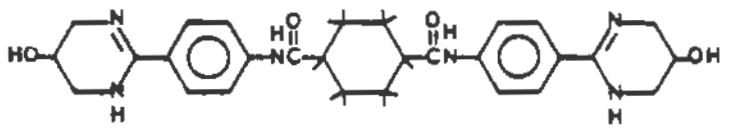
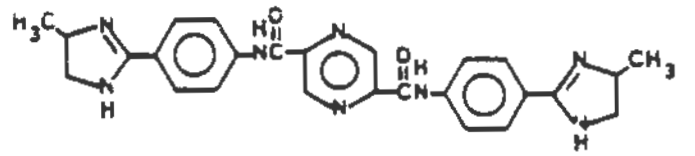
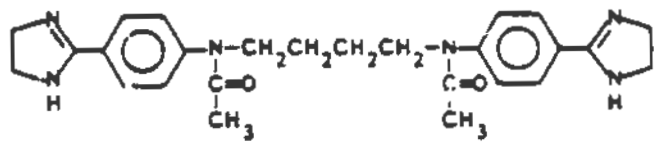
Compound	JSAMR1ID	SoRI Number	Amount Prepared
 ·2HCl	AVS-001990	6771	1.7 g
	AVS-002137	6788	2.0 g
 ·2HCl	AVS-002138	6789	2.0 g
 ·2HCl	AVS-002139	6790	2.0 g
 ·2HCl	AVS-002140	6791	2.0 g

Table 1 (Continued)

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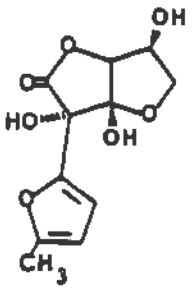
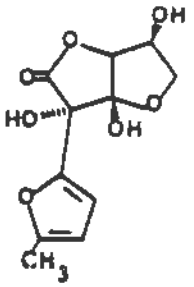
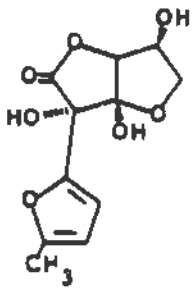
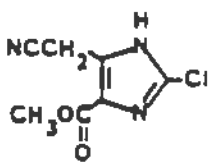
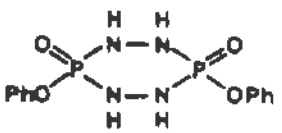
	002565	6834	1.98 g
 2:1 Complex with succinic anhydride	002288	6836	1.04 g
 2:1 Complex with succinimide	002287	6835	0.74 g
	002566	6842	2.0 g
	002569	6827	1.7 g

Table 1 (Continued)

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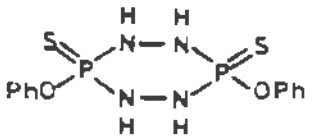
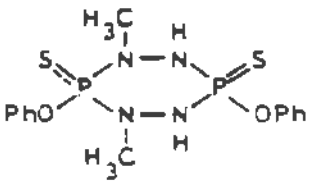
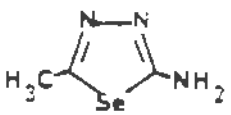
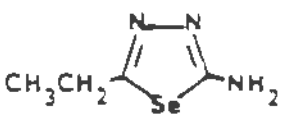
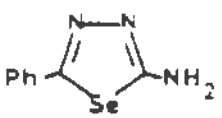
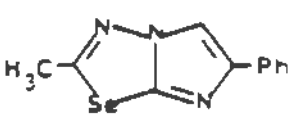
	6854	002739	0.9 g
	6855	002770	2.0 g
	6856	002740	1.5 g
	6862	002772	0.75 g
	6871	002774	0.85 g
	6861	002771	0.8 g

Table 1 (Continued)

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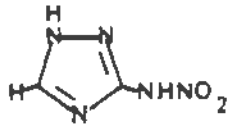
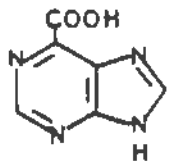
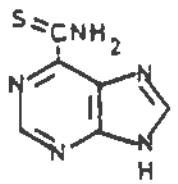
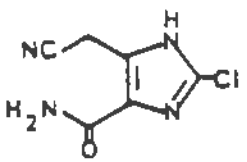
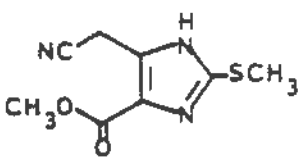
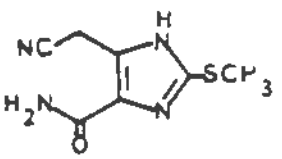
	6881	002787	1.05 g
	6860	002745	1.89 g
	6879	002701	1.6 g
	6842	002566	2.0 g
	6876	001176	1.2 g
	6884	002869	1.53 g

Table 2

Compounds Submitted from December 1, 1986 to November 30, 1987

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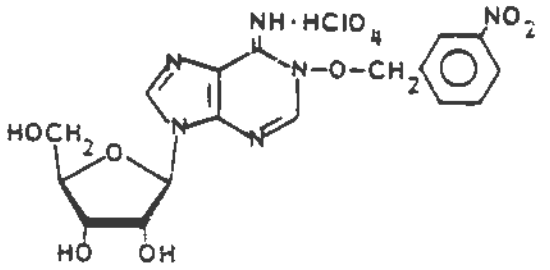
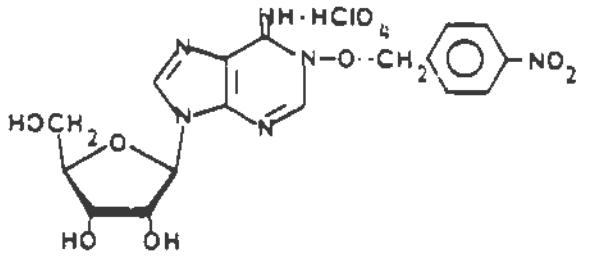
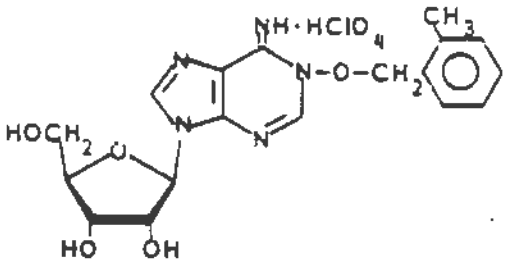
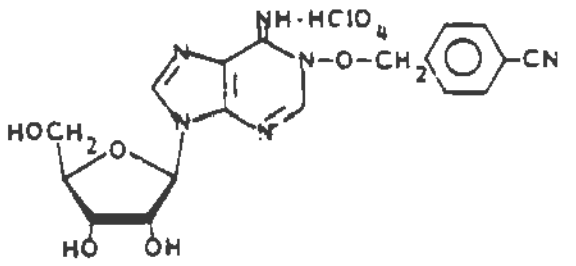
	6885	002873	1.9 g
	6886	002874	2.0 g
	6887	002875	2.0 g
	6888	002879	2.0 g

Table 2 (Continued)

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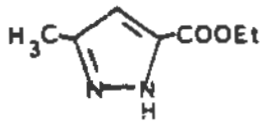
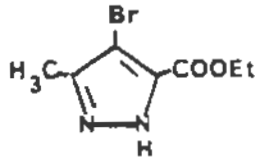
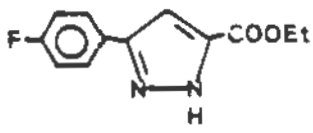
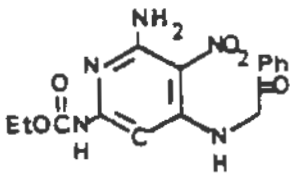
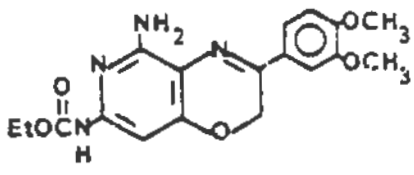
	6889	002876	1.5 g
	6891	002878	1.1 g
	6890	002877	1.5 g
	6053	002872	0.5 g
	6476	002870	0.5 g

Table 2 (Continued)

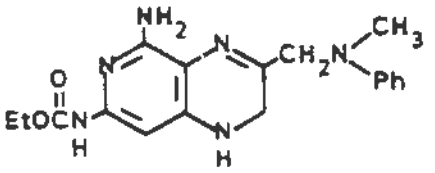
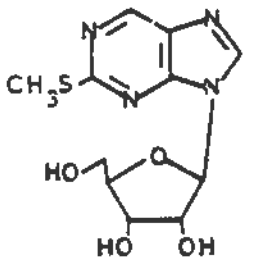
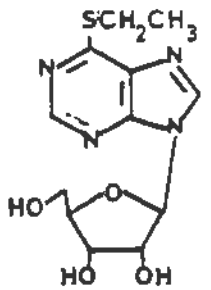
Compound	SoRI No.	AVS No.	Amount Submitted
	5261	002871	0.5 g
	915	002293	1.0 g
	1215	002700	1.0 g

Table 2 (Continued)

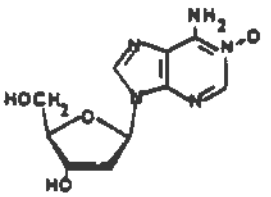
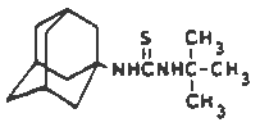
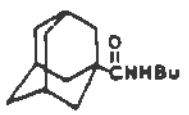
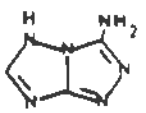
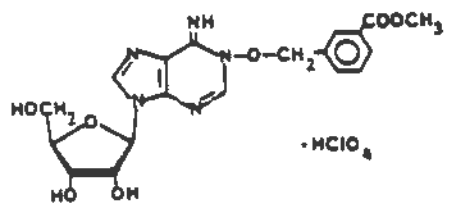
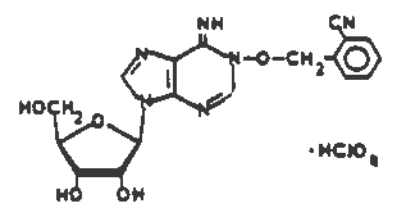
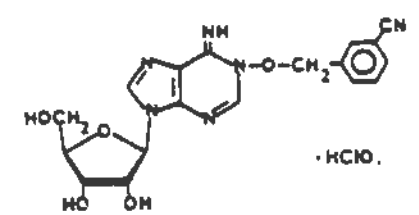
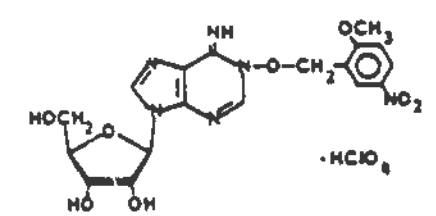
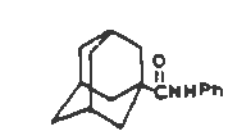
Compound	SoRI No.	AVS No.	Amount Submitted
	4305	002995	850 mg
	6892	002885	1.0 g
	6905	002886	0.54 g
	6907	002887	1.53 g
	6908	002882	2.0 g
	6909	002889	2.0 g
	6910	002890	2.0 g
	6911	002891	2.0 g
	6912	002894	1.25 g

Table 2 (Continued)

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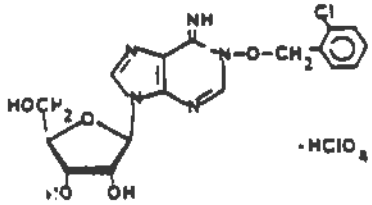
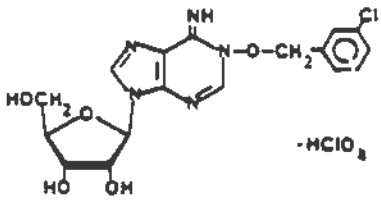
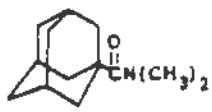
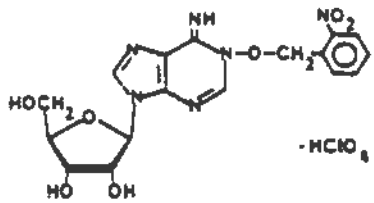
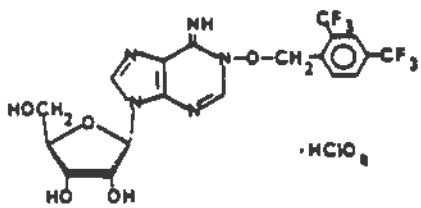
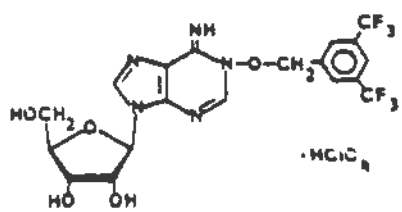
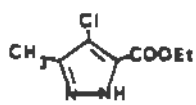
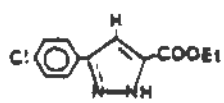
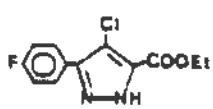
	6915	002895	2.0 g
	6916	002896	2.0 g
	6925	002908	1.5 g
	6927	0029 1	1.8 g
	6928	002912	1.5 g
	6929	002913	2.0 g
	6930	002914	0.58 g
	6931	002915	1.2 g
	6932	002916	1.4 g

Table 2 (Continued)

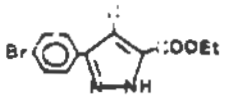
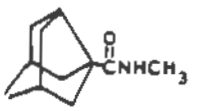
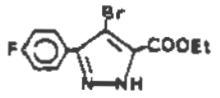
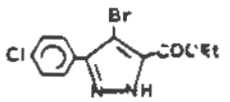
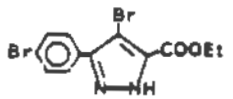
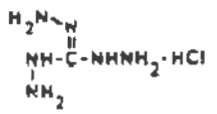
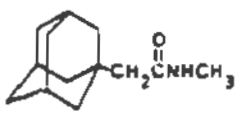
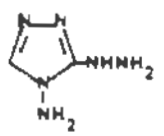
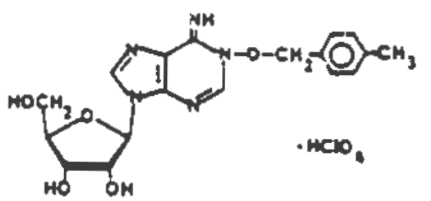
Compound	SoRI No.	AVS No.	Amount Submitted
	6933	00`917	1.9 g
	6934	002918	0.73 g
	6943	002957	1.1 g
	6944	002958	1.4 g
	6945	002959	1.7 g
	6946	002960	1.5 g
	6955	002861	1.0 g
	6956	000244	1.5 g
	6957	002994	1.5 g

Table 2 (Continued)

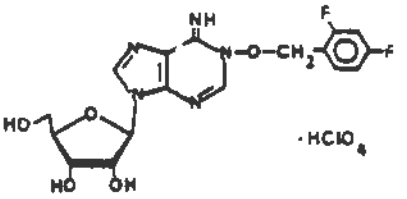
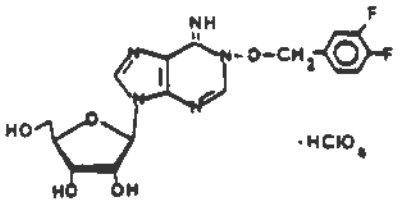
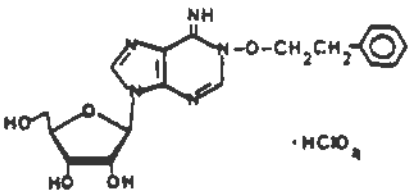
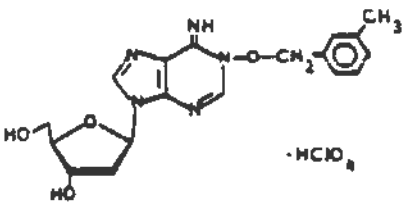
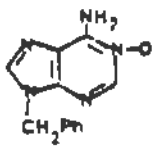
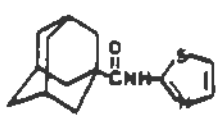
Compound	SoRI No.	AVS No.	Amount Submitted
	6987	003533	1.4 g
	6988	003534	850 mg
	6989	003535	1.8 g
	6990	003536	1.9 g
	6991	003537	1.2 g
	6992	003538	0.62 g
	6995	003546	2.0 g

Table 2 (Continued)

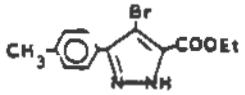
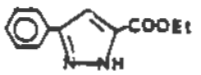
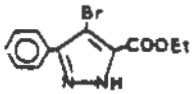
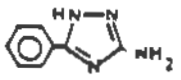
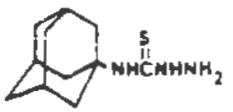
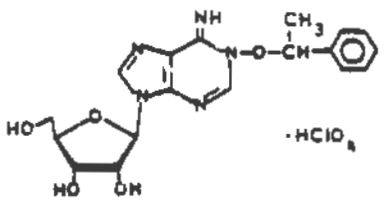
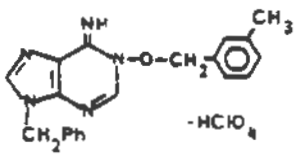
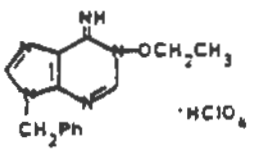
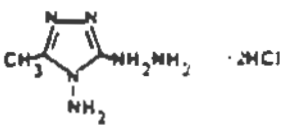
Compound	SoRI No.	AVS No.	Amount Submitted
	6996	003547	1.7 g
	6998	003548	1.8 g
	6999	003549	1.1 g
	7000	003550	1.5 g
	7002	003551	2.0 g
	7008	003607	1.4 g
	7009	003608	1.1 g
	7010	003609	1.0 g
	7017	003610	1.5 g

Table 2 (Continued)

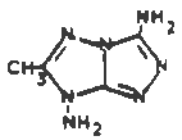
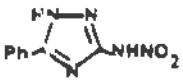
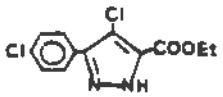
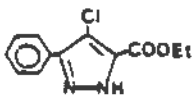
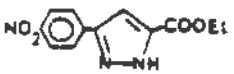
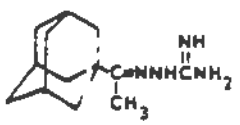
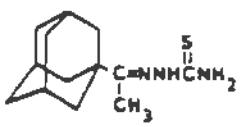
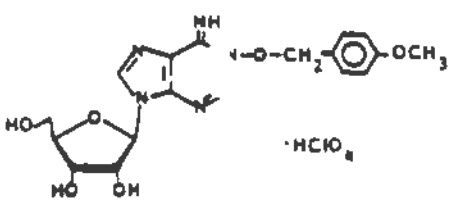
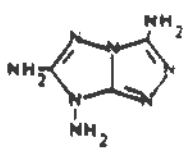
Compound	SoRI No.	AVS No.	Amount Submitted
	7018	003611	1.5 g
	7019	003612	1.5 g
	7020	003613	1.5 g
	7021	003614	0.75 g
	7022	003615	2.0 g
	7023	003677	2.0 g
	7024	003678	2.0 g
	7037	003679	2.0 g
	7038	003680	1.5 g

Table 2 (Continued)

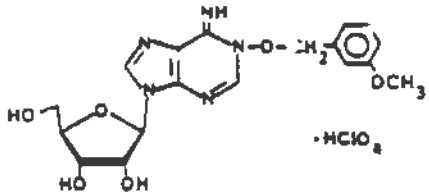
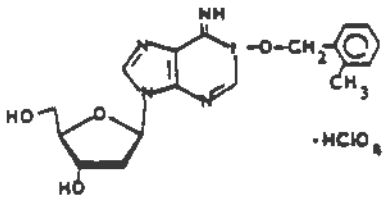
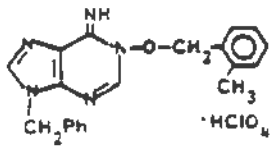
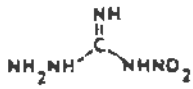
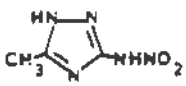
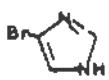
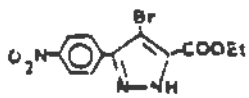
Compound	SoPI No.	AVS No.	Amount Submitted
	7055	003912	2 g
	7056	003913	0.9 g
	7057	003914	0.85 g
	7058	003915	1.6 g
	7059	003916	1.86 g
	7060	003917	3.0 g
	7061	003918	2.0 g
	7062	003919	1.5 g

Table 2 (Continued)

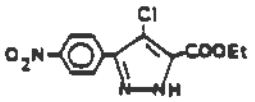
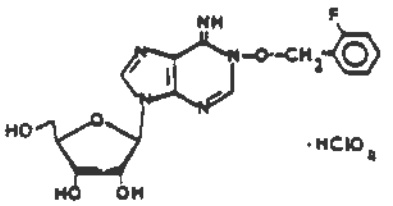
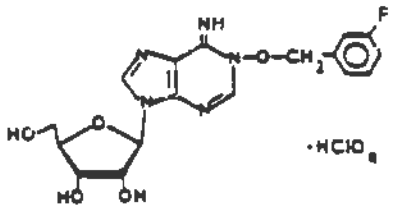
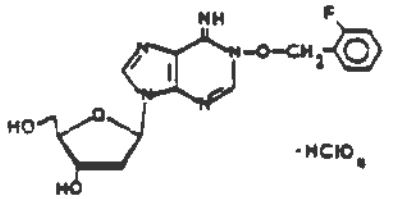
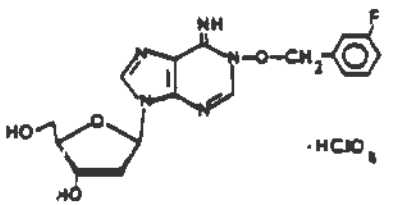
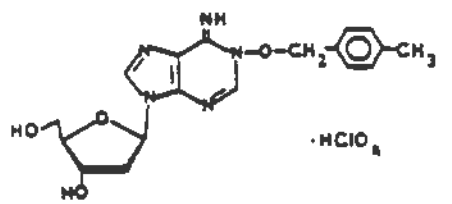
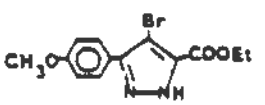
Compound	SoRI No.	AVS No.	Amount Submitted
	7063	003920	1.5 g
	7065	003940	2.0 g
	7066	003941	2.0 g
	7067	003942	1.5 g
	7068	003943	1.2 g
	7069	003944	1.1 g
	7071	003945	1.5 g
	7072	003946	1.56 g

Table 2 (Continued)

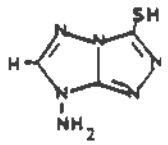
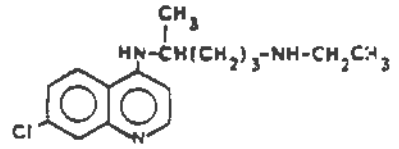
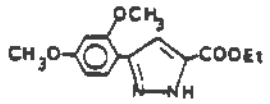
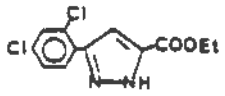
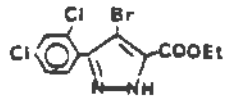
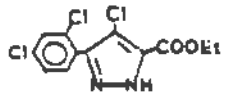
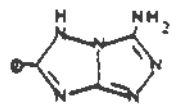
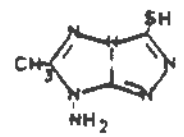
Compound	SoRI No.	AVS No.	Amount Submitted
	7074		1.39 g
	7086	003980	5.26 g
	7091	003996	2.0 g
	7092	003997	2.0 g
	7093	003998	1.5 g
	7094	003999	1.5 g
 ·Hdr	7095	004000	1.05 g
	7096	004001	1.15 g

Table 3

Compounds Submitted from December 1, 1987 to November 30, 1988

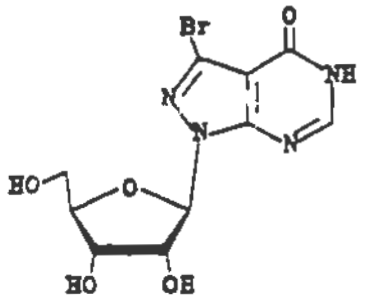
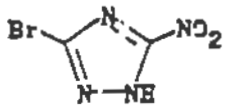
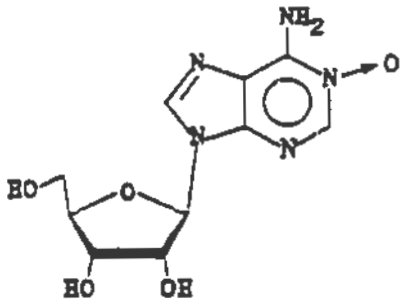
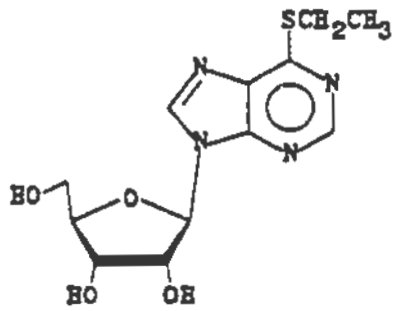
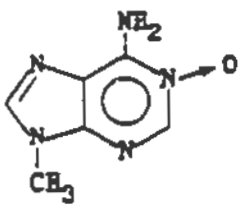
Compound	SRI Number	AVS Number	Amount Submitted
	7122	000161	5.0 g
	7123	000231	5.0 g
	4544	001985	5.0 g
	1215	002700	5.0 g
	7132	004121	0.5 g

Table 3 (Continued)

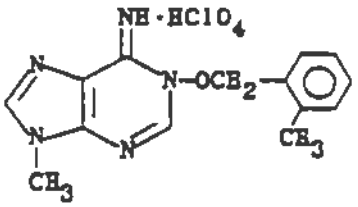
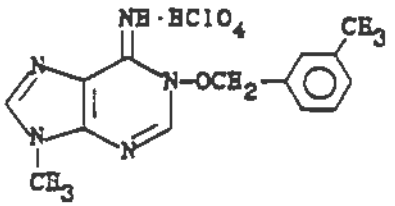
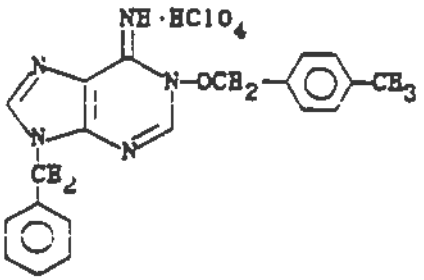
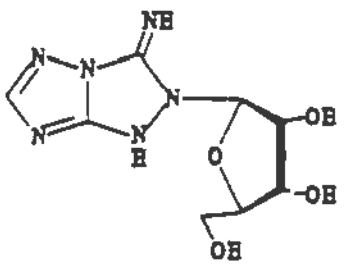
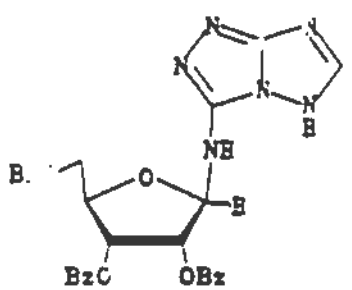
Compound	SRI Number	AVS Number	Amount Submitted
	7133	004122	1.1 g
	7134	004123	1.2 g
	7135	004124	2.0 g
	7150	004204	0.7 g
	7151	004205	0.64 g

Table 3 (Continued)

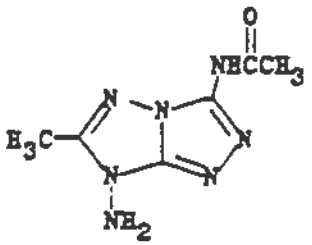
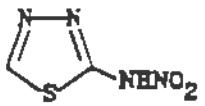
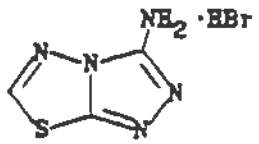
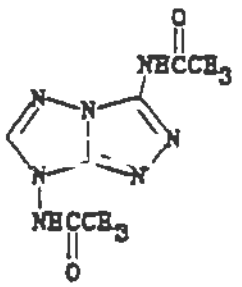
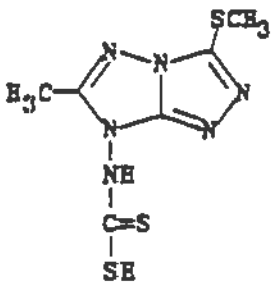
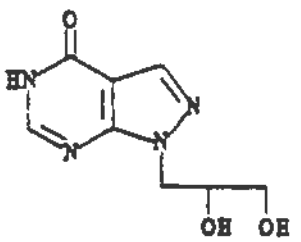
Compound	SRI Number	AVS Number	Amount Submitted
	7152	004206	1.2 g
	7153	004207	1.15 g
	7154	004208	0.82 g
	7158	004213	0.8 g
	7159	004214	1.2 g
	7148	004215	0.8 g

Table 3 (Continued)

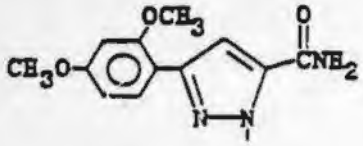
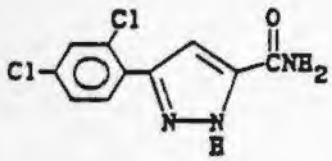
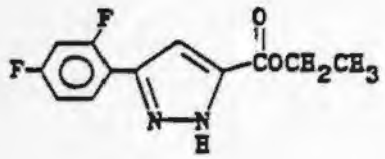
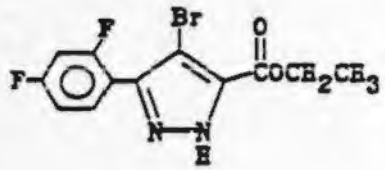
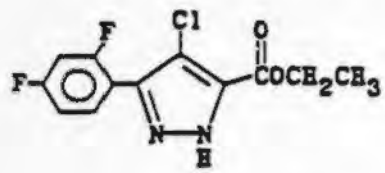
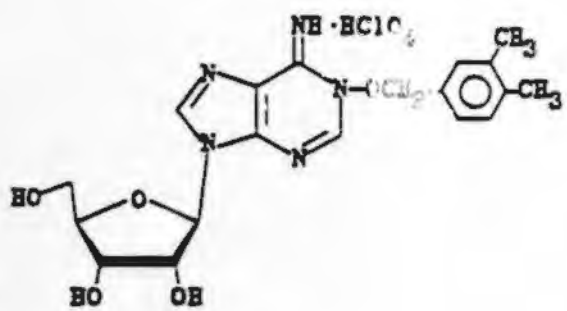
Compound	SRI Number	AVS Number	Amount Submitted
	7160	004215	1.6 g
	7161	004217	1.3 g
	7162	004218	1.9 g
	7163	004219	1.1 g
	7164	004220	1.0 g
	7168	004224	1.5 g

Table 3 (Continued)

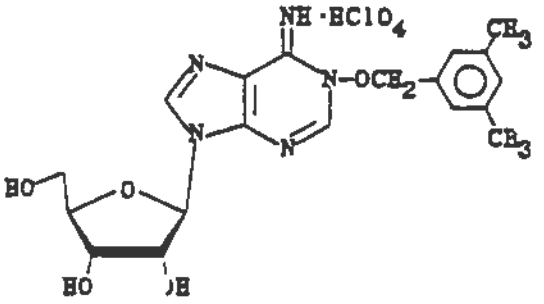
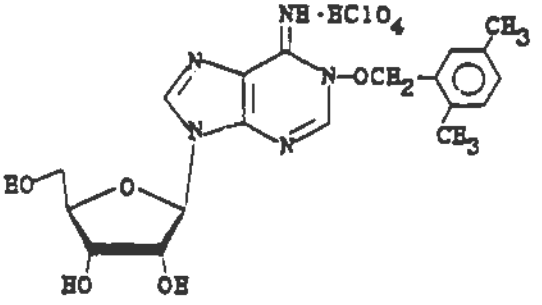
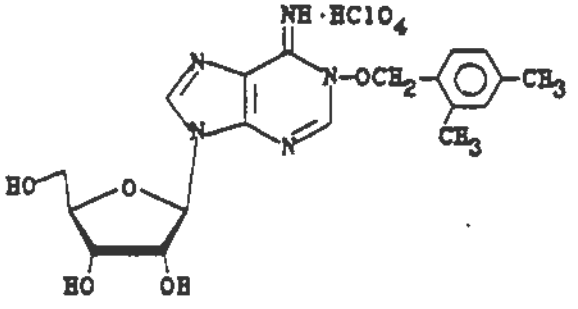
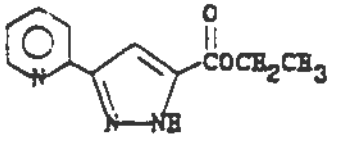
Compound	SRI Number	AVS Number	Amount Submitted
	7169	004225	2.0 g
	7170	004226	1.2 g
	7171	004227	0.8 g
	7172	004228	1.6 g

Table 3 (Continued)

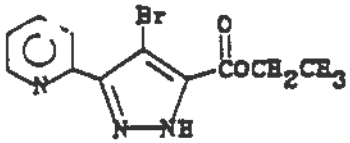
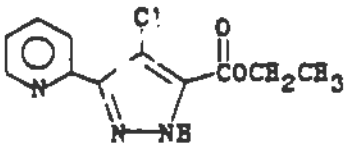
Compound	SRI Number	AVS Number	Amount Submitted
	7173	004229	2.0 g
	7174	004230	1.8 g

Table 3 (Continued)

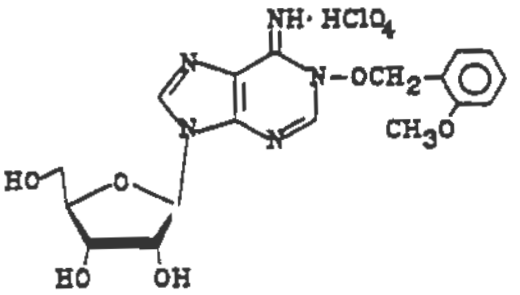
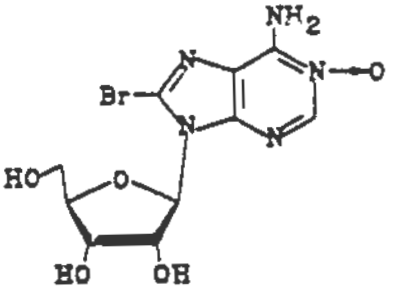
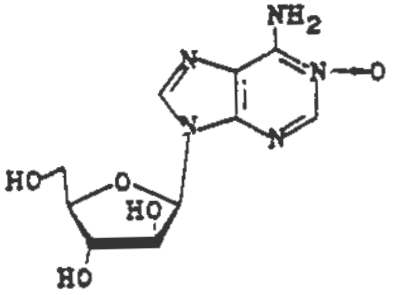
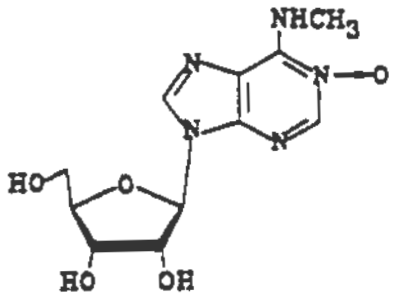
Compound	SRI Number	AVS Number	Amount Submitted
	7187	004533	850 mg
	7188	004532	440 mg
	7189	004531	700 mg
	7190	004530	500 mg

Table 3 (Continued)

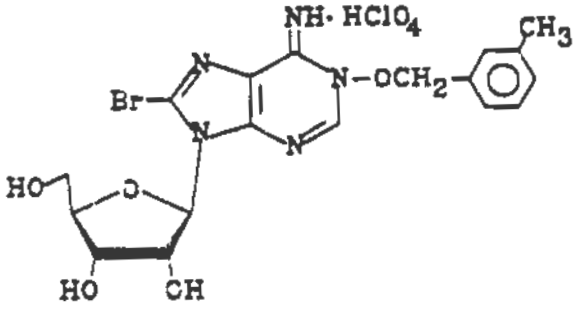
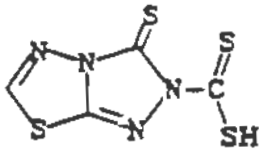
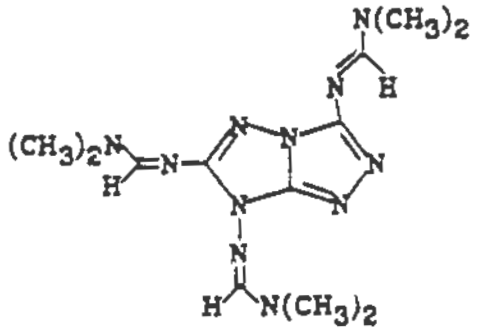
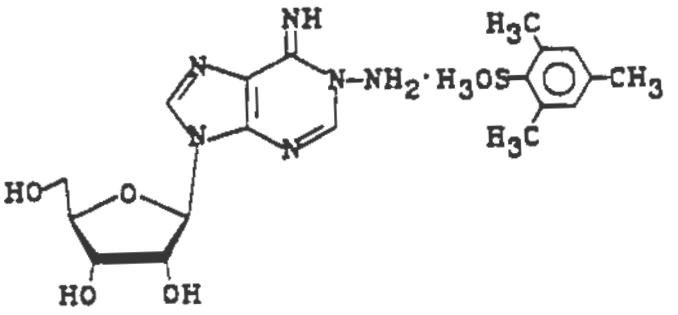
Compound	SRI Number	AVS Number	Amount Submitted
	7191	004528	900 mg
	7192	004589	1.8 g
	7193	004587	1.5 g
	7194	004588	0.7 g

Table 3 (Continued)

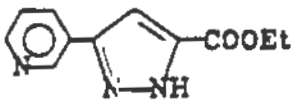
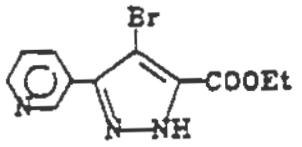
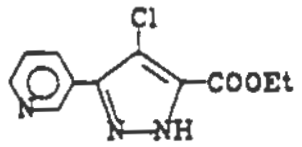
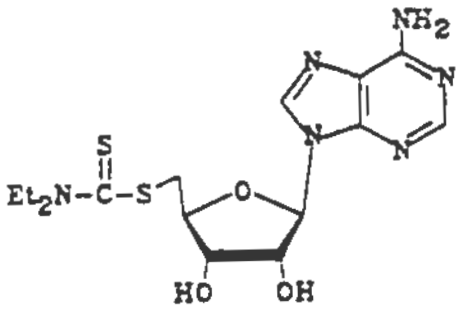
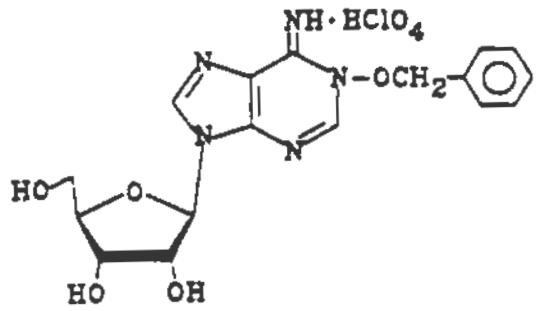
Compound	SRI Number	AVS Number	Amount Submitted
	7205	004612	1.4 g
	7206	004613	1.5 g
	7207		1.2 g
	7208	004618	0.6 g
	7214	004619	2.0 g

Table 3 (Continued)

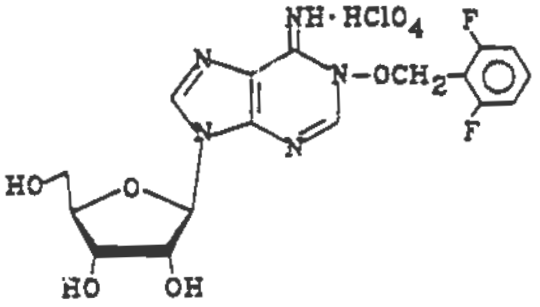
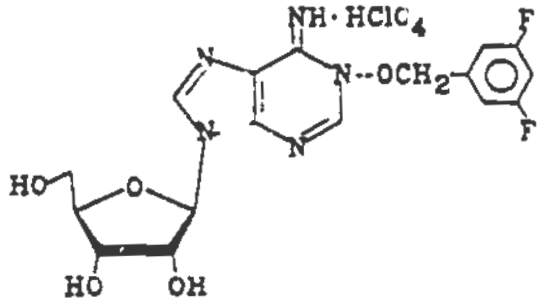
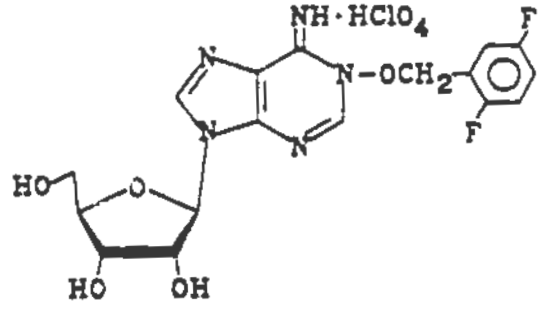
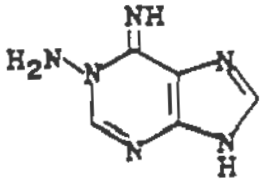
Compound	SRI Number	AVS Number	Amount Submitted
	7215	004620	1.0 g
	7216	004621	1.0 g
	7217	004622	2.0 g
	7220	004623	450 mg

Table 3 (Continued)

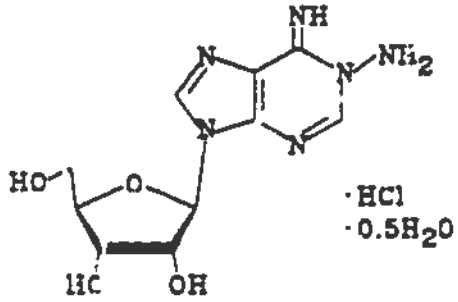
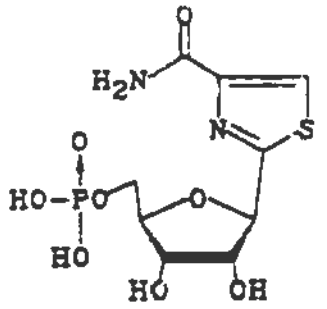
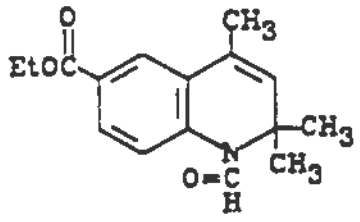
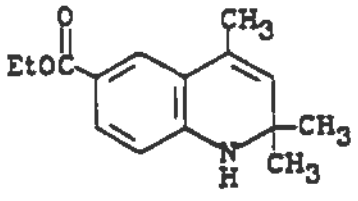
Compound	SRI Number	AVS Number	Amount Submitted
 ·HCl ·0.5H_2O	7221	004624	696 mg
	7186		4.75 g
	7226	004721	1.0 g
	7227	004720	0.9 g

Table 3 (Continued)

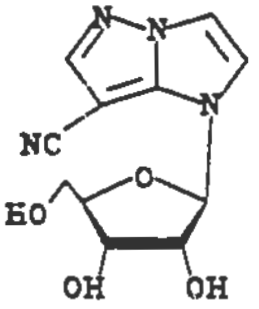
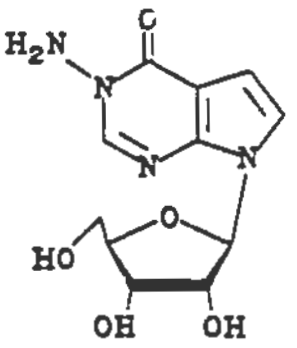
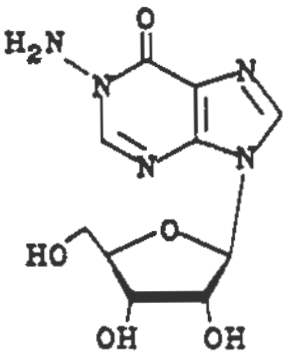
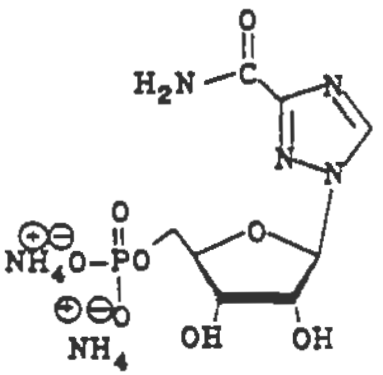
Compound	SRI Number	AVS Number	Amount Submitted
	7259	004926	0.4 g
	4961	004685	0.200 g
	7238	004866	0.247 g
	7251	004871	0.210 g

Table 3 (Continued)

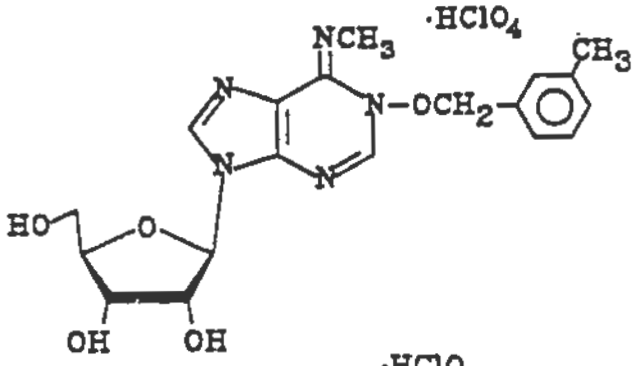
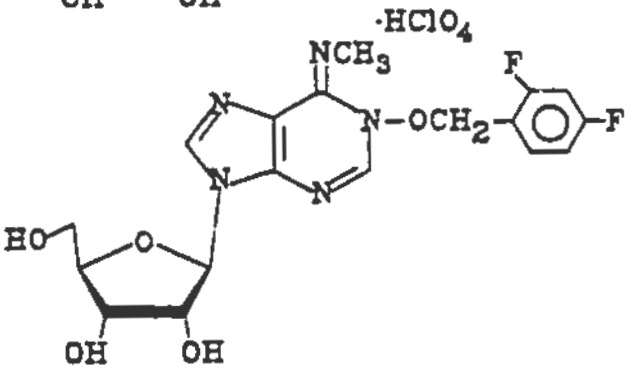
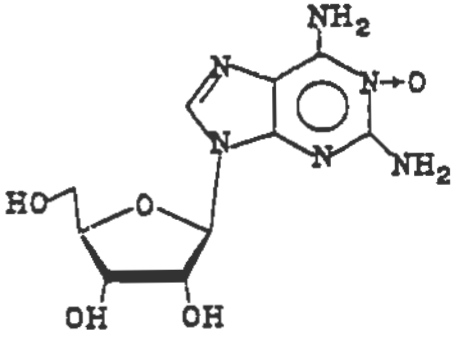
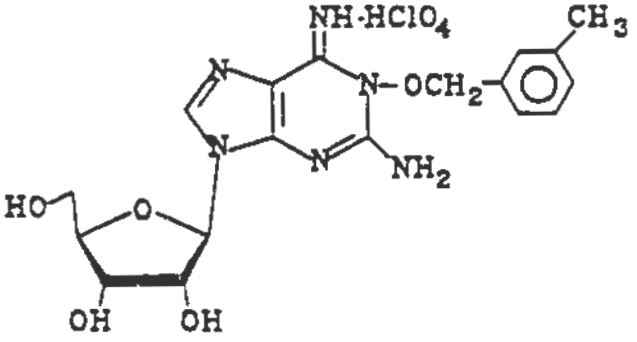
Compound	SRI Number	AVS Number	Amount Submitted
	7252	004872	0.800 g
	7253	004873	0.450 g
	7254	004874	0.450 g
	7255	004875	0.500 g

Table 3 (Continued)

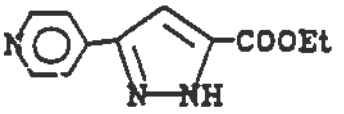
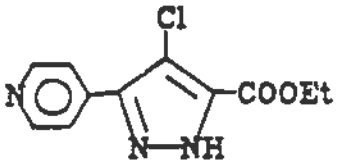
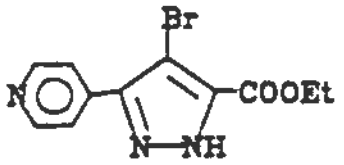
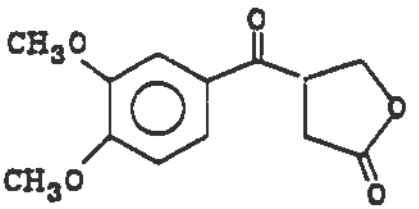
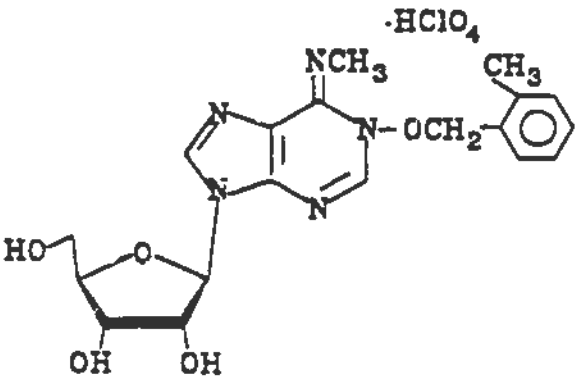
Compound	SRI Number	AVS Number	Amount Submitted
	7269	005047	1.3 g
	7270	005031	1.4 g
	7271	005032	0.7 g
	7272	005033	1.5 g
	7274	005034	0.275 g

Table 3 (Continued)

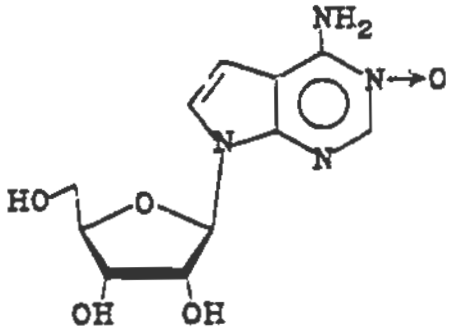
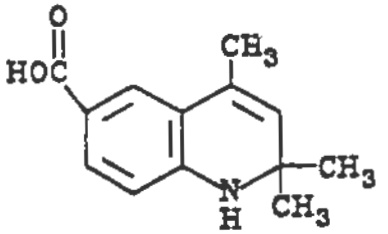
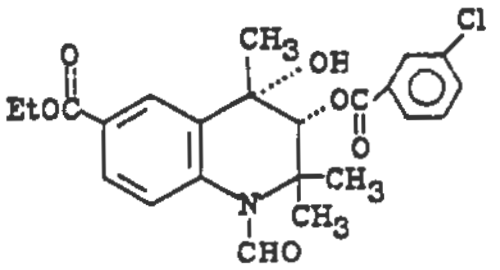
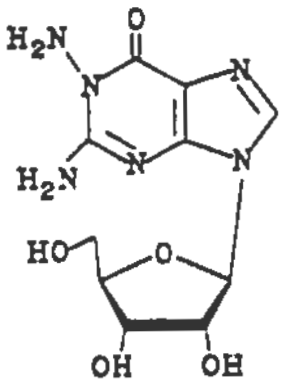
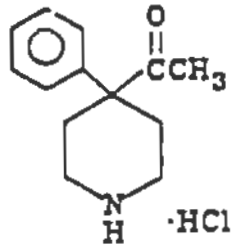
Compound	SRI Number	AVS Number	Amount Submitted
	7275	005035	0.500 g
	7276	005036	0.600 g
	7277	005037	0.600 g
	7278	005038	2.2 g
	7288	005048	4.0 g

Table 3 (Continued)

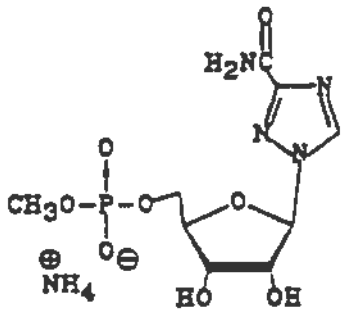
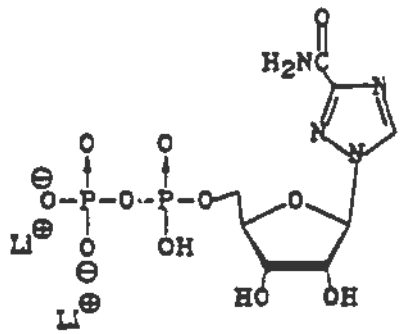
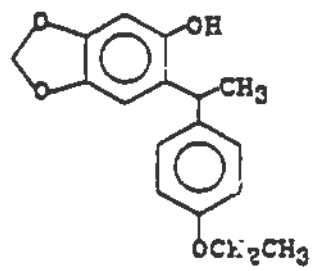
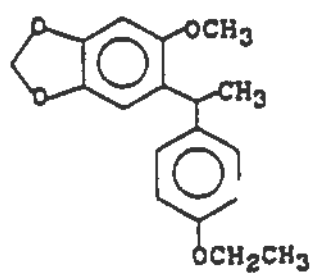
Compound	SoRI Number	AVS Number	Amount Submitted
	7301	005067	2.05 g
	7304	005075	190 mg
	7319	005082	1.2 g
	7320	005083	1.2 g

Table 3 (Continued)

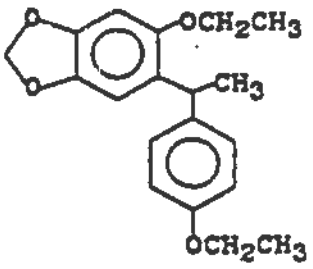
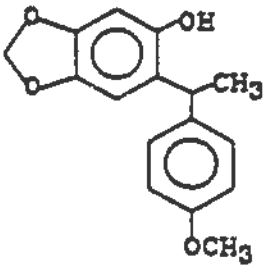
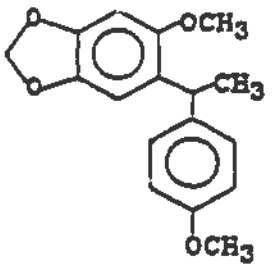
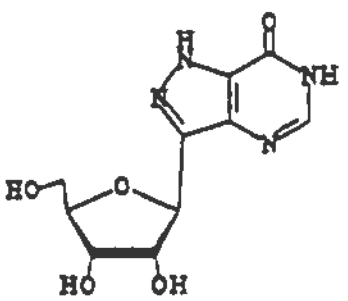
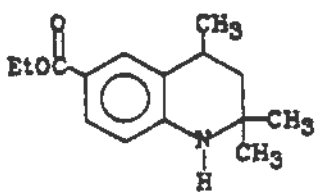
Compound	SoRI Number	AVS Number	Amount Submitted
	7321	005084	1.2 g
	7322	005085	1.2 g
	7323	005086	1.2 g
	7328		5.0 g
	7329	005223	0.6 g

Table 4

Compounds Submitted from December 1, 1988 to November 30, 1989

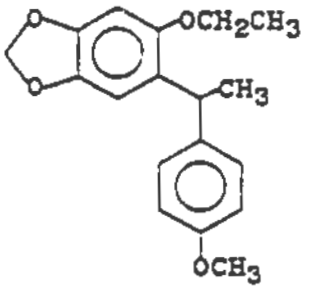
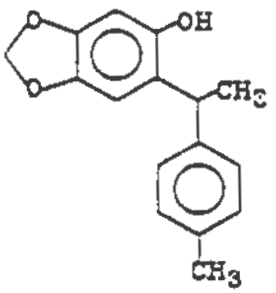
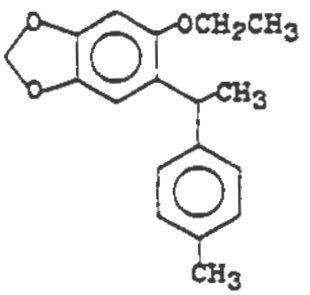
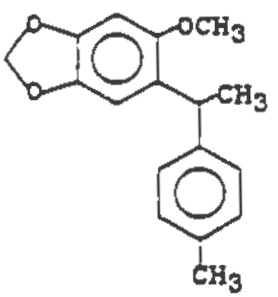
Compound	SoRI Number	AVS Number	Amount Submitted
	7369	005475	1.2 g
	7370	005476	1.2 g
	7371	005477	1.2 g
	7372	005478	1.2 g

Table 4 (Continued)

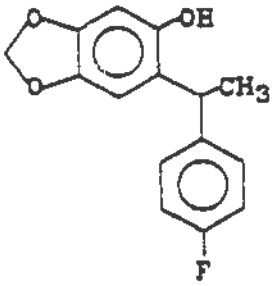
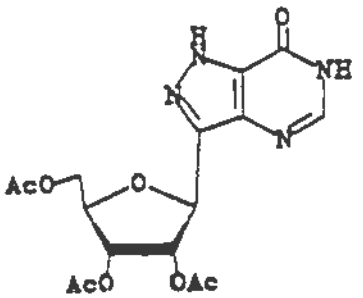
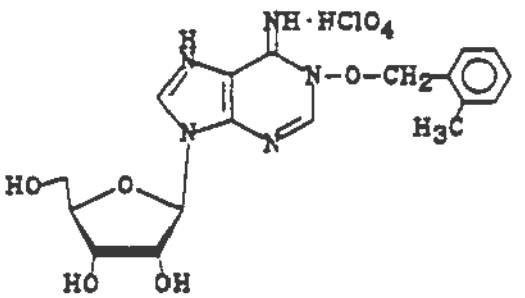
Compound	SoRI Number	AVS Number	Amount Submitted
	7373	005479	1.2 g
	7367		5.0 g
	6867	002875	50 mg

Table 4 (Continued)

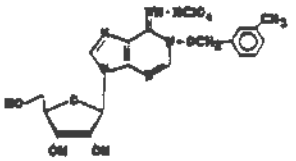
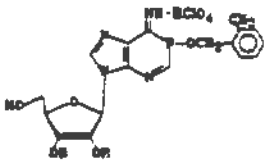
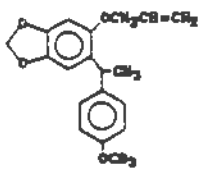
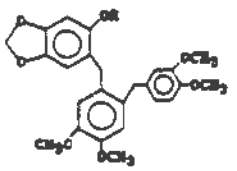
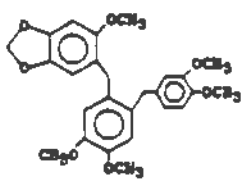
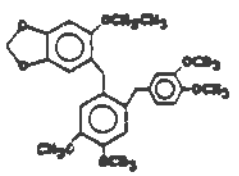
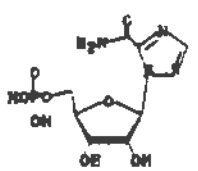
Compound	SRI Number	AVS Number	Amount Submitted
	6767	001986	100 mg
	6887	002875	100 mg
	7394	005576	700 mg
	7393	005575	1.2 g
	7395	005577	1.2 g
	7396	005578	1.2 g
	7398		105 mg

Table 4 (Continued)

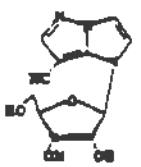
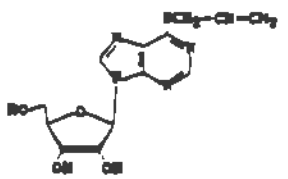
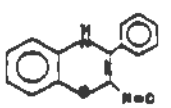
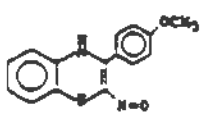
Compound	SRI Number	AVS Number	Amount Submitted
$ClCH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_2Cl$	6362	005586	1 g
$CH_3SO_2CH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_2SO_2CH_3$	6363	005584	1 g
$ClCH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_3$	6440	005583	1 g
$CH_3SO_2CH_2SO_2OCH_2CH_2CH_2CH_2OSO_2CH_3$	6441	005585	1 g
	7259	000223	2 g
	1214		500 mg
	7426	005603	2 g
	7427	005604	1.2 g

Table 4 (Continued)

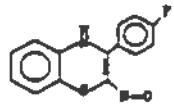
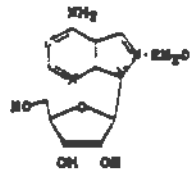
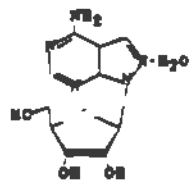
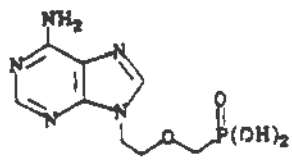
Compound	SRI Number	AVS Number	Amount Submitted
	7428	005605	1.2 g
	7429		3 g
	7430		0.7 g
	7496	005996	1.9 g

Table 4 (Continued)

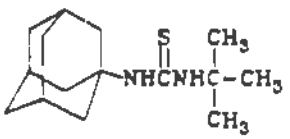
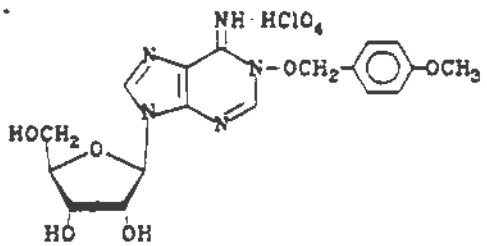
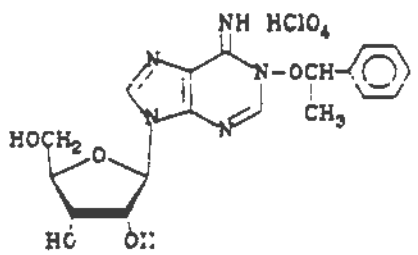
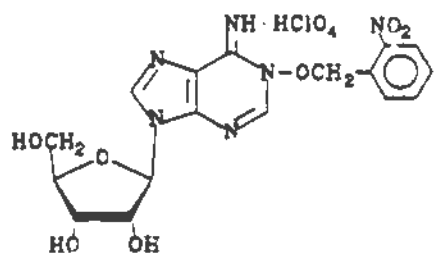
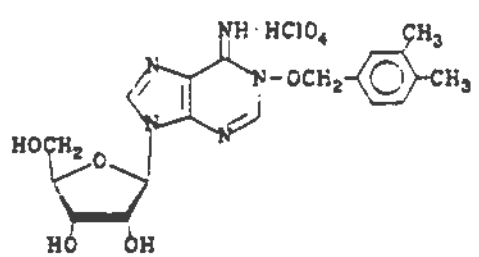
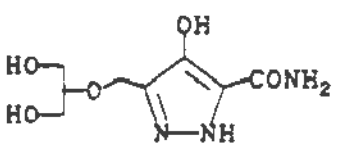
Compound	SRI Number	AVS Number	Amount Submitted
	6892	2885	3.3 g
	7037	3679	5.0 g
	7008	3607	2.0
	6927	2911	2.0 g
	7168	4224	2.0 g
	7494	6108	90 mg

Table 4 (Continued)

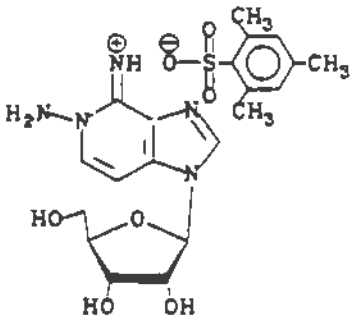
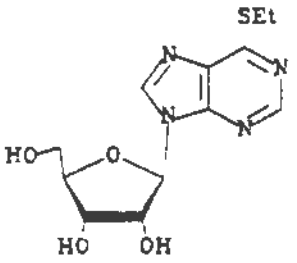
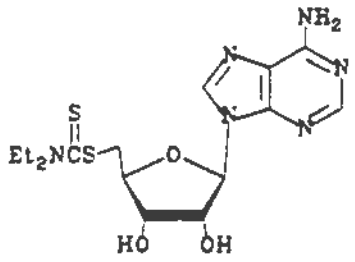
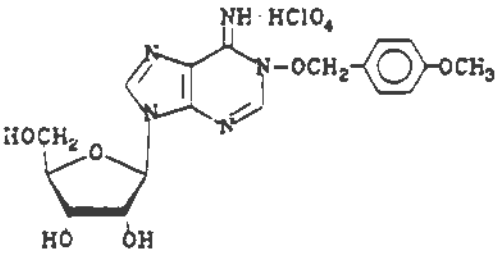
Compound	SRI Number	AVS Number	Amount Submitted
	7194	4588	2.0 g
	1215	2700	5.0 g
	7208	4618	2.0 g
	7037	3679 (second batch)	2.5 g

Table 5

Compounds Submitted from December 1, 1989 to November 30, 1990

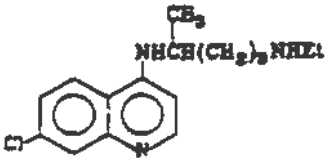
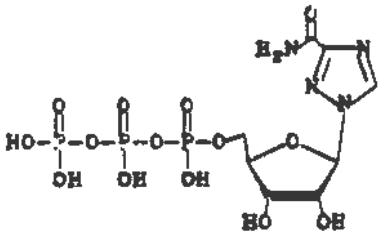
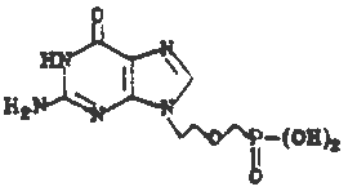
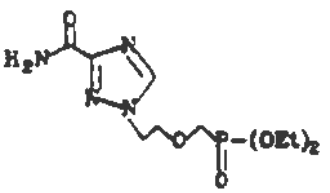
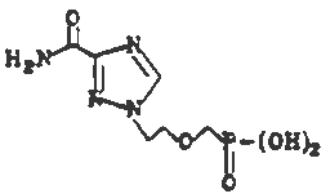
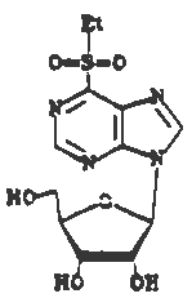
Compound	SRI Number	AVS Number	Amount Submitted
	7086	3980	2.5 g
	7557	6753	255 mg
	7553	6754	710 mg
	7541	6468	350 mg
	7542	6469	30 mg 25 mg
	7547	6752	693 mg

Table 5 (Continued)

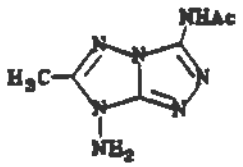
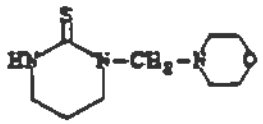
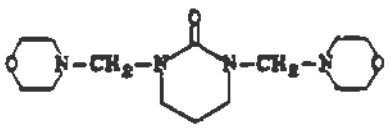
Compound	SRI Number	AVS Number	Amount Submitted
	7152	4206	2.4 g
	7572	6781	1.1 g
	7573	6782	1.0 g

Table 5 (Continued)

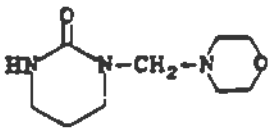
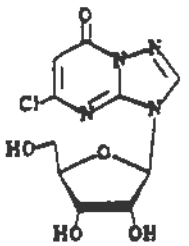
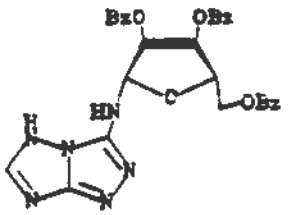
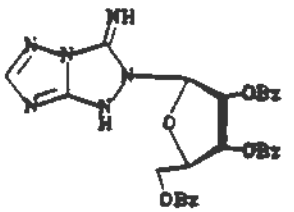
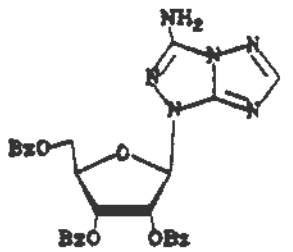
Compound	SRI Number	AVS Number	Amount Submitted
	7589	7120	2.3 g
	7597	124	100 mg
	7151	4205	666 mg
	7586	6787	2.2 g
	7587	6788	1.41 g

Table 5 (Continued)

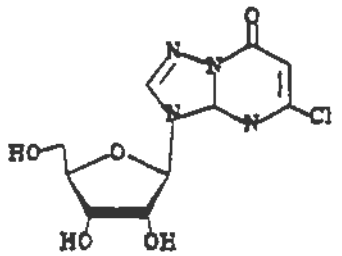
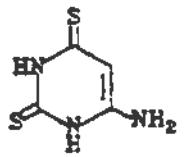
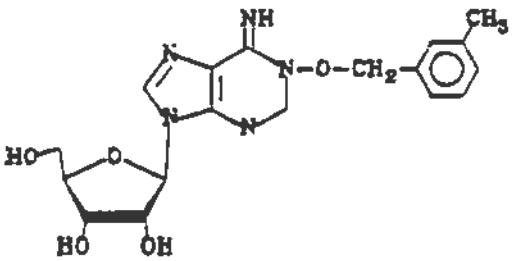
Compound	SRI Number	AVS Number	Amount Submitted
	7597	124	2.0 g
	7687		100 mg
	6767	1986	1.0 g

Table 5 (Continued)

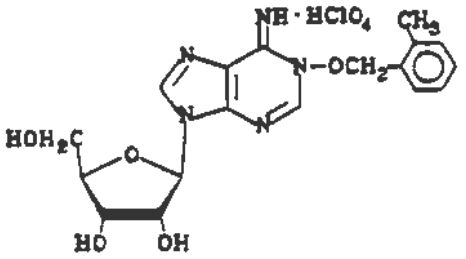
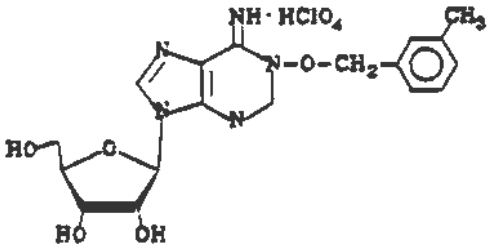
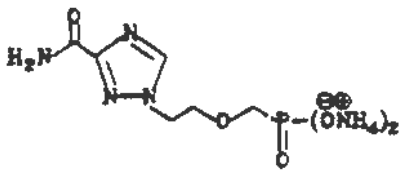
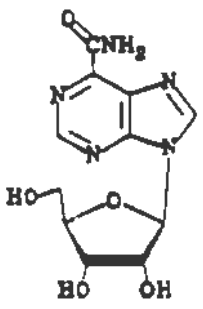
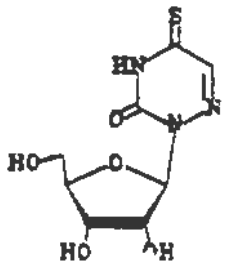
Compound	SRI Number	AVS Number	Amount Submitted
	6887	2875	1.0 g
	6767	1986	1.0 g
	7700	8354	497 mg
	7718	0015	1.9 g
	7717	8355	100 mg

Table 5 (Continued)

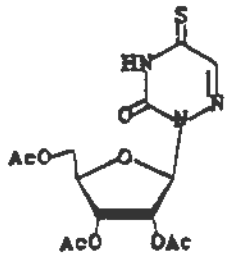
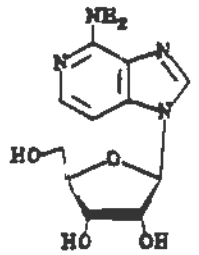
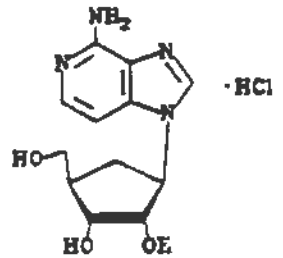
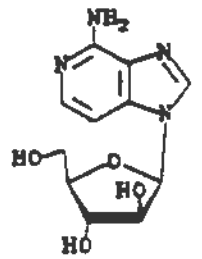
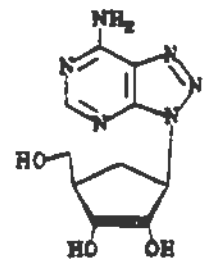
Compound	SRI Number	AVS Number	Amount Submitted
	7699	8353	300 mg
	5944		98 mg
	6251	303	97 mg
	5970		98 mg
	4395		20 mg

Table 5 (Continued)

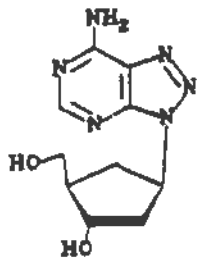
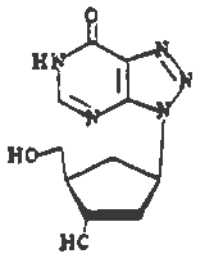
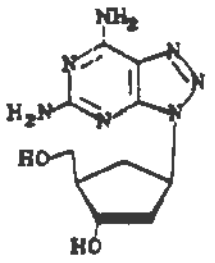
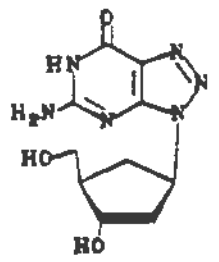
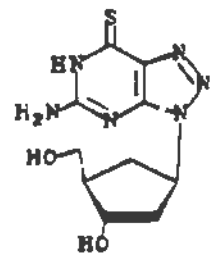
Compound	SRI Number	AVS Number	Amount Submitted
	4541		20 mg
	4552		20 mg
	5160		20 mg
	5174		20 mg
	5566		20 mg

Table 5 (Continued)

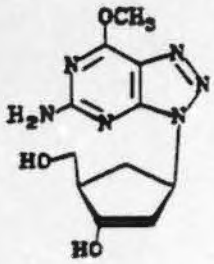
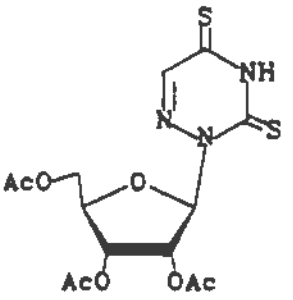
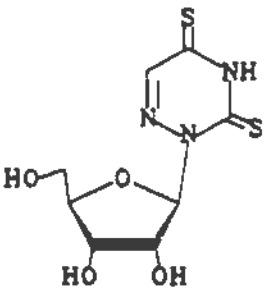
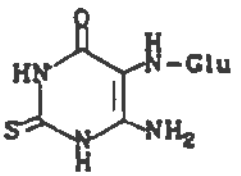
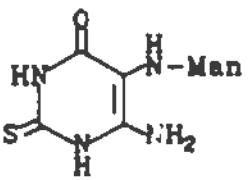
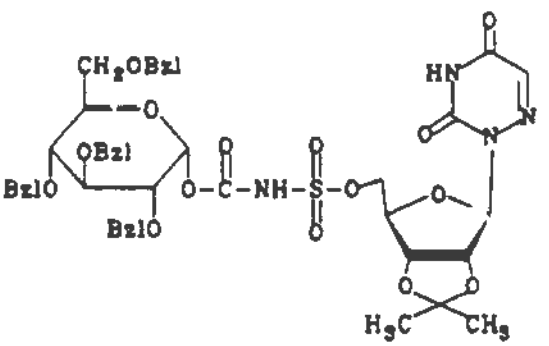
Compound	SRI Number	AVS Number	Amount Submitted
	6560		20 mg

Table 6

Compounds Submitted from December 1, 1990 to February 28, 1991

Compound	SRI Number	AVS Number	Amount Submitted
	7778		300 mg
	7779		300 mg
	7787		200 mg
	7788		200 mg
	7790		46.4 mg

appears in the tables more than once, since additional amounts of the promising compounds were required for more thorough testing.

IV. Chemistry

As previously mentioned, our efforts were directed toward a number of target compounds and compound classes. The following paragraphs provide a synopsis of our activities for each year.

Much of the first year was used in setting up and organizing the laboratory. Furthermore, our targeting of compounds was slowed by the delayed development and distribution of the USAMRIID list of antiviral compounds. Still, we were able to select and synthesize a number of target compounds, basing our choices on our experience and on reported antiviral compounds in the literature. The compounds prepared in the first year included: substituted N^1-benzyloxy adenosine/adenine compounds; *N,N'*-substituted 1,4-phenyldicarboxamide analogs; tetraazadiphosphorines; and ascorbic acid derivatives [as analogs of β-L-*threo*-L-glycero-3-hexulofuranosonic acid, 2-(5'-methyl-2-furanyl)-α-lactone]. We also began pursing the preparation of substituted imidazoles (as precursors to substituted 3-deazaguanines) and 6-substituted (and 6-substituted-8-aza) purine nucleoside analogs.

During the second year, we continued to pursue many of these compounds as well as other targets. A summary of all compounds submitted during this year includes: substituted N^1-benzyloxy adenosine/adenine compounds; selenadiazoles; triazolotriazole compounds; various related 6-substituted analogs in the purine and 8-azapurine; 8-chloro-and 8-methylthio-3-deazapurine; ethyl 5-(substituted phenyl)-2,4-dioxobutyrates as analogs of methyl 4-chloro-5-[2,4-dichlorophenyl]pyrazole-3-carboxylate [AVS-000332]; adamantane derivatives; and allopurinol (or 4-hydroxypyrazolo[3,4-*d*]pyrimidine) analogs. In addition, we also synthesized these USAMRIID requested compounds: 4(5)-bromo-1(3*H*)-imidazole; and desethyl chloroquine; and we submitted five previously synthesized compounds from the SRI compound archives including: ethyl 6-amino-5-nitro-4-[(2-phenyl-2-oxoethyl)amino]pyridin-2-ylcarbamate oxime; ethyl 5-amino-3-(3',4'-dimethoxyphenyl)-2*H*-pyrido[4,3-*b*][1,4]oxazin-7-ylcarbamate; ethyl 5-amino-1,2-dihydro-3-[(*N*-methylanilino)methyl]pyrido[3,4-*b*]pyrazine-7-carbamate, hemiethanolate; 9-ribofuranosyl-2-methylthiopurine; and 9-ribofuranosyl-6-ethylthiopurine.

Our targets for the third year included: substituted N^1-benzyloxy adenosine/adenine compounds (analogs of 2'-deoxyadenosine, 9-benzyladenine, 9-methyladenine, 8-bromoadenosine, 9-β-D-arabinofuranosyladenine, 9-β-D-ribofuranosyl-6-methylaminopurine, 2,6-diamino-9-β-D-ribofuranosylpurine, and 7-deazaadenosine); N^1-aminoadenine and N^1-aminopurinenucleosides; other 5-(substituted phenyl)pyrazole carboxylates and carboxamides; triazolotriazole nucleosides and triazolothiadiazoles; allopurinol acyclonucleosides; and dihydroquinolines and tetrahydroquinolines. Among the USAMRIID-specified compounds were 3-bromo-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one; 5-bromo-3-nitro-1,2,4-triazole; adenosine-N^1-oxide; 6-ethylmercaptopurine riboside; tiazofurin 5'-monophosphate; 7-cyanoimidazo[1,2-*b*]pyrazole; ribavirin 5'-monophosphate, ribavirin 5'-methylphosphate, and ribavirin 5'-diphosphate; and Formycin B. One other USAMRIID-requested activity was the further purification of a USAMRIID-supplied sample of 4-acetyl-4-phenylpiperidine.

Compounds synthesized during the fourth year included: more N^1-benzyloxyadenosines; 6-benzyl-1,3-dioxoles (as podophyllotoxin and Justicidin B analogs); 3-phenyl-1,4-benzothiazin-2-one oximes; methanesulfonic acid derivatives; formycin B 2′,3′,5′-triacetate [AVS-0096]; the free acid of ribavirin monophosphate; 1-ribofuranosyl-7-cyanoimidazo[1,2-*b*]pyrazole; 6-allylmercaptopurine riboside; 6-ethylmercaptopurine riboside [AVS-2700]; 4-amino-1-β-D-ribofuranosyl-pyrazolo[3,4-*d*]pyrimidine; 3-*t*-butyl-1-adamantylthiourea; 9-(2-phosphonylmethoxyethyl)adenine (PMEA); 5-(1,3-dihydroxy-2-propoxy)-4-hydroxy-1,2-pyrazole-3-carboxamide; N^1-aminoadenosine mesitylenesulfonate salt; and adenosine 5′-diethylthiocarbamate.

During the fifth year, the compounds submitted for screening included: 4-(4′-ethylamino-1′-methylbutylamino)-7-chloroquinoline [AVS-3980]; ribavirin triphospbate; 9-[2-(phosphonylmethoxy)ethyl]-guanine (PMEG); 1-(2-(phosphonylmethoxyethyl)-1,2,4-triazole-3-carboxamide; the diammonium salt of 1-[(phosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide (AVS-6469); 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide; 6-ethylsulfonyl-9-β-D-ribofuranosylpurine; 3-acetamido-7-amino-6-methyl-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (AVS-4206); 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)pyrimidinone; 1-morpholinomethyltetrahydro-2(1*H*)pyrimidinethione; 1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinone; two batches of 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (AVS-0124); 3-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (AVS-4205); 3-imino-2*H*-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole; 3-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole; 6-amino-2,4-dithiouracil; multiple batches of 1-(3-methylbenzyloxy)adenosine (AVS 1986), 1-(2-methylbenzyloxy)adenosine (AVS-2875); 6-carboxamidopurine riboside (AVS-0015); 4-thio-6-azauridine; the triacetate of 4-thio-6-azauridine; 3-deazaadenosine; carbocyclic 3-deazaadenosine; arabino-3-deazaadenosine; carbocyclic 8-azaadenosine; carbocyclic 2′-deoxy-8-azaadenosine; carbocyclic 2′-deoxy-8-azainosine; carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside; carbocyclic 2′-deoxy-8-azaguanosine; carbocyclic 2′-deoxy-8-aza-6-thioguanosine; and carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside.

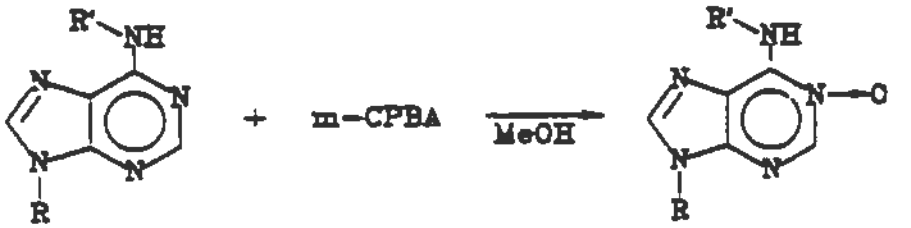
During the final three months comprising the contract extension period, we synthesized and submitted the following compounds for screening: 4-amino-5-glucosylamino-2-thiouracil; 4-amino-5-mannosylamino-2-thiouracil; 2,4-dithio-6-azauridine; 2′,3′,5′-tri-*O*-acetyl-2,4-dithio-6-azauridine; and 5′-*O*-[[[[2′,3′,4′,6′-tetra-*O*-benzyl-α-D-(glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2′,3′-isopropylidene-6-azauridine.

The following paragraphs provide descriptions of the procedures used to synthesize the compounds under this contract.

Substituted N^1-Benzyloxy Adenosine/Adenine Compounds

These compounds were pursued because they had been previously prepared at SRI and had been found to have some antiviral activity. The preparations for all of the *O*-alkylated analogs of adenosine N^1-oxide followed the same general procedure, and therefore, only summarized data will be presented for many of the analogs. The precursor for these analogs was the parent compound adenosine N^1-oxide (1a), which was prepared by oxidation of adenosine with *m*-chloroperoxybenzoic acid,[1-3] as shown in Scheme I. Compound 1a was alkylated with the appropriately substituted benzyl and alkyl bromides to give the corresponding alkylated N^1-oxyadenosines, and the resulting adducts were then immediately converted to and isolated as their respective perchlorate salts, as shown and listed in Figure 1. The submitted alkylated N^1-oxyadenosines are

Scheme I



1

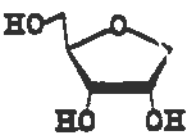
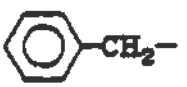
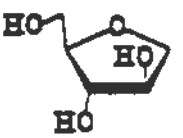
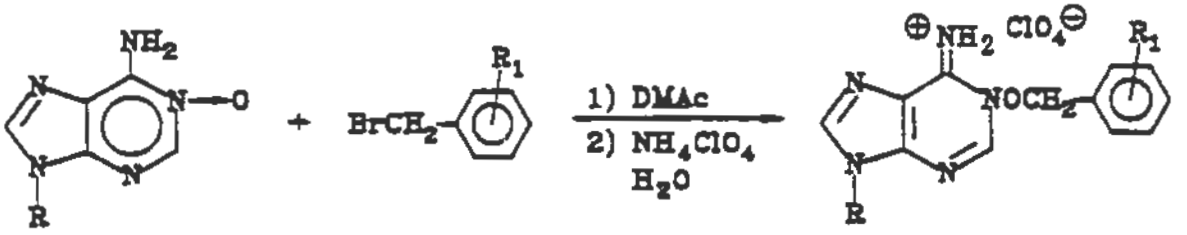
	R	R'
1a		H
1b		H
1c		H
1d	CH_3–	H
1e		CH_3–
1f		H

Figure 1



2

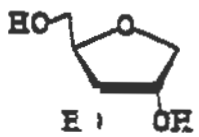
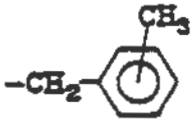
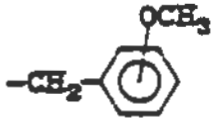
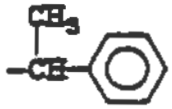
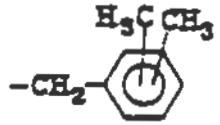
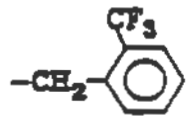
	R	R_1	Position
2a			2 3 4
2b	"		2 3 4
2c	"		
2d	"		2 3 4
2e	"		2,4 3,4 2,5 2,6 3,5
2f	"		2,4 3,4 2,5 3,5
2g	"		

Figure 1 (Continued)

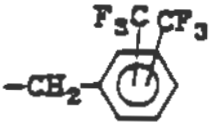
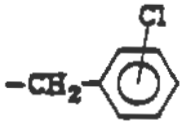
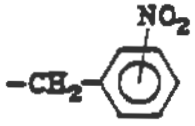
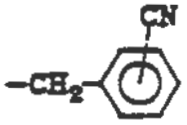
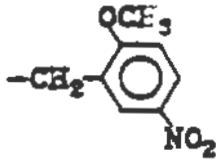
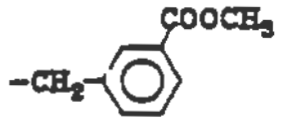
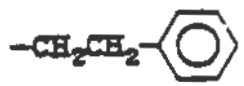
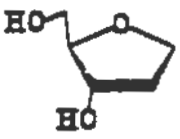
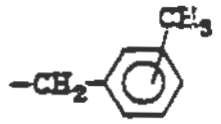
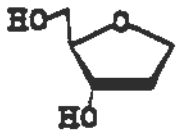
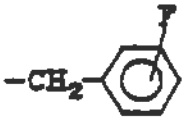
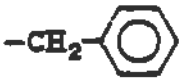
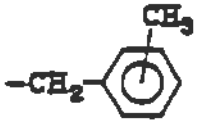
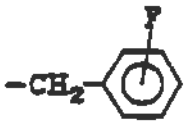
	R	R_1	Position
2h			2,4 3,5
2i	"		2 3
2j	"		2 3 4
2k	"		2 3 4
2l	"		
2m	"		
2n	"		
2o	"		
2p			2 3 4

Figure 1 (Continued)

	R	R_1	Position
2q			2 3 4
2r			2 3 4
2s	"		2 3 4
2t	"	$-CH_2CH_3$	
2u	$-CH_3$		2 3

indicated as **2a-o**. (Pertinent data for these compounds and the following alkylated N^1-oxyadenine analogs are also given in **Tables 1** and **2**.)

We also synthesized N^1-oxy- and N^1-benzyloxy- analogs of 2′-deoxyadenosine, 9-benzyladenine,[4,5] and 9-methyladenine. As is also shown in **Schemes I** and **II**, the N^1-oxide precursors for these compounds were also made by treatment of the corresponding, 2′-deoxyadenosine, 9-benzyladenine, and 9-methyladenine with *m*-chloroperoxybenzoic acid[1-3] to give their corresponding N^1-oxides **1b-d**. (The syntheses for 9-benzyl- and 9-methyladenine are given in **Scheme III**.) These N^1-oxides were then alkylated with the appropriately substituted benzyl bromides as indicated and converted to their respective perchlorate salts **2p-u**, as shown in **Figure 1**. Since, the procedures for making all of these compounds again were identical, we have supplied only summarized information and analytical data for these compounds in the experimental section. No detailed synthetic procedures have been provided for these compounds.

Other synthesized N^1-oxide- and 1-benzyloxy- analogs include those of the following compounds: 9-β-D-ribofuranosyl-6-methylaminopurine;arabinofuranosyladenine;8-bromoadenosine;2,6-diamino-9-β-D-ribofuranosylpurine, and 7-deazaadenosine. (**Scheme IV** shows the synthesis of 9-β-D-ribofuranosyl-6-methylaminopurine.) As shown in **Schemes I, II**, and **IV**, the N^1-oxides of these compounds, **1e-i**, respectively were prepared by the oxidation of these nucleosides with *m*-chloroperoxybenzoic acid. N^1-oxides **1e** and **1g-h** were then alkylated with the indicated benzyl bromides to give the 1-benzyloxyadenosine analogs **2v-w**, **2x**, and **2y**, respectively, as shown in Figure 2.

<u>*N,N′*-Substituted 1,4-Phenyldicarboxamide analogs</u>

Compounds **4-9** had been previously prepared at SRI, and therefore, submittable quantities were already available in our compound archives. Before these compounds were submitted, they were purified and recharacterized to ensure their integrities (**Scheme V**).

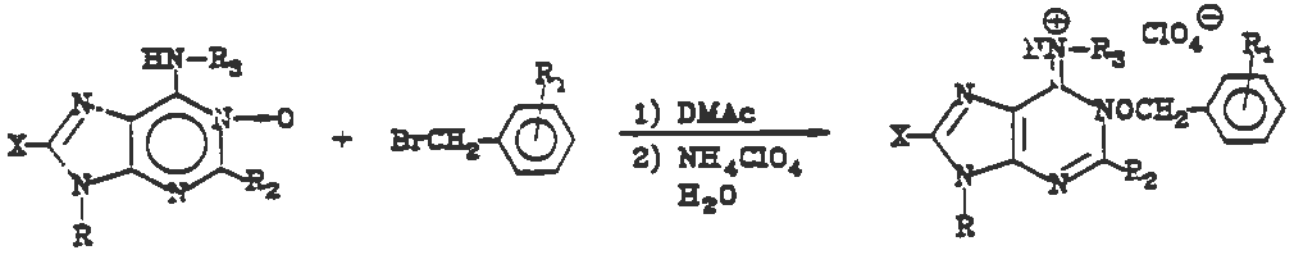
<u>Tetraazadiphosphorines</u>

The synthesis of these compounds was based on the activity that compound **10** had shown in the USAMRIID screen. Compound **12** was synthesized by adding phenyl dichlorophosphate in acetonitrile to a solution of triethylamine and anhydrous hydrazine in acetonitrile, while analogous routes were used to synthesize other congeners. We made compounds **15**[6] and **17**[7,8] by following the route shown in **Scheme VI**. The main difficulty in preparing these compounds was the separation and purification of the desired products from the mixtures obtained in the reaction sequences. Similar, but more severe problems were encountered in our attempts to synthesize compound **16** by the analogous approach also shown in **Scheme III**. Since this meant that the isolation of compound **16** would probably be labor and time intensive, we decided to shift our efforts toward other potential targets.

<u>Ascorbic Acid Derivatives (As Analogs of β-L-*Threo*-L-glycero-3-hexulofuranosonic Acid, 2-(5′-Methyl-2-furanyl)-g-lactone)</u>

Compounds **18-20** were requested by Dr. Ussery and were synthesized by the route shown in **Scheme VII**.[9] Dimethoxymethylfuran (**22**) was first made from 2-methylfuran by treatment with bromine and potassium acetate,[10] and then it was coupled with L-ascorbic acid to produce **18**. Complexes **19** and **20** were then formed by incubation of **18** with succinic anhydride and succinimide, respectively.[9]

Figure 2



2

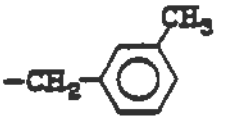
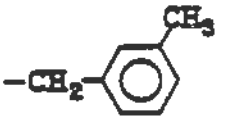
	R	R_1	Position	R_2	R_3	X
2v			2 3	H	CH_3	H
2w	"		2,4	H	CH_3	H
2x	"			NH_2	H	H
2y	"			H	H	Br

Table 7

Product	Nucleoside	MCPBA	MeOH	Yield	Mp cap.	M.F. C, H, N Theory	Found
Ado-N^1-Ox (1a)	Ado 5 g (18.7 mmol)	5.4 g	500 mL	3.7 g (70%)	222-225 °C	$C_{10}H_{13}N_5O_5$ C = 42.40, H = 4.63, N = 24.73	C = 42.45 H = 4.64 N = 24.66
dAdo-N^1-Ox (1b)	dAdo 1.0 g (3.72 mmol)	1.2 g	100 mL	1.0 g (100%)	219-221 °C dec.	$C_{10}H_{13}N_5O_4 \cdot 0.40H_2O$ C = 43.76, H = 5.07, N = 25.52	C = 43.83 H = 5.06 N = 25.28
9-Bn-Ad-N^1-Ox (1c)	9-Bn-Ad 2 g (8.89 mmol)	1.9 g	160 mL	1.3 g (62%)	270-272 °C dec.	$C_{12}H_{11}N_5O$ C = 59.74, H = 4.60, N = 29.03	C = 59.74 H = 4.64 N = 28.98
9-Me-Ad-N^1-Ox (1d)	9-Me-Ad 9.5 g (63.8 mmol)	16.5 g	800 mL	5.3 g	>300 °C	$C_6H_7N_5O$ C = 43.63, H = 4.27, N = 42.41	C = 43.62 H = 4.30 N = 42.36
N^6-Me-Ado-N^1-Ox (1e)	N^6-Me-Ado 2.0 g (7.12 mmol)	3.5 g	80 mL	620 mg (30%)	142-152 °C	$C_{11}H_{15}N_5O_5 \cdot 0.25CHCl_3 \cdot$ 0.30EtOH C = 42.03, H = 5.08, N = 20.68	C = 42.12 H = 5.02 N = 20.74
9-Ara-Ad-N^1-Ox (1f)	9-Ara-Ad 930 mg (3.48 mmol)	900 mg	100 mL	840 mg (85%)	>250 °C	$C_{10}H_{13}N_5O_5 \cdot 0.05EtOH$ C = 42.48, H = 4.69, N = 24.53	C = 42.59 H = 4.69 N = 24.46

Table 7 (Continued)

Product	Nucleoside	MCPBA	MeOH	Yield	Mp cap.	M.F. C, H, N Theory	Found
8-Br-Ado-N^1-Ox (1g)	8-Br-Ado 2 g (5.8 mmol)	1.5 g	175 mL	490 mg (23%)	180-190 °C dec.	$C_{10}H_{12}BrN_5O_5$ · 0.10MeOH	C = 33.38 H = 3.37 N = 19.16
						C = 33.20, H = 3.42, N = 19.17	
2,6-DAPR-N^1-Ox (1h)	2,6-DAPR 780 mg (2.77 mmol)	780 mg	100 mL	630 mg (76%)	>250 °C	$C_{10}H_{14}N_6O_5 \cdot 0.60H_2O$ · 0.30EtOH	C = 39.42 H = 5.10 N = 25.91
						C = 39.43, H = 5.26, N = 26.03	
C^7-Ado-N^1-Ox (1i)	7-D-Ado 1 g (3.76 mmol)	960 mg	100 mL	1.03 g (97%)	>250 °C	$C_{11}H_{14}N_4O_5$ · 0.40EtOAc · $0.10H_2O$	C = 47.41 H = 5.46 N = 17.39
						C = 47.40, H = 5.49, N = 17.54	

Table 8. Substituted N'-Benzyloxyadenosines

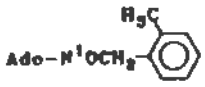
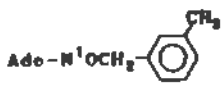
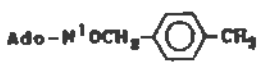
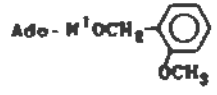
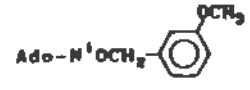
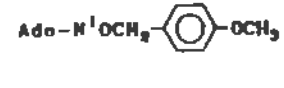
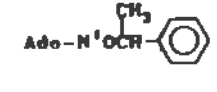
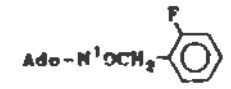
	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4CHO_2	Yield (%)	M.P. Cap	M.F. C, H, N Theory	Found
2n-2		3 g (10.6 mmol)	9.8 g (53 mmol)	60 mL	6.25 g 25 mL H_2O	4 g (77%)	122-125 °C dec.	$C_{18}H_{22}ClN_5O_9 \cdot 0.75H_2O$ C = 43.12, H = 4.72, N = 13.97	C = 43.18 H = 4.67 N = 14.18
2n-3		2.7 g (9.54 mmol)	8.82 g (47.7 mmol)	60 mL	5.85 g 25 mL H_2O	2.6 (56%)	116-118 °C	$C_{18}H_{22}ClN_5O_9 \cdot H_2O$ C = 42.74, H = 4.78, N = 13.85	C = 42.70 H = 4.67 N = 13.70
2n-4		2.5 g (8.83 mmol)	4.9 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	1.9 g (44%)	117-122 °C dec.	$C_{18}H_{22}ClN_5O_9 \cdot 0.25H_2O$ C = 43.91, H = 4.61, N = 14.22	C = 44.06 H = 4.66 N = 14.36
2b-2		2.5 g (8.83 mmol)	5 g	40 mL	5 g 25 mL H_2O	900 mg (20%)	157-162 °C	$C_{18}H_{22}ClN_5O_{10} \cdot 0.25Et_2O$ C = 43.68, H = 4.73, N = 13.41	C = 43.72 H = 4.56 N = 13.34
2b-3		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	2.3 g (52%)	109-119 °C	$C_{18}H_{22}ClN_5O_{10} \cdot 1.25H_2O$ C = 41.07, H = 4.50, N = 13.31	C = 40.86 H = 4.60 N = 13.32
2b-4		2.5 g (8.83 mmol)	5 mL	50 mL	5 g 25 mL H_2O	2.4 g (55%)	123-129 °C	$C_{18}H_{22}ClN_5O_{10} \cdot H_2O$ C = 41.43, H = 4.64, N = 13.42	C = 41.33 H = 4.68 N = 13.32
2c		2.5 g (8.83 mmol)	5 mL	50 mL	5 g 25 mL H_2O	1.7 g (40%)	128-133 °C	$C_{18}H_{22}ClN_5O_9 \cdot H_2O$ C = 42.74, H = 4.78, N = 13.84	C = 42.66 H = 4.71 N = 13.96
2d-2		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	3.3 g (77%)	110-116 °C	$C_{17}H_{19}ClFN_5O_9 \cdot H_2O$ C = 40.05, H = 4.15, N = 13.74	C = 40.16 H = 4.08 N = 13.79

Table 8 (Continued)

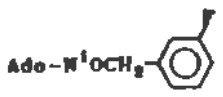
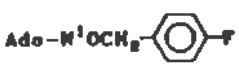
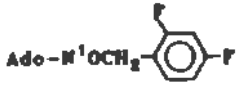
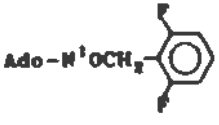
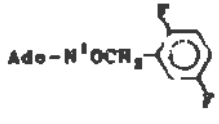
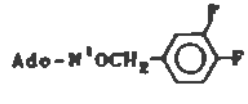
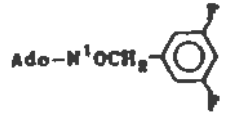
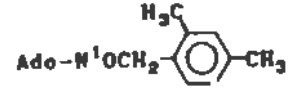
	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P.	M.F. C, H, N Theory	Found
2d-3		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	3.3 g (77%)	106-114 °C	$C_{17}H_{19}ClFN_5O_9 \cdot H_2O$ C = 40.05, H = 4.15, N = 13.74	C = 40.20 H = 4.03 N = 13.81
2d-4		3 g (10.6 mmol)	10 g (53 mmol)	60 mL	6.2 g 25 mL H_2O	2.3 g (44%)	143-146 °C	$C_{17}H_{19}ClFN_5O_9 \cdot 0.75H_2O$ C = 40.40, H = 4.09, N = 13.86	C = 40.20 H = 4.13 N = 13.99
2e-2,4		2.5 g (8.83 mmol)	5 g (24.2 mmol)	50 mL	5 g 25 mL H_2O	1.7 g (38%)	116-120 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot H_2O$ C = 38.68, H = 3.82, N = 13.27	C = 38.58 H = 3.66 N = 13.40
2e-2,6		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	1.75 g (39%)	114-122 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot H_2O$ C = 38.68, H = 3.82, N = 13.27	C = 38.81 H = 3.81 N = 13.24
2e-2,5		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	3.4 g (76%)	108-118 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot 0.75H_2O$ C = 39.02, H = 3.76, N = 13.38	C = 39.00 H = 3.76 N = 13.30
2e-3,4		2.5 g (8.83 mmol)	5 g (24.2 mmol)	50 mL	5 g 25 mL H_2O	1.1 g (24%)	116-122 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot 0.75H_2O$ C = 39.02, H = 3.76, N = 13.38	C = 38.98 H = 3.60 N = 13.48
2e-3,5		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	2 g (44%)	129-134 °C	$C_{17}H_{18}ClF_2N_5O_9 \cdot 0.625H_2O$ C = 39.18, H = 3.72, N = 13.44	C = 39.22 H = 3.74 N = 13.36
2f-2,4		2 g (7.09 mmol)	3 mL	30 mL	4 g 20 mL H_2O	1.1 g (31%)	120-130 °C	$C_{19}H_{24}ClN_5O_9 \cdot 0.75H_2O$ C = 44.28, H = 4.99, N = 13.59	C = 44.38 H = 4.90 N = 13.65

Table 8 (Continued)

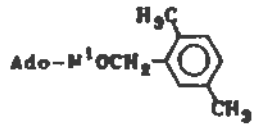
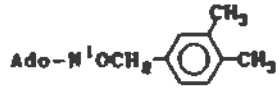
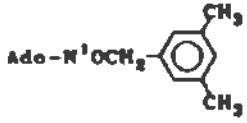
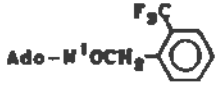
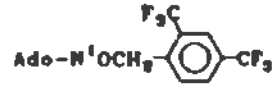
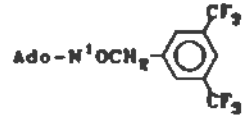
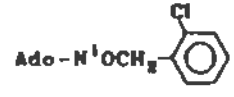
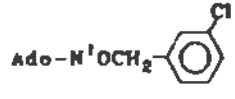
	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P. Cap	M.F. C, H, N Theory	Found
2f-2,5		1.5 g (5.32 mmol)	2 mL	30 mL	3 g 15 mL H_2O	1.8 g (67%)	117-123 °C	$C_{19}H_{24}ClN_5O_9 \cdot H_2O$ C = 43.89, H = 5.04, N = 13.47	C = 43.96 H = 5.12 N = 13.58
2f-3,4		1.5 g (5.32 mmol)	3 mL	30 mL	3 g 15 mL H_2O	2.25 g (84%)	139-142 °C	$C_{19}H_{24}ClN_5O_9 \cdot H_2O$ C = 43.89, H = 5.04, N = 13.47	C = 44.00 H = 5.02 N = 13.38
2f-3,5		2.5 g (8.83 mmol)	5 g	50 mL	5 g 25 mL H_2O	3.5 g (80%)	154-158 °C	$C_{19}H_{24}ClN_5O_9 \cdot 0.625H_2O$ C = 44.47, H = 4.96, N = 13.65	C = 44.46 H = 5.11 N = 13.74
2g		3 g (10.6 mmol)	10.5 g (43.9 mmol)	85 mL	6.2 g 25 mL H_2O	3 g (53%)	108-111 °C	$C_{18}H_{19}ClF_3N_5O_9 \cdot 1.5H_2O$ C = 38.00, H = 3.90, N = 12.31	C = 37.86 H = 3.87 N = 12.35
2h-2,4		2.5 g (8.83 mmol)	5 g (16.3 mmol)	50 mL	5 g 25 mL H_2O	1.9 g (35%)	114-119 °C dec.	$C_{19}H_{18}ClF_6N_5O_9 \cdot 0.25H_2O$ C = 37.15, H = 3.04, N = 11.40	C = 37.02 H = 3.12 N = 11.38
2h-3,5		2.5 g (8.83 mmol)	5 g (16.3 mmol)	50 mL	5 g 25 mL H_2O	3.3 g (61%)	113-124 °C dec.	$C_{19}H_{18}ClF_6N_5O_9 \cdot 0.75H_2O$ C = 36.61, H = 3.15, N = 11.24	C = 36.66 H = 3.09 N = 11.32
2i-2		2.5 g (8.83 mmol)	5 g (24.3 mmol)	50 mL	5 g 25 mL H_2O	3.6 g (80%)	126-130 °C dec.	$C_{17}H_{19}Cl_2N_5O_9 \cdot 0.25H_2O$ C = 39.82, H = 3.83, N = 13.66	C = 39.86 H = 3.82 N = 13.79
2i-3		2.5 g (8.83 mmol)	5 g (24.3 mmol)	50 mL	5 g 25 mL H_2O	3.5 g (78%)	140-145 °C dec.	$C_{17}H_{19}Cl_2N_5O_9 \cdot 0.50H_2O$ C = 39.48, H = 3.90,	C = 39.52 H = 3.80 N = 13.62

Table 8 (Continued)

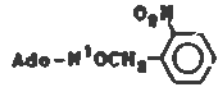
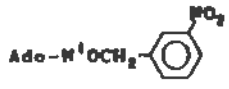
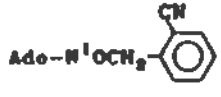
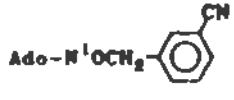
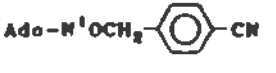
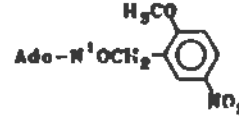
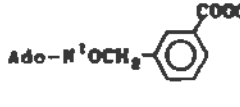
	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P. Cap	M.F. C, H, N Theory	Found
2j-2		2.5 g (8.83 mmol)	5.7 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	2.19 g (47%)	117-124 °C dec.	$C_{17}H_{19}ClN_6O_{11} \cdot H_2O$ C = 38.03, H = 3.92, N = 15.66	C = 38.12 H = 3.78 N = 13.86
2j-3		3 g (10.6 mmol)	11.4 g (53 mmol)	60 mL	6.25 g 25 mL H_2O	2.1 g (38%)	128-132 °C dec.	$C_{17}H_{19}ClN_6O_{11} \cdot 0.50H_2O$ C = 38.68, H = 3.76, N = 15.92	C = 38.64 H = 3.84 N = 15.80
2j-4		2.5 g (8.83 mmol)	9.5 g (44.2 mmol)	50 mL	5.2 g 20 mL H_2O	3.2 g (70%)	112-122 °C dec.	$C_{17}H_{19}ClN_6O_{11} \cdot 0.50H_2O$ C = 38.68, H = 3.76, N = 15.92	C = 38.72 H = 3.78 N = 15.88
2k-2		2.5 g (8.83 mmol)	5.19 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	3.5 g (79%)	117-124 °C	$C_{18}H_{19}ClN_6O_9 \cdot 0.25H_2O$ C = 42.95, H = 3.90, N = 16.70	C = 42.84 H = 3.92 N = 16.63
2k-3		2.5 g (8.83 mmol)	5.19 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	3.2 g (73%)	135 °C	$C_{18}H_{19}ClN_6O_9 \cdot 0.5H_2O$ C = 42.52, H = 3.97, N = 16.55	C = 42.42 H = 3.90 N = 16.48
2k-4		2 g (7.04 mmol)	4.3 g (21.9 mmol)	40 mL	4.2 g 15 mL H_2O	2.74 g (78%)	112-118 °C dec.	$C_{18}H_{19}ClN_6O_9 \cdot H_2O$ C = 41.83, H = 4.10, N = 16.26	C = 41.60 H = 3.98 N = 16.20
2l		2.5 g (8.83 mmol)	5 g (20.3 mmol)	50 mL	5 g 25 mL H_2O	4 g (83%)	200-208 °C	$C_{19}H_{21}ClN_6O_{12}$ C = 39.39, H = 3.86, N = 15.31	C = 39.43 H = 3.86 N = 15.30
2m		2.5 g (8.83 mmol)	5 g (21.8 mmol)	50 mL	5 g 25 mL H_2O	3.6 g (77%)	176-181 °C	$C_{19}H_{22}ClN_5O_{11} \cdot 0.25H_2O$ C = 42.55, H = 4.23, N = 13.06	C = 42.54 H = 4.18 N = 13.04

Table 8 (Continued)

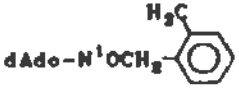
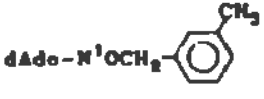
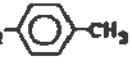
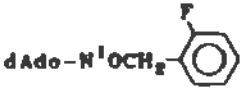
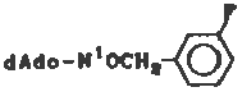
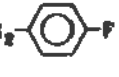
	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P. Cap	M.F. C, H, N Theory	Found
2o	Ado-N^1OCH_2- 	2.5 g (8.83 mmol)	4.5 g	50 mL	5 g 25 mL H_2O	3.1 g (74%)	150-154 °C	$C_{17}H_{20}ClN_5O_9 \cdot H_2O \cdot 0.10Et_2O$ C = 41.86, H = 4.64, N = 14.03	C = 42.00 H = 4.50 N = 14.12
2o	Ado-$N^1OCH_2CH_2$- 	2.5 (8.83 mmol)	4.9 g (26.5 mmol)	50 mL	5 g 25 mL H_2O	2.1 g (49%)	92-100 °C	$C_{18}H_{22}ClN_5O_9 \cdot 0.75H_2O$ C = 43.12, H = 4.72, N = 13.97	C = 42.98 H = 4.64 N = 13.94
2p-2	dAdo-N^1OCH_2- 	1.5 g (5.62 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.26 g (47%)	108-116 °C	$C_{19}H_{22}ClN_5O_8 \cdot H_2O$ C = 44.13, H = 4.94, N = 14.30	C = 44.24 H = 4.93 N = 14.38
2p-3	dAdo-N^1OCH_2- 	2 g (7.49 mmol)	5.5 g (30 mmol)	40 mL	4 g 20 mL H_2O	2.3 g (66%)	118-122 °C	$C_{19}H_{22}ClN_5O_8 \cdot H_2O$ C = 44.13, H = 4.94, N = 14.30	C = 44.28 H = 4.92 N = 14.44
2p-4	dAdo-N^1OCH_2- 	1.5 g (5.62 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.5 g (57%)	97-105 °C	$C_{19}H_{22}ClN_5O_8 \cdot 0.75H_2O$ C = 44.54, H = 4.88, N = 14.43	C = 44.40 H = 4.89 N = 14.45
2q-2	dAdo-N^1OCH_2- 	1.5 g (5.62 mmol)	3.19 g	30 mL	3 g 15 mL H_2O	1.9 g (71%)	88-90 °C	$C_{17}H_{19}ClFN_5O_8 \cdot H_2O$ C = 41.35, H = 4.29, H = 14.18	C = 41.28 H = 4.30 N = 14.20
2q-3	dAdo-N^1OCH_2- 	1.5 g (5.62 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.6 g (60%)	94-99 °C	$C_{17}H_{19}ClFN_5O_8 \cdot H_2O$ C = 41.35, H = 4.29, N = 14.18	C = 41.36 H = 4.28 N = 14.40
2q-4	dAdo-N^1OCH_2- 	1.5 g (5.62 mmol)	3.12 g	30 mL	3 g 15 mL H_2O	1.9 g (71%)	152-156 °C	$C_{17}H_{19}ClFN_5O_8 \cdot 0.125H_2O$ C = 42.71, H = 4.06, N = 14.65	C = 42.58 H = 3.96 N = 14.88

Table 8 (Continued)

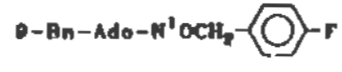
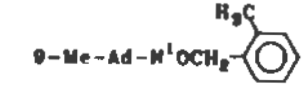
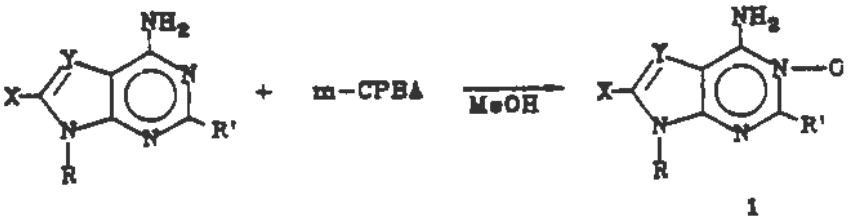
	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P. Cap	M.F. C, H, N Theory	Found
2r-2		1.5 g (6.22 mmol)	3.45 g	30 mL	3 g 15 mL H_2O	1.2 g (43%)	107-112 °C	$C_{20}H_{20}ClN_5O_5 \cdot 0.25H_2O$ C = 53.34, H = 4.59, N = 15.55	C = 53.40 H = 4.56 N = 15.53
2r-3		1 g (4.15 mmol)	2.3 g (12.45 mmol)	20 mL	2 g 10 mL H_2O	1.4 g (76%)	199-202 °C	$C_{20}H_{20}ClN_5O_5$ C = 53.88, H = 4.52, N = 15.71	C = 54.04 H = 4.60 N = 15.75
2r-4		1.5 g (6.22 mmol)	3.5 g	30 mL	3 g 15 mL H_2O	2.65 g (95%)	190-194 °C	$C_{20}H_{20}ClN_5O_5 \cdot 0.125Et_2O$ C = 54.10, H = 4.71, N = 15.59	C = 54.28 H = 4.80 N = 15.26
2s-2		1.5 g (6.22 mmol)	3.5 g	30 mL	3 g 15 mL H_2O	2.35 g (84%)	203-205 °C	$C_{19}H_{17}ClFN_5O_5$ C = 50.73, H = 3.81, N = 15.57	C = 50.77 H = 3.88 N = 15.51
2s-3		1.2 g (4.98 mmol)	2.8 g	25 mL	2.5 g 15 mL H_2O	1.95 g (87%)	180-185 °C	$C_{19}H_{17}ClFN_5O_5 \cdot 0.25H_2O$ C = 49.73, H = 3.95, N = 15.26	C = 49.90 H = 3.84 N = 15.30
2s-4		1.2 g (4.98 mmol)	2.8 g	25 mL	2.5 g 15 mL H_2O	1.5 g (68%)	200-203 °C	$C_{19}H_{17}ClFN_5O_5$ C = 50.73, H = 3.81, N = 15.57	C = 50.70 H = 3.86 N = 15.53
2t		1 g (4.15 mmol)	3.32 g (21.3 mmol)	20 mL	2 g 10 mL H_2O	1.3 g (85%)	248-252 °C	$C_{14}H_{16}ClN_5O_5$ C = 45.47, H = 4.36, N = 18.94	C = 45.36 H = 4.43 N = 18.77
2u-2		1 g (6.06 mmol)	2.8 g	20 mL	2 g 10 mL H_2O	1.5 g (68%)	202-204 °C	$C_{14}H_{16}ClN_5O_5$ C = 45.47, H = 4.36, N = 18.94	C = 45.53 H = 4.389 N = 18.92

Table 8 (Continued)

	Product	N'-Oxide	$BrCH_2R$	DMAc	NH_4ClO_4	Yield (%)	M.P. Cap	M.F. C, H, N Theory	Found
2u-3	9-Me-Ad-N^1OCH_2-(3-CH_3-Ph)	1 g (6.06 mmol)	2.8 g	20 mL	2 g 10 mL H_2O	1.65 g (74%)	198-200 °C	$C_{14}H_{19}ClN_5O_3 \cdot 0.125EtOH$ C = 45.58, H = 4.50, N = 18.65	C = 45.68 H = 4.41 N = 18.80
2v-2	N^6-Me-Ad-N^1OCH_2-(2-CH_3-Ph)	1 g (3.36 mmol)	1.86 g	10 mL	1.2 g 10 mL H_2O	310 mg (18%)	174-177 °C	$C_{19}H_{24}ClN_5O_4 \cdot 0.30H_2O$ C = 44.98, H = 4.89, N = 13.81	C = 44.86 H = 4.92 N = 13.94
2v-3	N^6-Me-Ado-N^1OCH_2-(3-CH_3-Ph)	1.65 g (5.55 mmol)	3.1 g	30 mL	2 g 10 mL H_2O	1.06 g (38%)	94-102 °C	$C_{19}H_{24}ClN_5O_5 \cdot 0.50H_2O$ C = 45.06, H = 4.88, N = 13.83	C = 45.04 H = 4.92 N = 13.70
2w	N^6-Me-Ado-N^1OCH_2-(2,6-diF-Ph)	800 mg (2.69 mmol)	1.68 g	15 mL	2 g 10 mL H_2O	550 mg (36%)	165-169 °C	$C_{19}H_{20}ClF_2N_5O_5 \cdot 0.50H_2O$ C = 40.57, H = 3.97, N = 13.14	C = 40.56 H = 3.80 N = 13.08
2x	2,6-DAPR-N^1OCH_2-(3-CH_3-Ph)	750 mg (2.52 mmol)	960 mg	10 mL	885 mg 5 mL H_2O	780 mg (67%)	152-156 °C	$C_{19}H_{23}ClN_6O_5 \cdot 0.50H_2O$ C = 42.23, H = 4.73, N = 16.42	C = 42.36 H = 4.64 N = 16.30
2y	8-Br-Ado-N^1OCH_2-(3-CH_3-Ph)	1 g (2.76 mmol)	1.37 g	10 mL	650 mg 5 mL H_2O	1.1 g (71%)	151-153 °C	$C_{18}H_{21}BrClN_5O_5 \cdot 0.05NH_4ClO_4$ C = 33.75, H = 3.73, N = 12.35	C = 37.79 H = 3.74 N = 12.48

Ado = adenosine. dAdo = 2'-deoxyadenosine. 9-Bn Ad = 9-benzyladenine. 9-Me-Ad = 9-methyladenine. N^6-Me-Ado = 6-methylaminopurine riboside. 9-Ara-A = 9-β-D-arabinofuranosyladenine. 8-Br-Ado = 8-bromoadenosine. 2,6 DAPR = 2,6-diaminopurine riboside. C^7-Ado = 7-deazaadenosine.

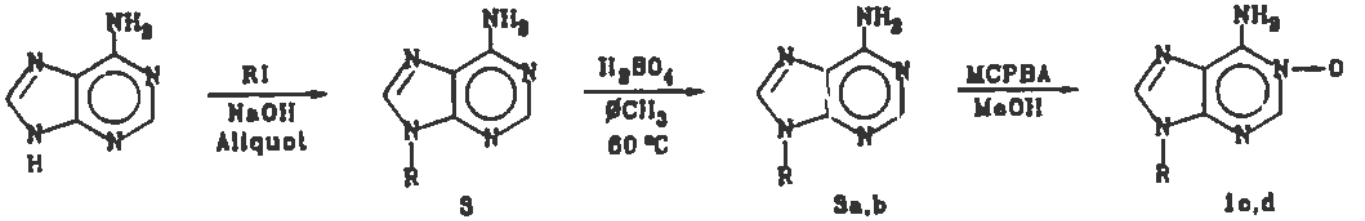
Scheme II



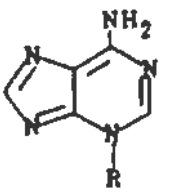
1

	R	R'	X	Y
1g		H	Br	N
1h	"	NH_2	H	N
1i	"	H	H	CH

Scheme III



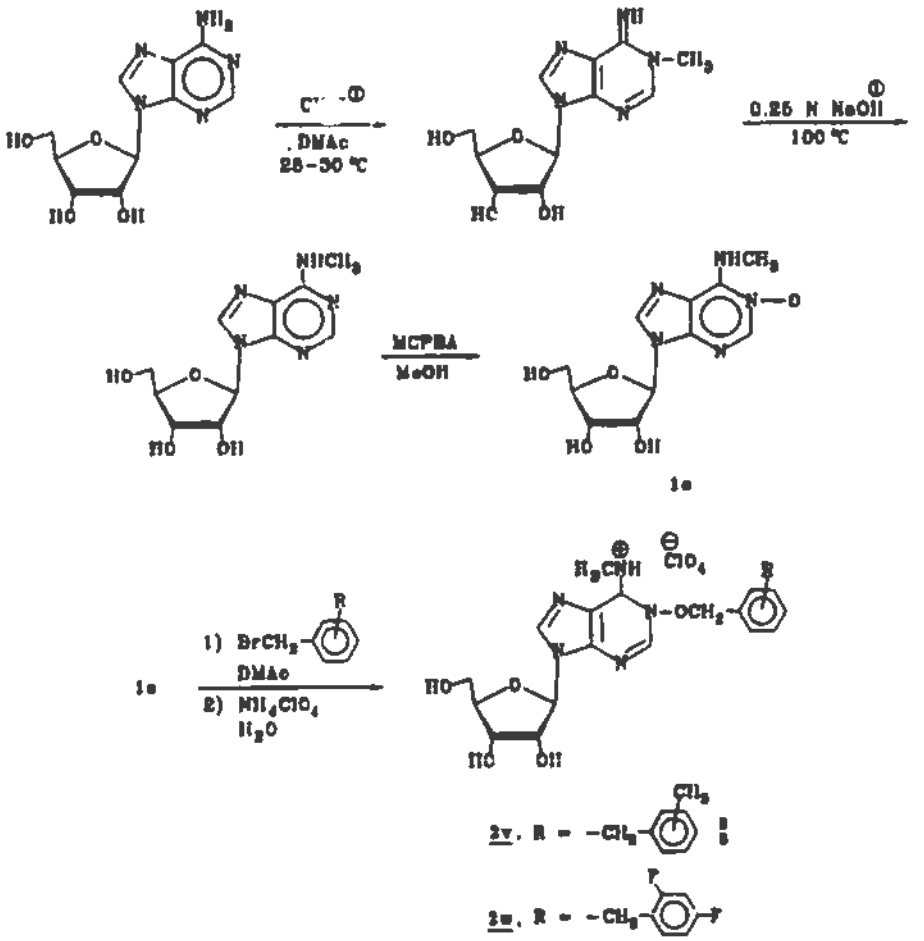
3 3a,b 1c,d



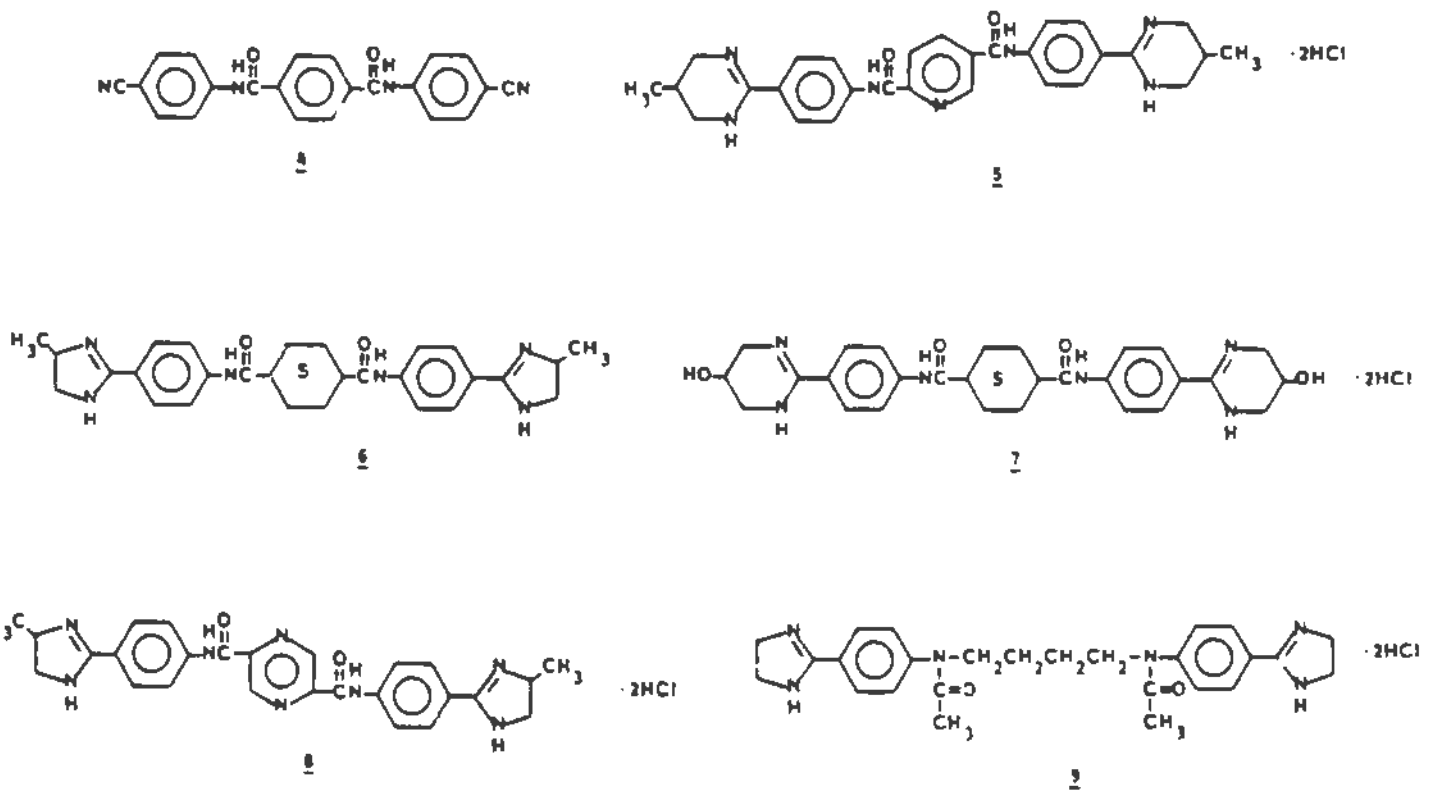
3a, 1c, R = CH_2-Ø

3b, 1d, R = CH_3

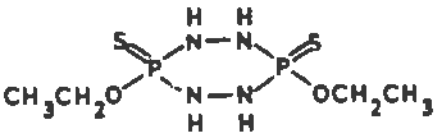
Scheme IV



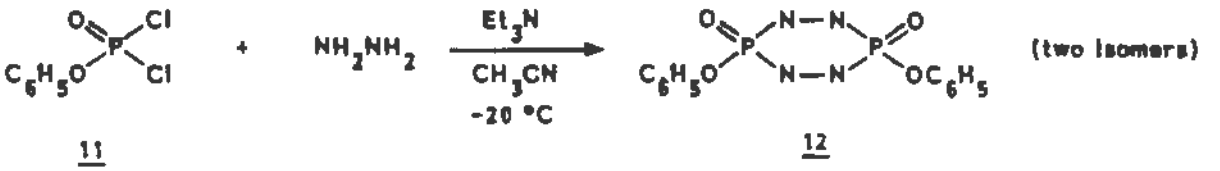
Scheme V



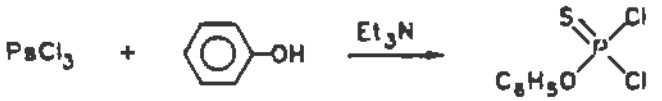
Scheme VI



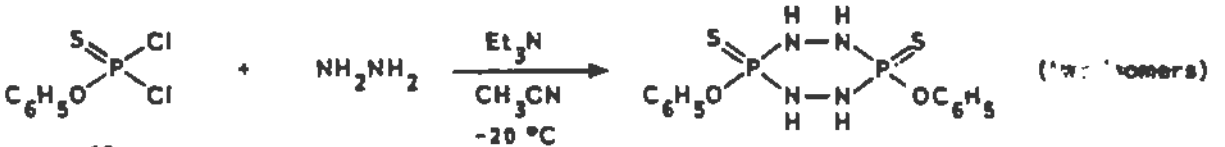
10



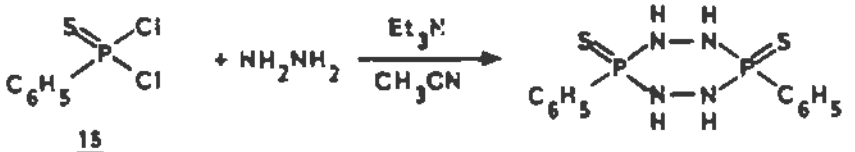
11 12 (two isomers)



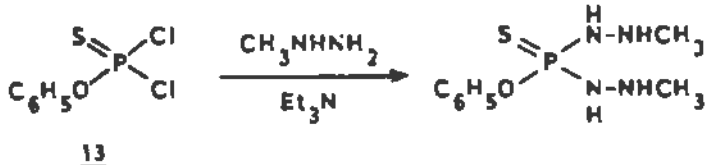
13



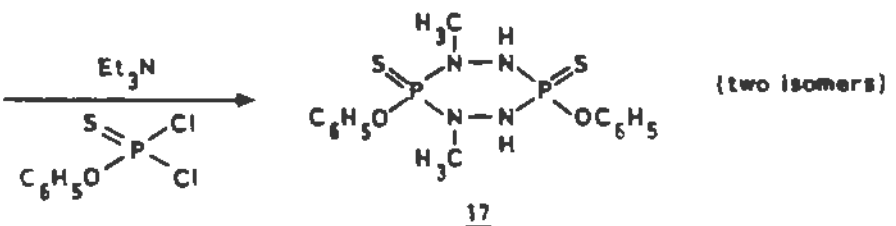
13 14 (two isomers)



15 16

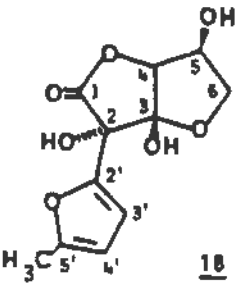


13



17 (two isomers)

Scheme VII



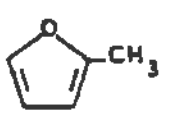
18

2:1 complex (18: succinic anhydride)

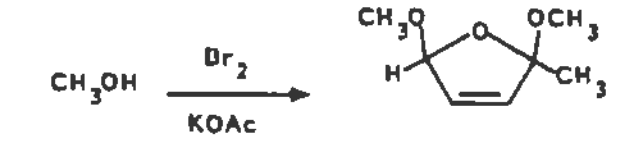
19

2:1 complex (18: succinimide)

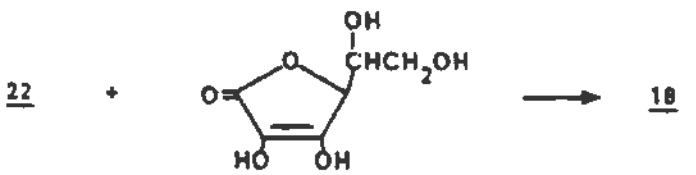
20

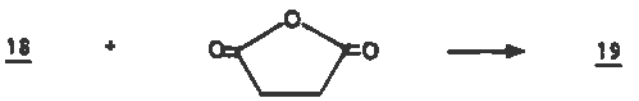


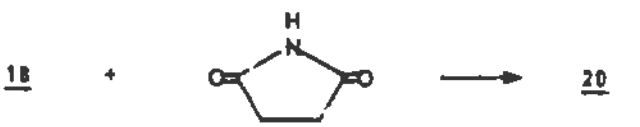
21



22







Selenadiazoles, Triazolotriazoles, Triazolothiadiazoles, Triazolotriazole Nucleosides

This series of triazolotriazoles, selenadiazoles, and thiadiazoles was synthesized on the basis of the activity of lead compound **23**. We synthesized selenadiazoles **24a-c** by following **Scheme VIII**. We also obtained bicyclic compound[11] **25** from aminoselenadiazole[12] (**24a**) by treating this compound with 2-chloroacetophenone. When we tried to make closely related compounds **24d**, **24e**, and **26** by following the procedures for **24a-c** and **25** we obtained extremely low yields of the desired products. Furthermore, when we varied reaction conditions (*e.g.* increases in either or both reaction time and temperature as well as modifications in the sequence of addition of reaction components), we were still unable to improve the yields. Because of these problems, we shifted our interests away to the following, more easily obtained analogs.

We made the following triazolotriazole compounds by the approaches that are shown in **Scheme IX**. We first made *N*-nitroaminotriazole (**27**, R = H) in good yield by nitrating 3-amino-1,2,4-triazole.[13] This compound was then reduced with activated zinc to give hydrazinotriazole (**28**, R = H),[14] a compound that was too unstable to submit. However, we were able to use this compound in the synthesis of triazolotriazole **29a**, which as shown in **Scheme IX** was made by the treatment of **28** with cyanogen bromide.[15] We also were able to use this general procedure to make analogs **29b,c** by the routes shown in **Schemes IX** and **X**. The corresponding phenyl and methyl substituted aminotriazoles for these compounds were first synthesized, since they were not commercially available.

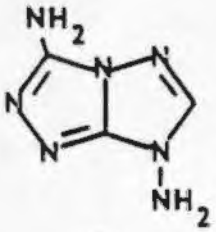
To prepare triazolotriazole **29b**, aminoguanidine was benzoylated in pyridine to give **30** and then cyclized at 220 °C[16] to give aminotriazole **31**. This compound was then nitrated to give nitroaminotriazole **27b**.[13] Reduction of the nitroamino compound to the hydrazinotriazole **28b** followed by cyclization with cyanogen bromide produced triazolotriazole **29b**.[14,15]

We synthesized triazolotriazole **29c** by following a similar approach. Nitroguanidine was treated with hydrazine to give **33**, which was acetylated to **34**, and then cyclized with aqueous sodium carbonate giving nitroaminotriazole **27c**.[17,18] Reduction with zinc/acetic acid followed by treatment with cyanogen bromide gave the desired compound **29c**.[15]

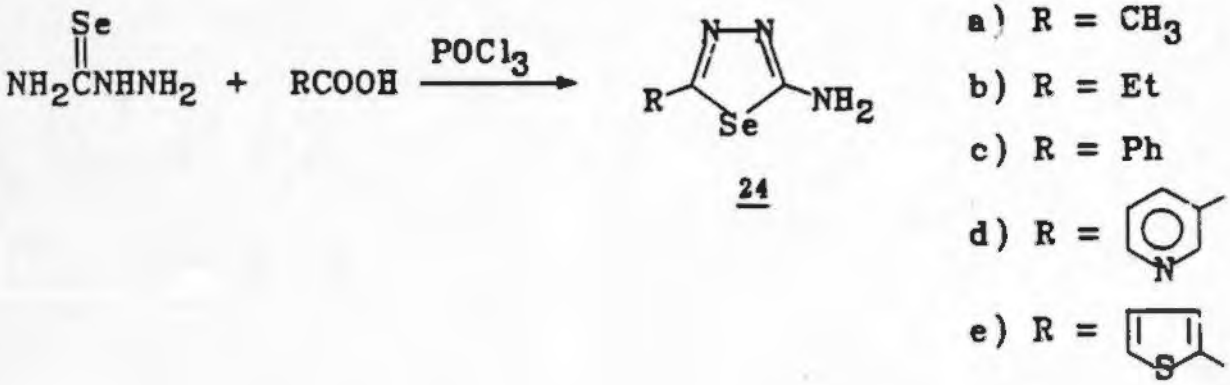
As shown in **Scheme X**, bicyclic compounds **37-39** and **41** were made from triaminoguanidine (**35**), which was easily obtained by the addition of hydrazine to aminoguanidine. Compound **37** was made via a two-step process: triaminoguanidine (**35**) was treated with acetic acid and heated so that the acetyltriaminoguanidine cyclized to triazole **36**.[19] Compound **36** was then further cyclized to triazolotriazole **37** by treatment with cyanogen bromide.[15] Similarly, triazolotriazole **38** was also obtained from triazole **36** by treatment with carbon disulfide. Triazolotriazole **39** was made directly from triaminoguanidine (**35**) by treatment with two equivalents of cyanogen bromide. The last triazolotriazole made by this approach was triazolotriazole **41**. Triaminoguanidine was heated with formic acid giving triazole **40**, which was then further cyclized by treatment with carbon disulfide to triazolotriazole **41**. Other compounds resulting from this series were the two triazolotriazole acetates (**42** and **43**) by treating **23** (the parent compound for this entire series) and previously submitted **37**[17] with acetic anhydride.

We also synthesized four new triazolotriazole derivatives as well as two new ribosylated triazoles and two triazolothiadiazole compounds. As shown in **Scheme XI**, triazolotriazole analog **44** was obtained by the

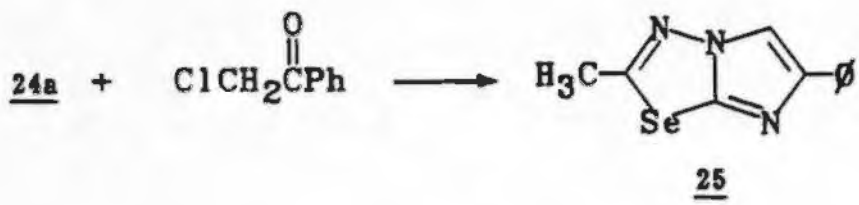
Scheme VIII



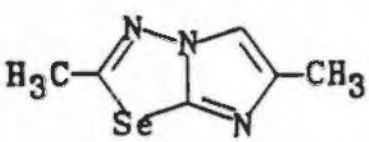
23



24

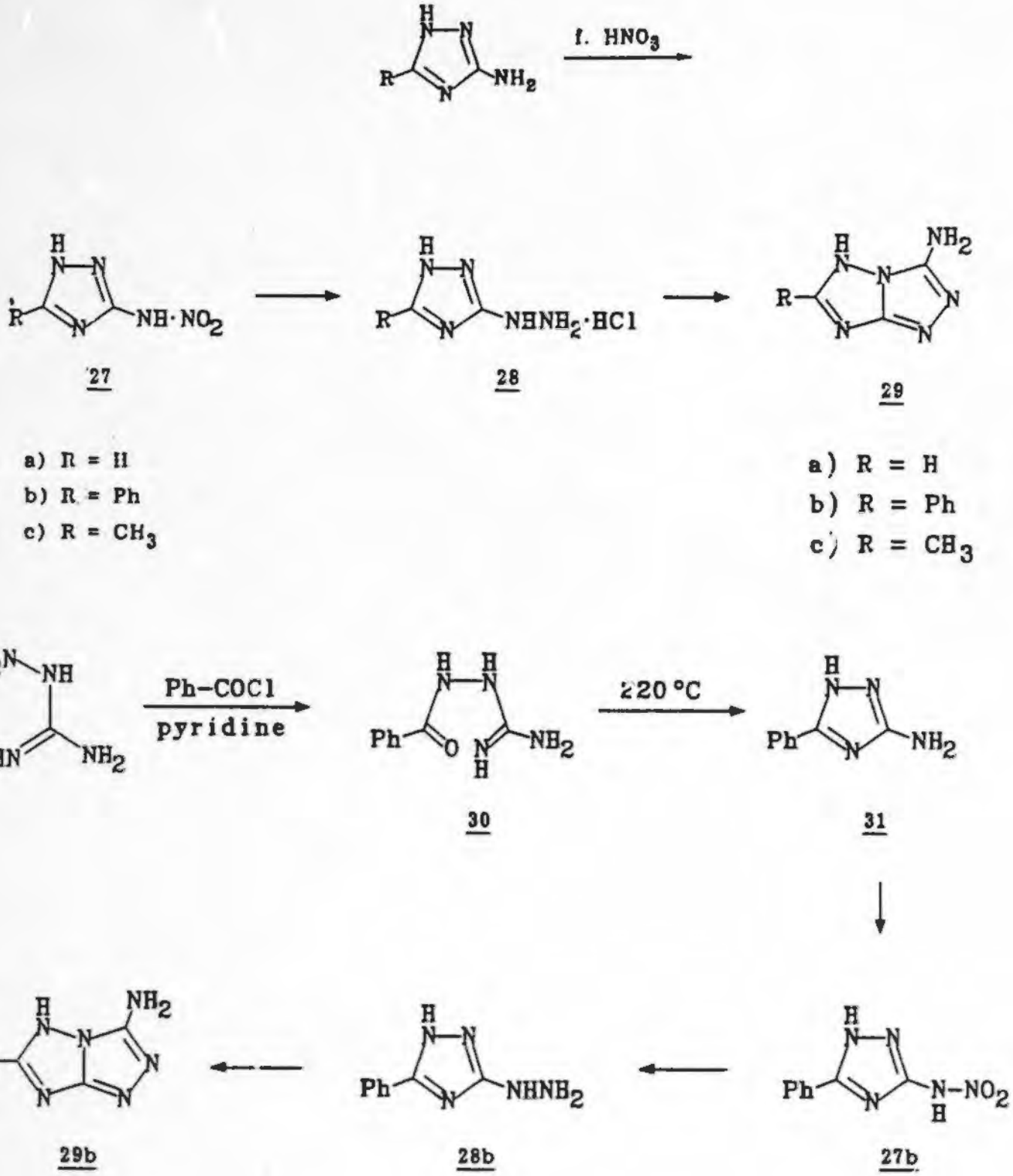


25

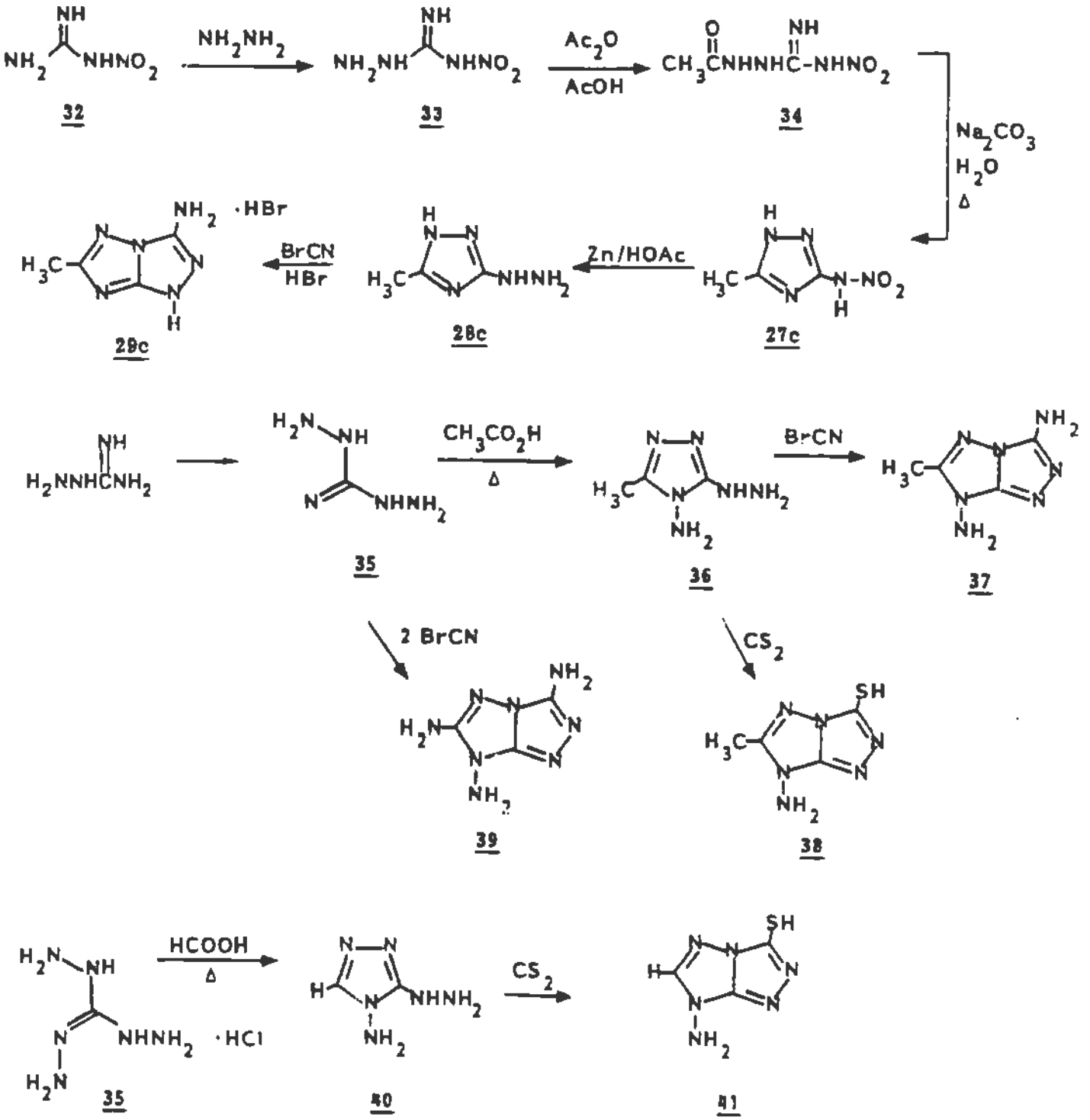


26

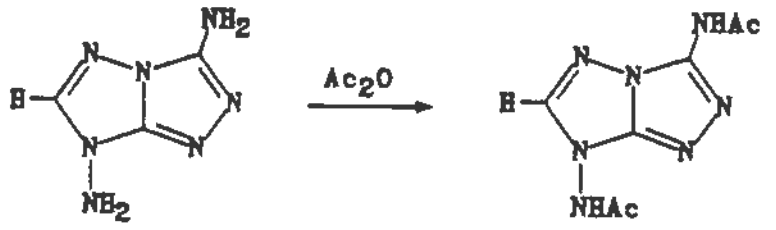
Scheme IX


f. HNO3
27
28
29
a) R = H
b) R = Ph
c) R = CH3
Ph-COCl
pyridine
220 °C
30
31
29b
28b
27b

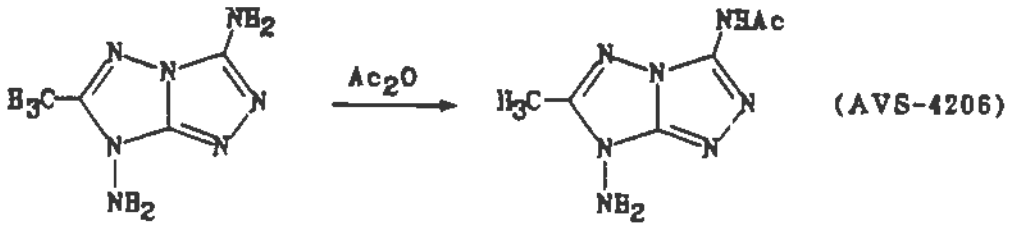
Scheme X


NH
NH2 NHNO2
32
NH2NH2
NH
NH2NH NHNO2
33
Ac2O
AcOH
O NH
CH3CNHNHC-NHNO2
34
Na2CO3
H2O
Δ
H
H3C N N
N-NO2
H
27c
Zn/HOAc
H
H3C N N
NHNH2
28c
BrCN
HBr
NH2 ·HBr
H3C N N N
H
29c
NH
H2NNHCNH2
H2N NH
N NHNH2
35
CH3CO2H
Δ
N N
H3C N NHNH2
NH2
36
BrCN
NH2
H3C N N N
NH2
37
2 BrCN
NH2
H2N N N N
NH2
39
CS2
SH
H3C N N N
NH2
38
H2N NH
N NHNH2 ·HCl
H2N
35
HCOOH
Δ
N N
H N NHNH2
NH2
40
CS2
SH
H N N N
NH2
41

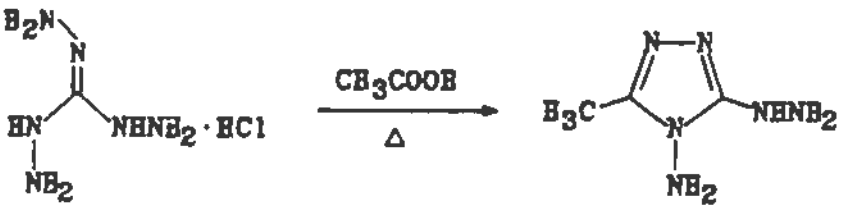
Scheme XI



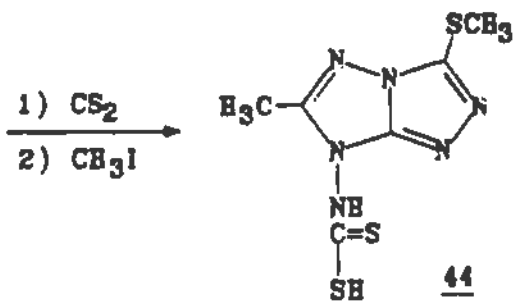
23 42



37 43



35 36



44

following two-step process: triaminoguanidine (**35**) was heated with acetic acid, and the resulting acetic acid adduct cyclized to give triazole **36**.[19] Triazole **36** was then cyclized to triazolotriazole dithionide **44** via sequential treatment with carbon disulfide and methyl iodide.

Scheme XII shows that the ribosylated triazolotriazoles were made by treating the series parent compound (**23**)[17] with stannic chloride and 2,3,5-tribenzoylribofuranosyl-1-acetate.[20] The major product from this reaction was adduct **45**, which was deprotected with NaOMe and MeOH to give ribosylated triazolotriazole **46**. One of the minor products, compound **47** was also isolated in sufficient quantity to allow deprotection to ribosylated triazolotriazole **48**. However, closer inspection of the literature revealed that this compound had been made under a previous DAMD contract in 1979. Therefore, we assumed that USAMRIID already had access to this compound, and it was not submitted to USAMRIID. Another of the minor products of the ribosylation reaction was compound **49**. This compound was submitted in its benzoylated form, because even the mildest of deprotection conditions also cleaved the ribosyl linkage.

As shown in **Scheme XIII**, triazolothiadiazole **52** was made by following the same general sequence used to make the other triazolotriazoles. Aminothiadiazole was nitrated[13,15] with fuming nitric acid to give nitroaminothiadiazole **51**. This compound was then reduced with zinc and acetic acid, and the resulting hydrazinothiadiazole was cyclized with cyanogen bromide to give triazolothiadiazole **52**. Nitroaminothiadiazole **51** was also used to make one other triazolothiadiazole. Reduction of **51** with zinc and acetic acid followed by treatment with carbon disulfide gave triazolothiadiazole **53**.

Scheme XIV shows the route followed for synthesizing one final triazolotriazole derivative **55**. This compound was obtained by treating previously submitted triazolotriazole **54** with Gold's reagent.[21]

Various Related 6-C-Substituted Analogs in the Purine and 8-Azapurine; 6-Carboxamidopurine Riboside (AVS-0015)

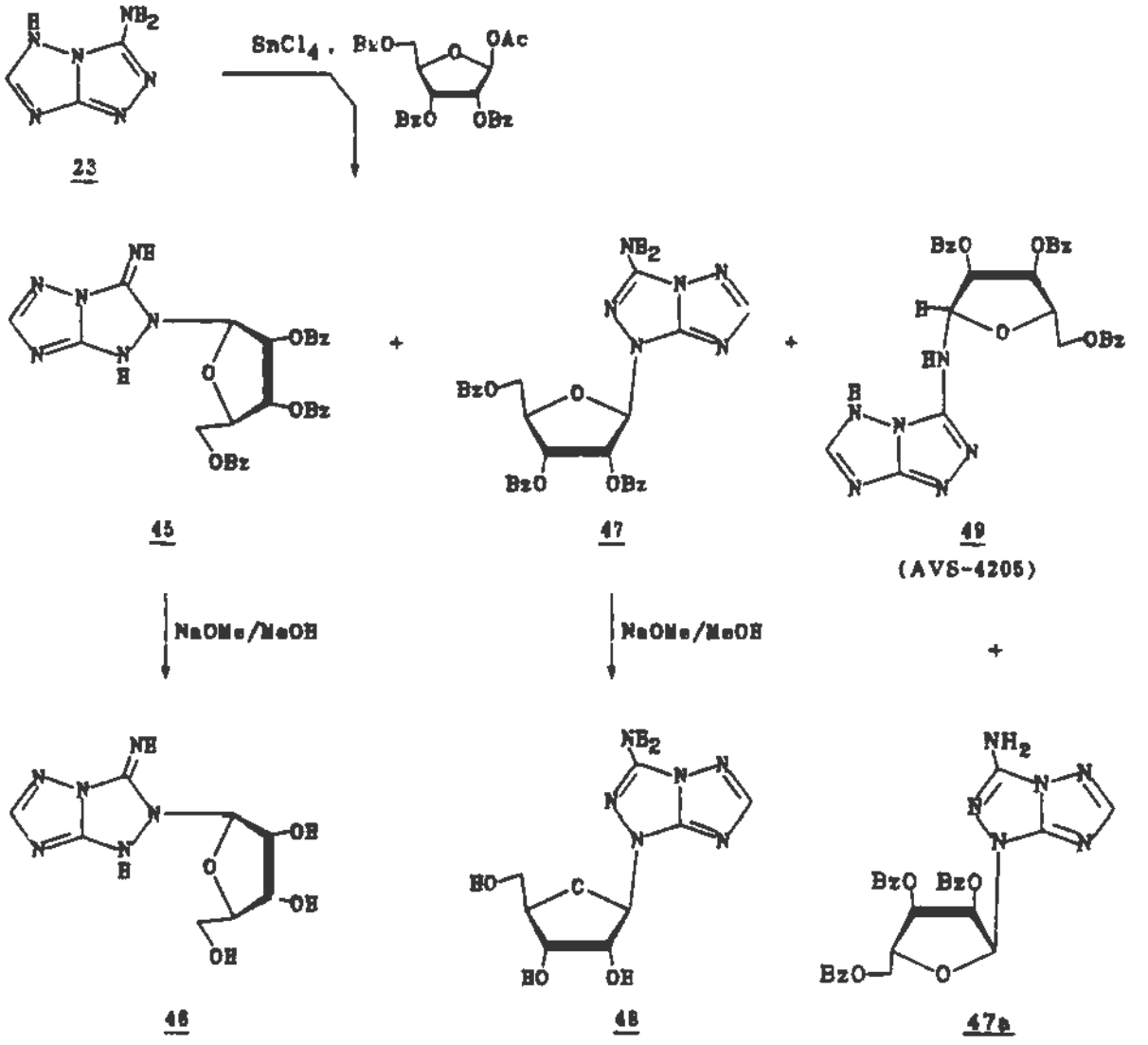
As a result of our efforts aimed at various 6-substituted analogs in the purine and 8-azapurine series, we synthesized purine-6-carboxylic acid (**57a**) and purine-6-thiocarboxamide (**57b**). **Scheme XV** shows that these compounds were made by treating commercially available 6-iodopurine with copper cyanide and then treating resulting 6-cyanopurine (**56**) with 2 *N* NaOH or H_2S/ethanolic ammonia to give **57a,b**, respectively.[22] We had hoped to alter these compounds further by halogenating the 8-position. Unfortunately, when we attempted a number of approaches to these alterations, all of these efforts resulted in complex product mixtures. Similarly, our attempts to synthesize purine and 8-azapurine analogs such as **58-60** from either 2,6-dichloropurine or 4,6-dichloro-5-nitropyrimidine failed to give promising results.

Our approach to the synthesis of 6-carboxamidopurine riboside (**63**)[22-24] is shown in **Scheme XVI**. 6-Carboxamidopurine **61** was made by carefully treating 6-cyanopurine (**56**) with sodium hydroxide and then, it was coupled with 1,2,3,5-tetra-*O*-acetylribofuranose using $SnCl_4$ as catalyst, according to the procedure of Robins *et al.*[24] The resulting nucleoside triacetate **62** was then deprotected with MeOH/NaOMe to give the desired nucleoside **63**.

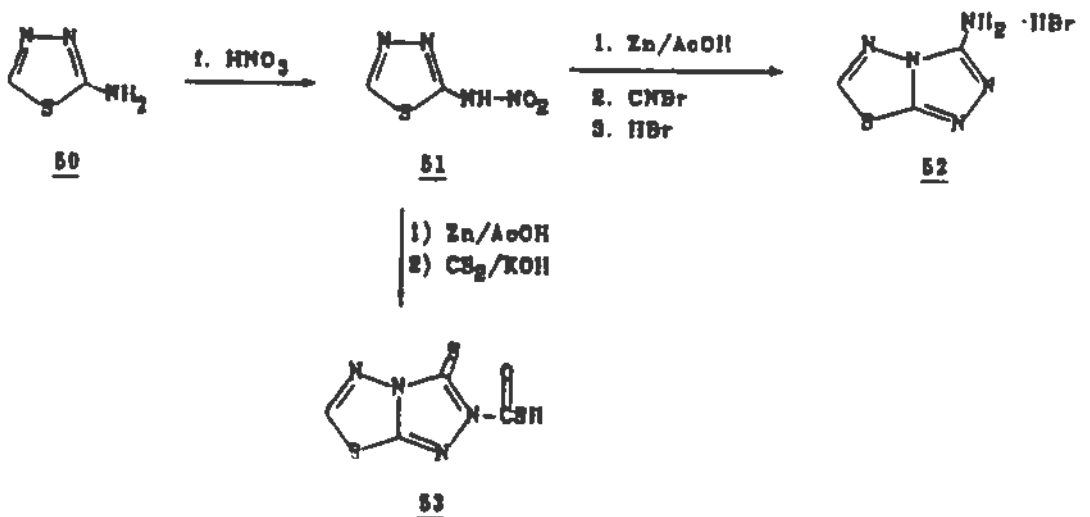
8-Chloro-and 8-Methylthio-3-deazapurine

We also attempted to synthesize 8-substituted 3-deazaguanines **64** following the approach shown in **Scheme XVII**.[25,26] In our pursuit of 8-chloro-3-deazaguanine (**64a**) we made and submitted precursor **65**.

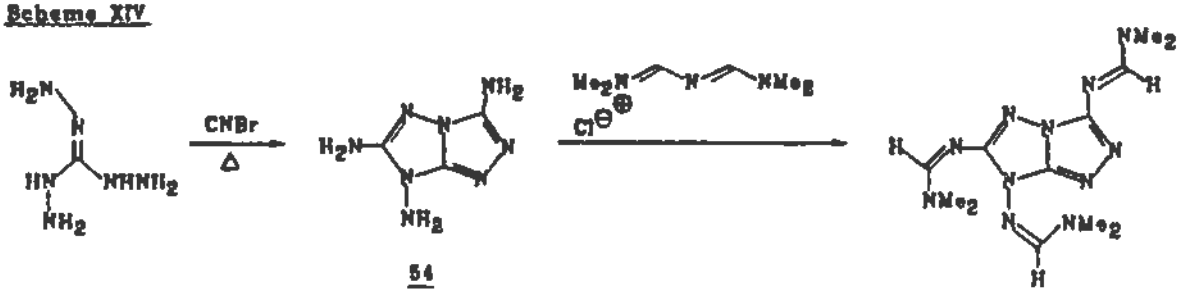
Scheme XII



Scheme XIII



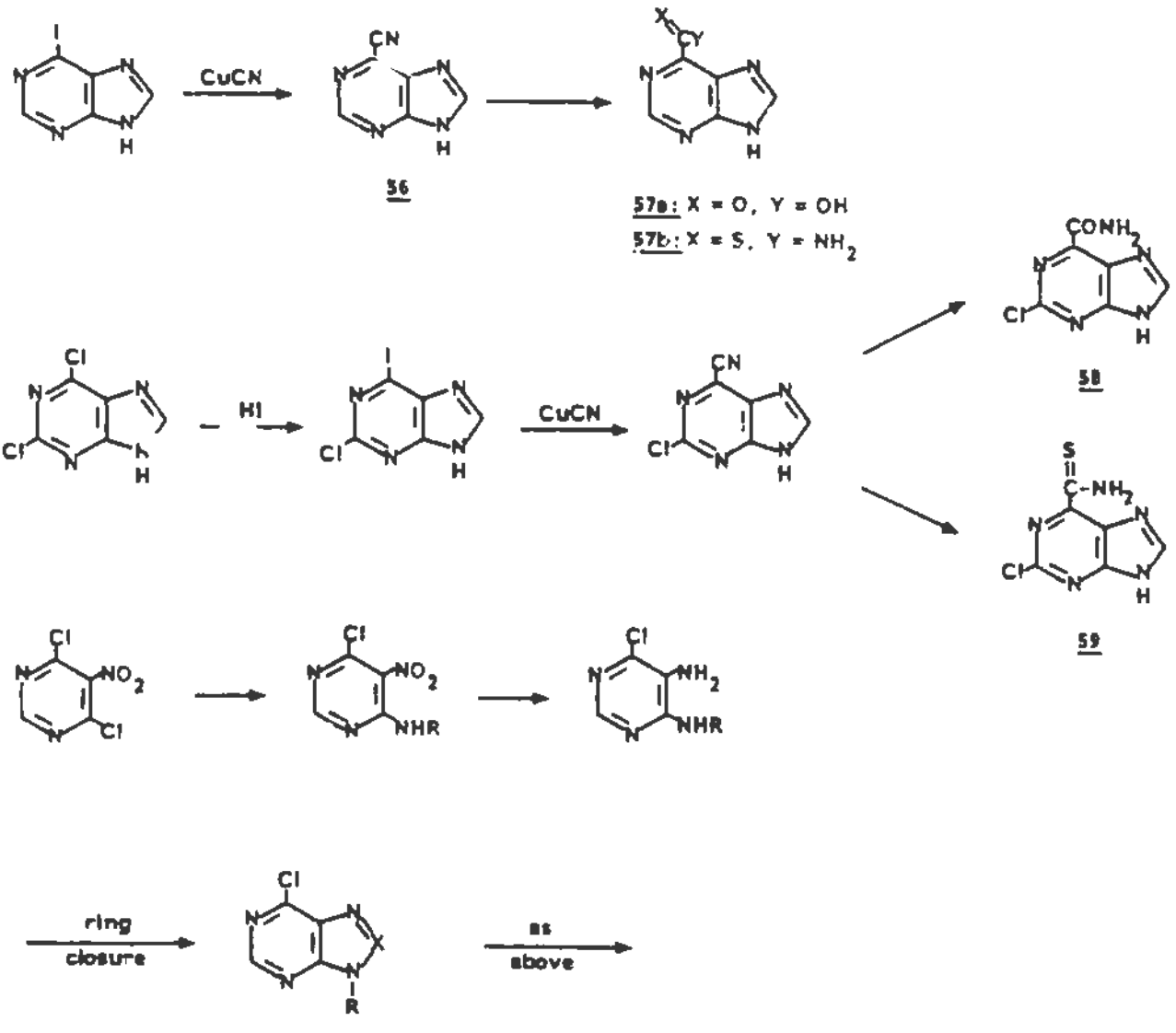
Scheme XIV



54

55

Scheme XV



56

57a: X = O, Y = OH

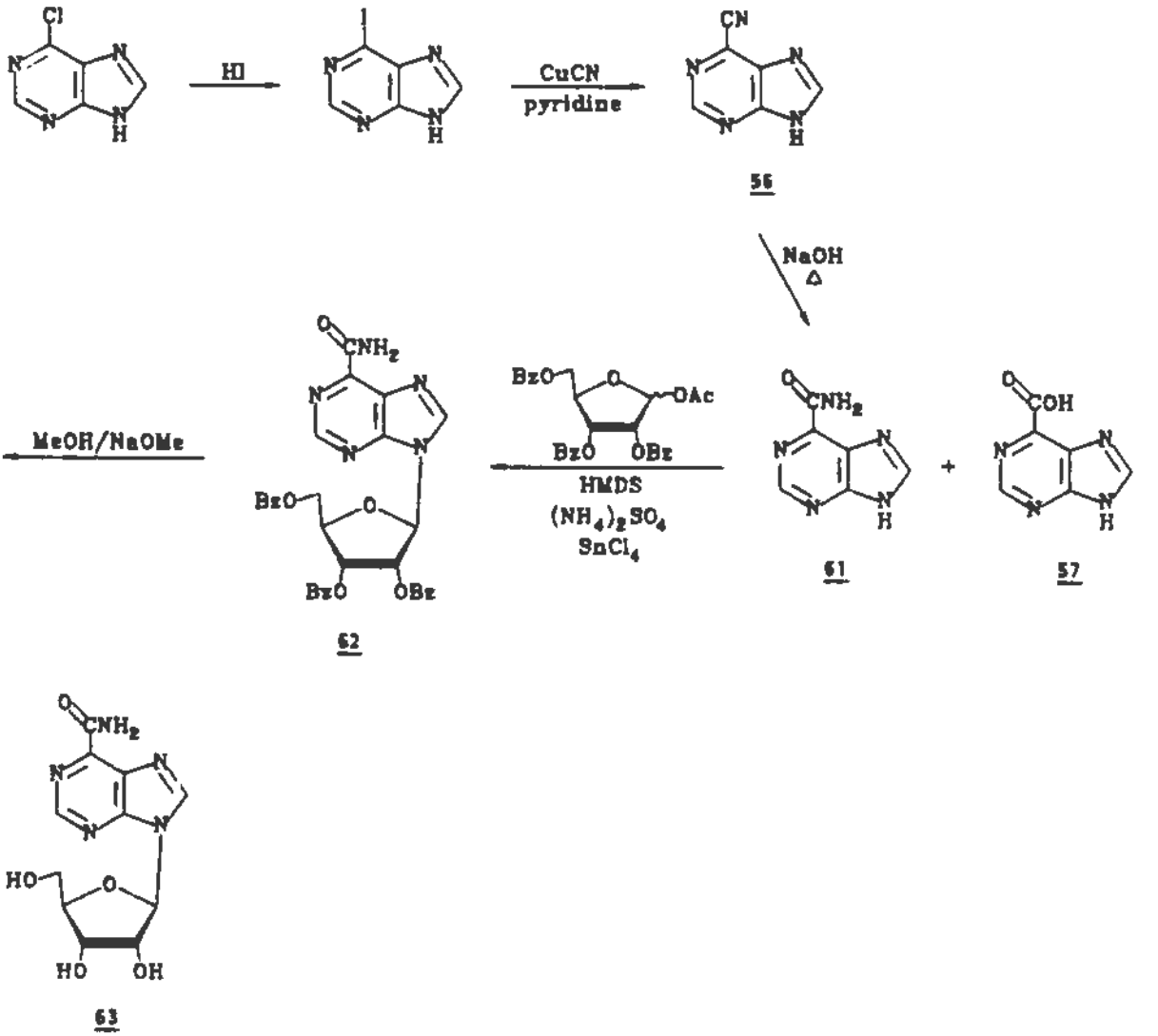
57b: X = S, Y = NH_2

58

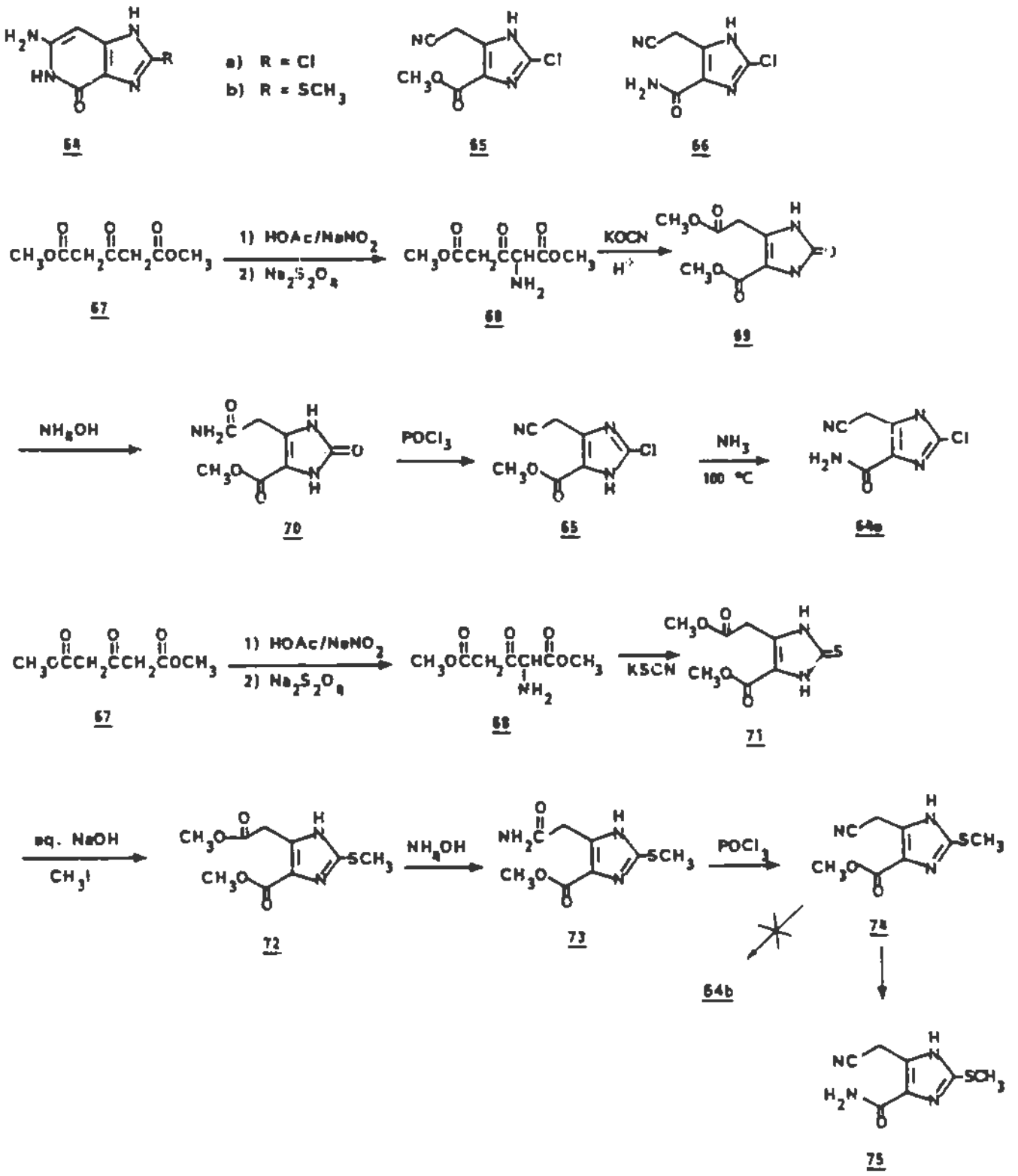
59

60

Scheme XVI


Cl
HI
I
CuCN
pyridine
CN
56
NaOH
Δ
CNH2
BzO
OAc
OBz
HMDS
(NH4)2SO4
SnCl4
COH
61
57
MeOH/NaOMe
62
HO
OH
63

Scheme XVII


a) R = Cl
b) R = SCH3
64
65
66
67
1) HOAc/NaNO2
2) Na2S2O8
68
KOCN
H+
69
NH4OH
70
POCl3
65
NH3
100 °C
64a
67
1) HOAc/NaNO2
2) Na2S2O8
68
KSCN
71
aq. NaOH
CH3I
72
NH4OH
73
POCl3
74
64b
75

Unfortunately, we could not cyclize this intermediate by treatment with ammonia, even after employing a number of treatment conditions. Instead, we obtained low yields of uncyclized amide **66** from all of our reaction attempts, suggesting that the chlorine was deactivating the system toward cyclization.

We also pursued the synthesis of methylthio-substituted **64b** by following the same general approach as followed for **64a**. As shown in **Scheme XVII**, we again were able to synthesize our target precursor **74**, but as with the chlorine-containing analog, we were not able to cyclize to **64b**, and the only recoverable product after the cyclization attempt was amide **75**.

Ethyl 5-(Substituted Phenyl)-2,4-dioxobutyrates (As Analogs of Methyl 4-Chloro-5-[2,4-dichlorophenyl]pyrazole-3-carboxylate [AVS-000332])

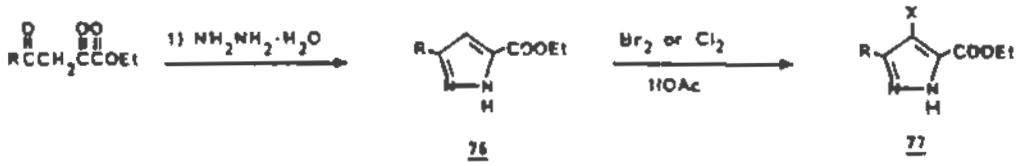
We also synthesized a number of substituted pyrazoles such as **76** and **77** as analogs of methyl 4-chloro-5-[2,4-dichlorophenyl]pyrazole-3-carboxylate [AVS-000332], which USAMRIID had shown to be effective against PIC, VEE, and JBE viruses. Following a procedure developed by Knorr *et al.*[27] we made ethyl 5-methylpyrazole-3-carboxylate (**76a**) from ethyl 2,4-dioxovalerate and hydrazine. Halogenation at the 4-position using the standard procedure of bromine or chlorine in acetic acid, as shown in **Scheme XVIII**, gave **77a** and **77b**.

The synthesis of our other pyrazole analogs with R = various substituted phenyls and pyridyls were essentially the same. The required ethyl 5-substituted-phenyl-2,4-dioxobutyrates were made by condensing the appropriately substituted acetophenones or acetylpyridines with diethyl oxalate.[28] As with the synthesis of pyrazole **75**, these butyrates were treated with hydrazine hydrate to produce the corresponding pyrazoles. These pyrazoles were then either submitted as is, or the pyrazole rings were halogenated by treatment with either bromine or chlorine in acetic acid. Interestingly, we were unsuccessful in our attempt to make the 4-chloro products of ethyl 5-(*p*-tolyl)pyrazole-3-carboxylate **76i** and ethyl 5-(*p*-methoxyphenyl)pyrazole-3-carboxylate **76h**. Similarly, we could not control either the chlorination or bromination of 5-(2,4-dimethoxyphenyl)pyrazole-3-carboxylate (**76l**). Chlorination of the activated phenyl rings of **76f**, **76h**, and **76l**, and bromination of the phenyl ring of **76l** were found to compete with the corresponding halogenations of the pyrazoles under our reaction conditions, and as a result, we routinely obtained mixtures of polychlorinated (or polybrominated) products. Since we were unable to find a chromatographic system to separate these compounds, and since we already had a large numbers of analogs, we decided that no additional effort should directed toward these specific compounds until we received screening data.

We were also unable to obtain one other target pyrazole, ethyl 5-(*p*-bromophenyl)-4-chloropyrazole-3-carboxylate. Our attempts to obtain this compound by chlorinating ethyl 5-(*p*-bromophenyl)-3-carboxylate (**76c**) resulted in the unexpected formation of ethyl 5-(*p*-chlorophenyl)-4-chloropyrazole-3-carboxylate (**77g**), even after reaction times as short as 1 h.

In addition, we also made pyrazolecarboxamides **78a,b**. As shown in **Scheme XIX**, these compounds were made by treating the corresponding ethyl pyrazolecarboxylates with ammonium hydroxide. Thus far, we have limited production of the pyrazolecarboxamides to just these two. However, if these compounds show promising activity, we will expand this series by converting other pyrazolecarboxylates to their corresponding carboxamides.

Scheme XVIII



76

a) R = CH_3

b) R = F-C$_6$H$_4$-

c) R = Br-C$_6$H$_4$-

d) R = Cl-C$_6$H$_4$-

e) R = C$_6$H$_5$-

f) R = CH_3-C$_6$H$_4$-

g) R = NO_2-C$_6$H$_4$-

h) R = CH_3O-C$_6$H$_4$-

i) R = CH_3O-(2,5-$(OCH_3)_2$)-C$_6$H$_3$-

j) R = Cl-(2,3-Cl_2)-C$_6$H$_3$-

k) R = F-(2,3-F_2)-C$_6$H$_3$-

l) R = 2-pyridyl

m) R = 3-pyridyl

n) R = 4-pyridyl

77

a) R = CH_3, X = Br

b) R = CH_3, X = Cl

c) R = F-C$_6$H$_4$-, X = Br

d) R = F-C$_6$H$_4$-, X = Cl

e) R = Br-C$_6$H$_4$-, X = Br

f) R = Cl-C$_6$H$_4$-, X = Br

g) R = Cl-C$_6$H$_4$-, X = Cl

h) R = C$_6$H$_5$-, X = Br

i) R = C$_6$H$_5$-, X = Cl

j) R = CH_3-C$_6$H$_4$-, X = Br

k) R = NO_2-C$_6$H$_4$-, X = Br

l) R = NO_2-C$_6$H$_4$-, X = Cl

m) R = CH_3O-C$_6$H$_4$-, X = Br

n) R = Cl-(2,3-Cl_2)-C$_6$H$_3$-, X = Br

o) R = Cl-(2,3-Cl_2)-C$_6$H$_3$-, X = Cl

p) R = F-(2,3-F_2)-C$_6$H$_3$-, X = Br

q) R = F-(2,3-F_2)-C$_6$H$_3$-, X = Cl

r) R = 2-pyridyl, X = Br

s) R = 2-pyridyl, X = Cl

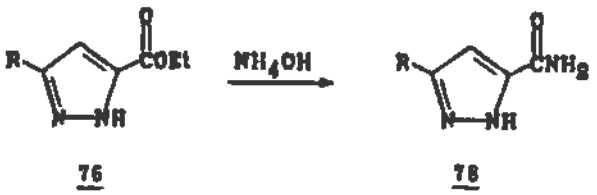
t) R = 3-pyridyl, X = Br

u) R = 3-pyridyl, X = Cl

v) R = 4-pyridyl, X = Br

w) R = 4-pyridyl, X = Cl

Scheme XIX

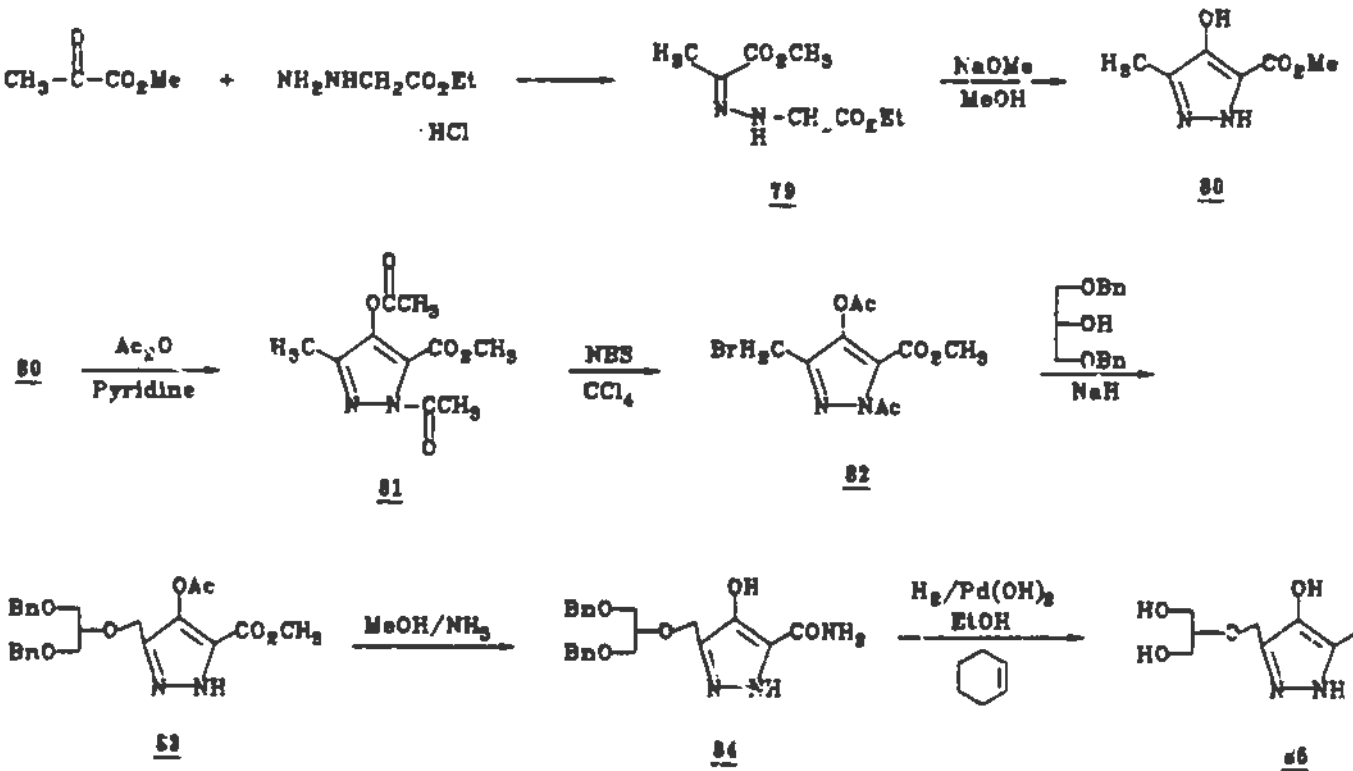


76 78

a: R = CH_3O, OCH_3

b: R = Cl, Cl

Scheme XX



5-(1,3-Dihydroxy-2-propoxy)-4-hydroxy-1,2-pyrazole-3-carboxamide

Finally, we also submitted one other pyrazolecarboxamide 5-[(1,3-dihydroxy-2-propoxy)methyl]-4-hydroxy-1,2-pyrazole-3-carboxamide (**85**). 4-Hydroxypyrazolecarboxamides such as **85** had been originally pursued in another USAMRIID-sponsored project (DAMD17-86-C-6003), but the antiviral activities of these compounds were not determined before the funding for the original project had been depleted. Since Dr. Gabrielsen had also expressed an interest in compounds similar to these, we decided to support the synthesis of one more pyrazolecarboxamide with our project funds. As shown in **Scheme XX**, the synthesis of this compound started with methylpyruvate hydrazine **79**, which had been prepared by reacting methylpyruvate with ethyl hydrazinoacetate.[29] Cyclization of adduct **79** with methanolic sodium methoxide gave **80**,[30] which was then acetylated with acetic anhydride/pyridine to give diacetylated **81**. Bromination with NBS/carbon tetrachloride gave 5-bromomethyl compound **82**. This intermediate was then reacted with 1,3-di-*O*-benzyl-2-propanol and sodium hydride to give a mixture of products containing adduct **83**. Without isolating adduct **83**, the mixture was treated with methanolic ammonia, and this simultaneously converted the ester to the amide while deacetylating the N^1-blocked pyrazole. The resulting compound **84** was then catalytically hydrogenated with $Pd(OH)_2$ in ethanol to give pyrazolecarboxamide **85**.

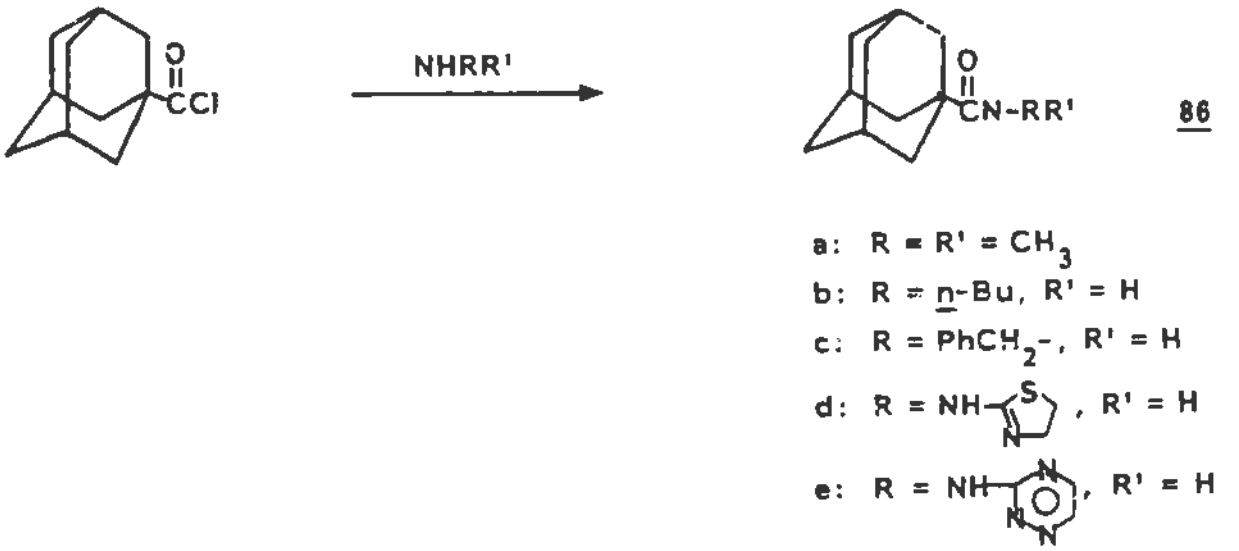
Adamantane Derivatives

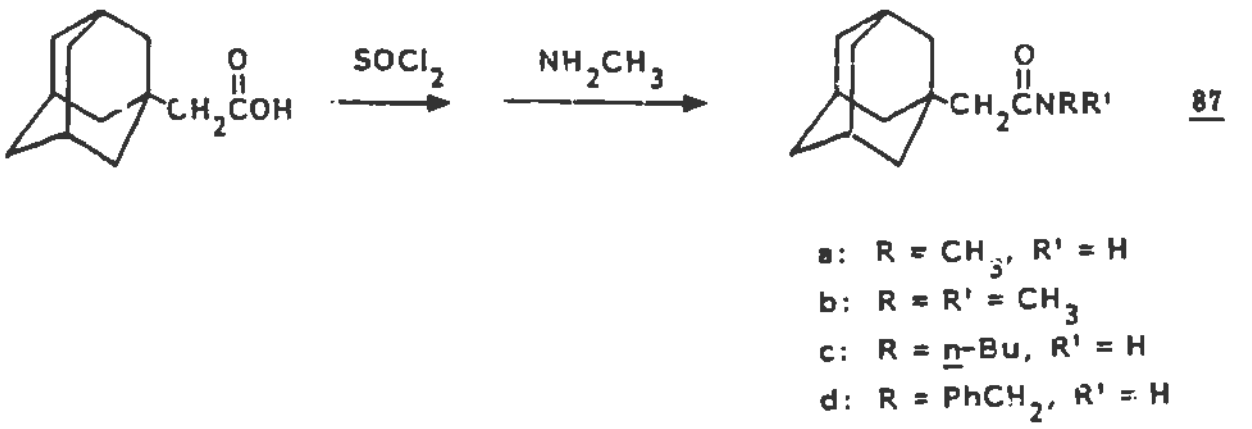
We also synthesized a number of adamantane-containing compounds. Since the methylamide of 1-adamantanecarboxylic acid had been shown to be active in the USAMRIID screen, our work was first directed toward producing similar amides of 1-adamantanecarboxylic acid and 1-adamantaneacetic acid. As shown in **Scheme XXI**, we made the dimethyl- and *n*-butylamides (**86a,b**, respectively) and the anilide **86c** of 1-adamantanecarboxylic acid starting with commercially available 1-adamantanecarboxylic acid chloride. We similarly made the methyl, dimethyl and *n*-butyl amides and the anilide of 1-adamantaneacetic acid **87a-d** and the methylamide of 1-noradamantanecarboxylic acid **88** by first generating the acid chloride by standard preparative procedures and then adding the requisite amines. Unfortunately, we could submit only **86a-c**, **87a**, and **88**, because we were unable to purify the other amides to the necessary analytical purity.

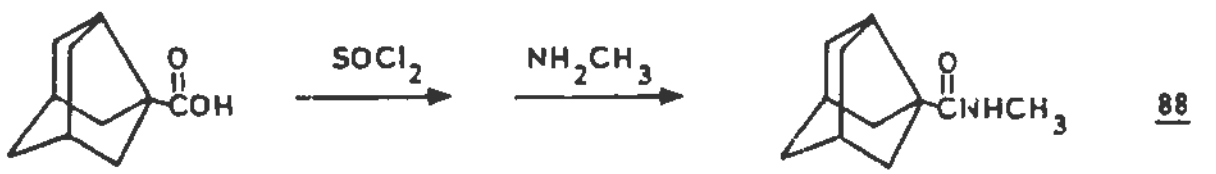
Amide **86d** was another 1-adamantanecarboxamide derivative that we synthesized. Using a procedure similar to those procedures for amides **86a-c**, we made this compound by adding 2-aminothiazole to adamantane carbonyl chloride. Interestingly, when we tried to make amide **86e** by virtually the same procedure, we did not obtain the desired product, but instead recovered mainly starting material. We also pursued alkylated 1-adamantamines such as monomethyl- and dimethyladamantylamine and trimethyladamantylammonium iodide (**89**, **90**). After numerous attempts with different reaction conditions we still obtained mixtures of all methylated forms. Therefore, we dropped this compound class and began pursuing the adamantane-containing compounds shown in **Scheme XXII**.

One of these compounds was an adamantyl thiourea, because members of this compound class had been reported to have antiviral activity against the PR8 strain of influenza comparable to that of 1-amino-

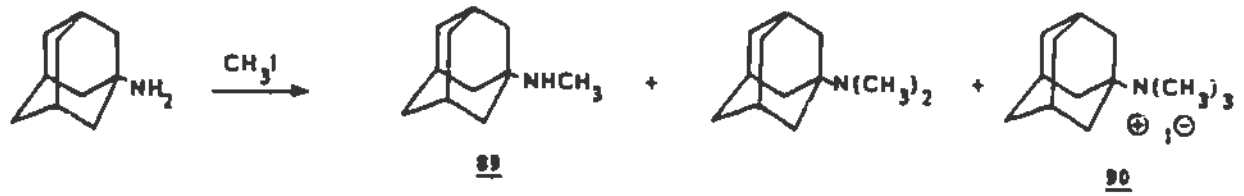
Scheme XXI


NHRR'
86
a: R = R' = CH3
b: R = n-Bu, R' = H
c: R = PhCH2-, R' = H
d: R = NH- , R' = H
e: R = NH- , R' = H

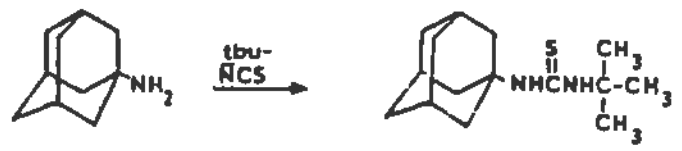

SOCl2
NH2CH3
87
a: R = CH3, R' = H
b: R = R' = CH3
c: R = n-Bu, R' = H
d: R = PhCH2, R' = H


SOCl2
NH2CH3
88

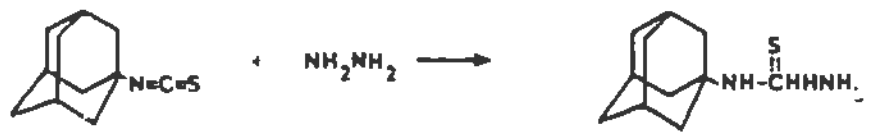
Scheme XXII



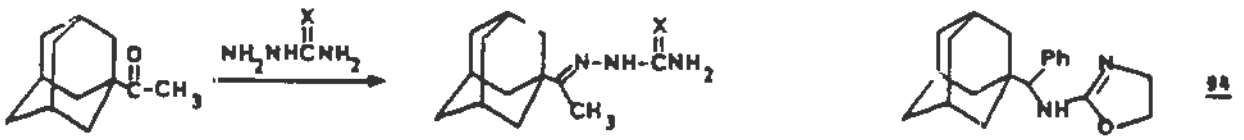
89 90



91

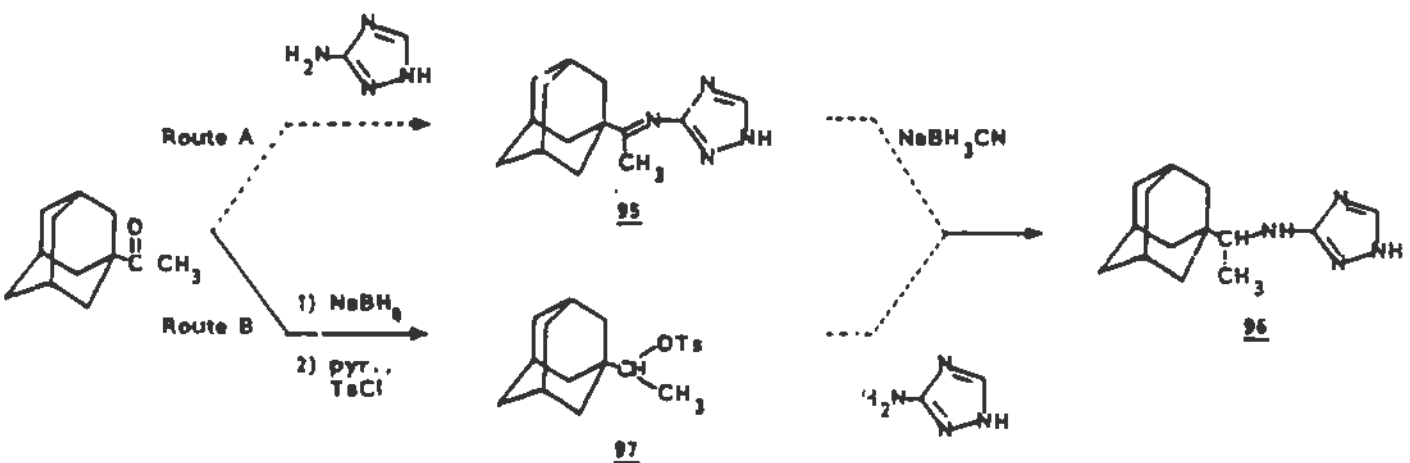


92



93 94

a: X = NH
b: X = S
c: X = O



95 96 97

adamantane hydrochloride.[31] We made one analog of this class, 1-adamantyl-3-*t*-butylthiourea (**91**), by adding adamantamine to *t*-butyl isothiocyanate.

We also synthesized adamantyl thiosemicarbazide (**92**)[32] by the addition of hydrazine to adamantyl isothiocyanate, and we made hydrazone **93a** and thiosemicarbazone **93b**[33] by the addition of aminoguanidine and thiosemicarbazide, respectively, to adamantyl methyl ketone. Interestingly, we were not able to synthesize the analogous semicarbazone **93c** by following the same general procedure. Another adamantane-containing compound class that we pursued was analogs of compound **94**. Unfortunately, our efforts to synthesize compounds from adamantyl methyl ketone were unsuccessful by either of our proposed routes. Route A was halted because we could not get 3-aminotriazole to add to the adamantyl methyl ketone. Route B was stopped because we were unable to form a tosylate from 1-adamantyl-1-ethanol with any success. We found that tosylation of this compound was very slow, and that any tosylate that formed rapidly eliminated; as a result of this we obtained only starting material and low yields of 1-vinyladamantane.

<u>Allopurinol (or 4-Hydroxypyrazolo[3,4-*d*]pyrimidine) Analogs; 4-Amino-1-β-D-ribofuranosyl-pyrazolo[3,4-*d*]pyrimidine; and 3-Bromo-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4-(5*H*)-one</u>

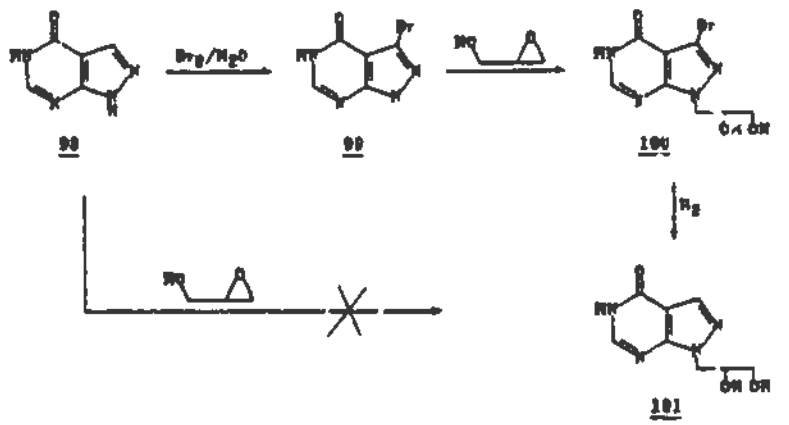
We also pursued a target class based on allopurinol (4-hydroxypyrazolo[3,4-*d*]pyrimidine), since the USAMRIID list of active antiviral compounds showed a number of active pyrazolopyrimidine compounds. Most of the related compounds were the usual ribosylated forms, and therefore, we felt that there was a need for analogs with altered sugar moieties such as the one shown in **Scheme XXIII**. Therefore, we synthesized compound (**100**) by condensing bromoallopurinol with glycidol.[34] Although this reaction proceeded cleanly and gave a reasonable yield, we found that it could not be repeated with allopurinol. Instead, we found that we routinely obtained complex mixtures of products alkylated at any or all of the possible sites. Furthermore, when we attempted to attach the other altered sugar moieties to either bromoallopurinol or allopurinol with a number of different conditions, we could not control the site of attachment.

We were able to obtain one other product from this particular route. The previously mentioned 1-(2',3'-dihydroxypropyl)allopurinol (**101**) was obtained from 3-bromo-(2',3'-dihydroxypropyl)allopurinol **100**[34] by removal of the 3-bromo group via catalytic hydrogenation.[35]

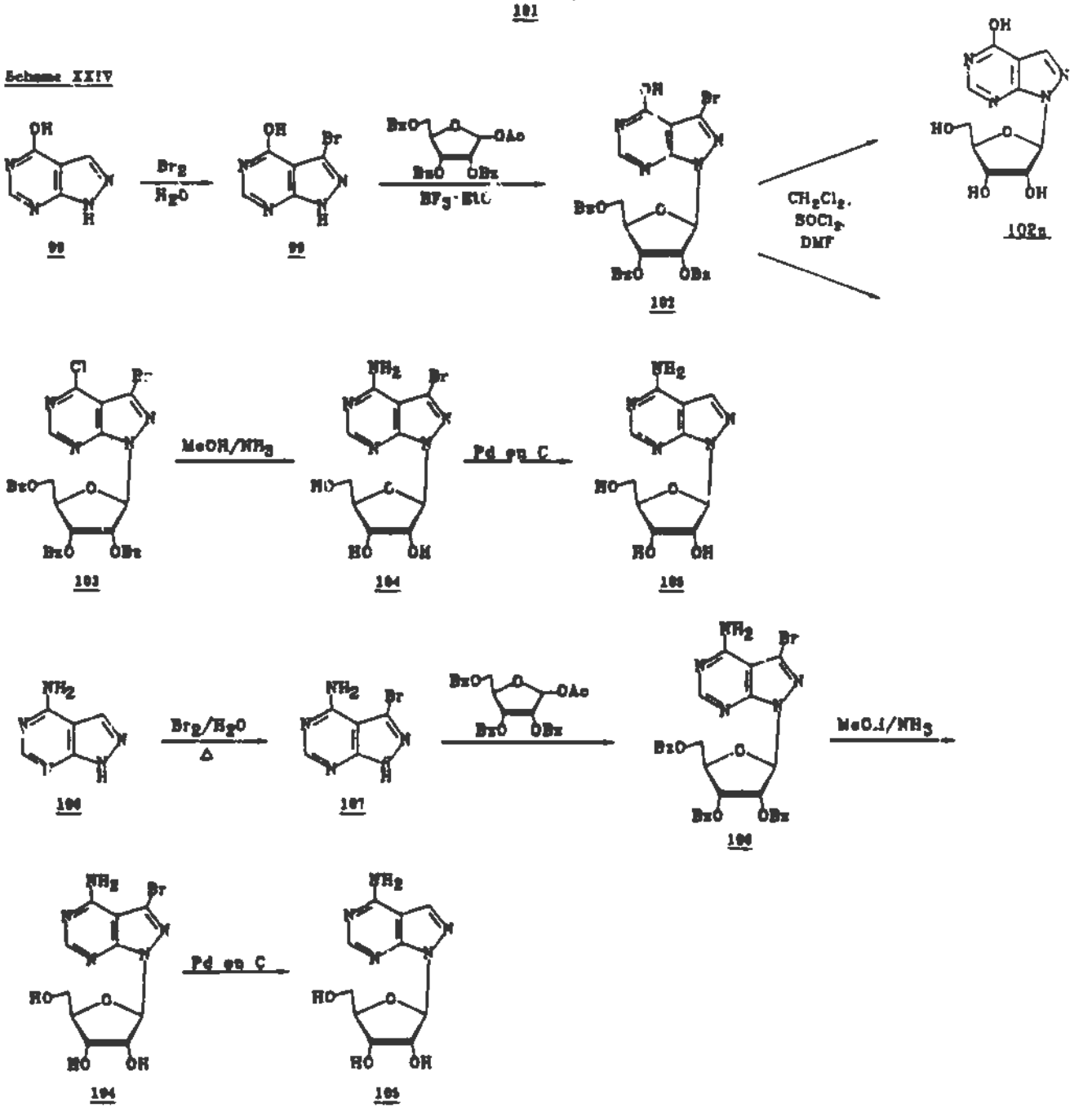
We also pursued allopurinol analogs with other functional groups at the 4-position. From these efforts, we developed two similar approaches to the synthesis of 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**105**).[35,36] **Scheme XXIV** shows the first approach in which allopurinol (**98**) was 3-brominated and then ribosylated with ribofuranose-1-acetate-2,3,5-tribenzoate to give protected nucleoside **102**. Thionyl chloride in DMF conversion of **102** to the 4-chloro analog **103** was followed by treatment with methanolic ammonia to deprotect the sugar and to displace the 4-chloro group, thus giving 3-bromonucleoside **104**. Catalytic reduction with palladium on carbon to remove the 3-bromo group then gave 4-amino-1-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**105**), but only in low yield.

The second approach was developed to allow us to reduce our effort by one synthetic step. Starting with 4-aminopyrazolo[3,4-*d*]pyrimidine (**106**), this approach offered an alternate route to common intermediate **104**. As is also shown in **Scheme XXIV**, **104** was obtained by the bromination of **106** followed by ribosylation and deprotection. Again, catalytic hydrogenolysis of **104** was again required to give nucleoside **105**.

Scheme XXIII



Scheme XXIV



We also synthesized one final allopurinol compound, 3-bromo-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**109**)[35,36] by the approach shown in **Scheme XXV**. We treated the previously discussed protected nucleoside analog **102** with ammonia and methanol, thus deprotecting it to give compound **109**.

4(5)-Bromo-1*H*(3*H*)-imidazole

The synthesis for 4(5)-bromo-1(3*H*)-imidazole (**111**)[37] is shown in **Scheme XXVI**. An aqueous solution of sodium sulfite and 2,4,5-tribromoimidazole (**110**) were refluxed, cooled, and refrigerated before the final product was isolated by extraction with ether, filtering, and evaporation of the solvent.

Desethyl Chloroquine (4-(4'-Ethylamino-1'-methylbutylamino)-7-chloroquinoline [AVS-3980])

We made desethyl chloroquine (**115a**),[38,39] by the route outlined in **Scheme XXVII**, and during its synthesis, we developed a new, more efficient synthesis of the side chain precursor, 4-aminopentanol (**113**) Instead of forming the oxime of 5-hydroxypentan-2-one and reducing it catalytically (with Raney nickel or palladium on carbon with pressure), we treated 5-hydroxypentan-2-one with $NaBH_3CN$ and ammonium acetate in ethanol, thus obtaining the amino alcohol in one step. This amino alcohol was then reacted with 4,7-dichloroquinoline at 145 °C under dry conditions to give 4-(4'-hydroxy-1'-methylbutylamino)-7-chloroquinoline (**114**). This compound was then first cautiously treated with 48% HBr followed by ethylamine to give the desired desethyl chloroquine (**115a**).

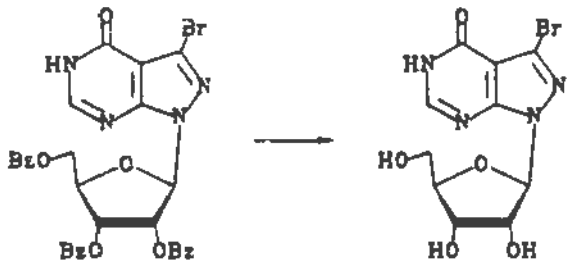
We also attempted to prepare bisdesethylchloroquine **115b** but found it to be very unstable (**Scheme XXVII**). During our attempts to isolate our bisdesthylchloroquine, we determined that our bisdesethylchloroquine intramolecularly cyclized to 4-(2'-methyl-1'-pyrolidyl)-7-chloroquinoline (**116**). Fortunately, a supply of this material was available at Walter Reed, and therefore, there was no need to continue pursuing this compound any further.

N^1-Aminoadenine and Four N^1-Aminonucleosides

We also synthesized N^1-aminoadenine and four N^1-aminonucleosides because of the structural similarities of these compounds to the adenosine-N^1-oxide analogs. As shown in **Scheme XXVII**, a methanolic solution of *O*-mesitylenesulfonyl hydroxylamine was used to effect N^1-amination of adenine and adenosine to form the corresponding N^1-aminoadenine **117** and N^1-aminoadenosine **118**.[40] Two separate samples of 1-aminoadenosine **118** were submitted: one as the mesitylenesulfonate salt and one as the hydrochloride salt. To make N^1-aminonucleosides **120**, **122**, and **123**, a slight procedural modification was used. An aqueous solution of hydroxylamine-*O*-sulfonic acid[41] was used to N^1-aminate the corresponding nucleosides **119**, **121**, and **125**. This gave the desired N^1-aminonucleosides in reasonable yields.

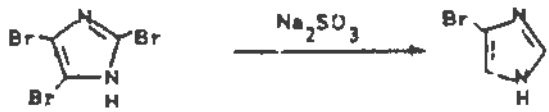
We also wanted to benzylate these N^1-aminonucleosides to obtain 1-benzylamino analogs similar to the 1-benzyloxyadenosine series that we had already been investigating. Unfortunately, we were never able to alkylate either N^1-aminoadenine or N^1-aminoadenosine. Our attempts to make either 1-benzylaminoadenine or 1-benzylaminoadenosine (**125**) with benzyl bromide or benzaldehyde using a number of variations of reagents and reaction conditions were all unsuccessful. We also tried to develop an *N*-benzylated hydroxylaminesulfonic acid reagent to try to circumvent the alkylation problem, but this approach was also unsuccessful since we were unable to make this reagent.

Scheme XXV



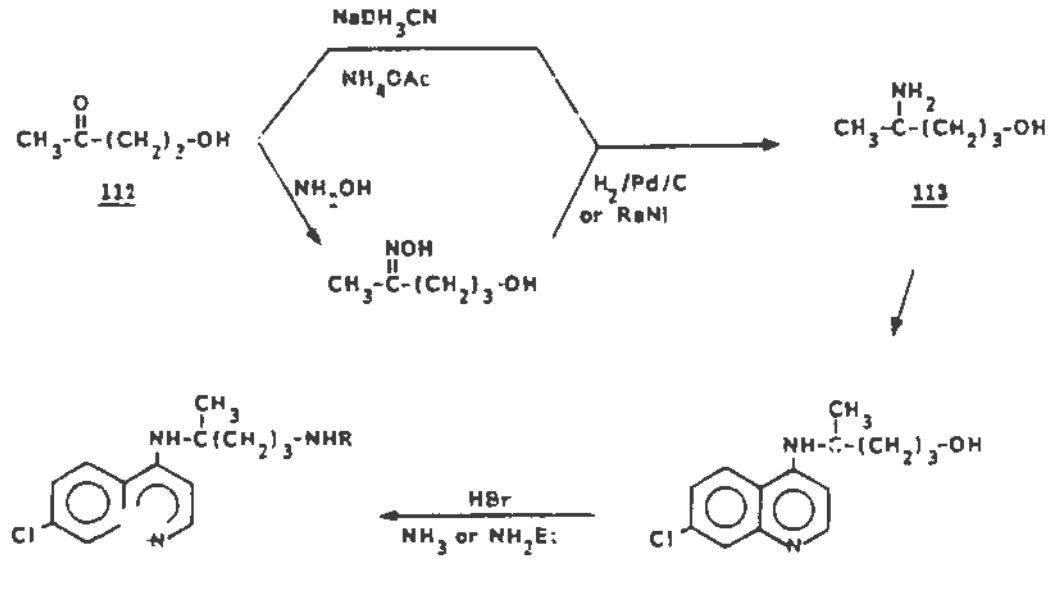
102 109

Scheme XXVI



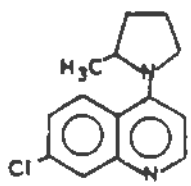
110 111

Scheme XXVII



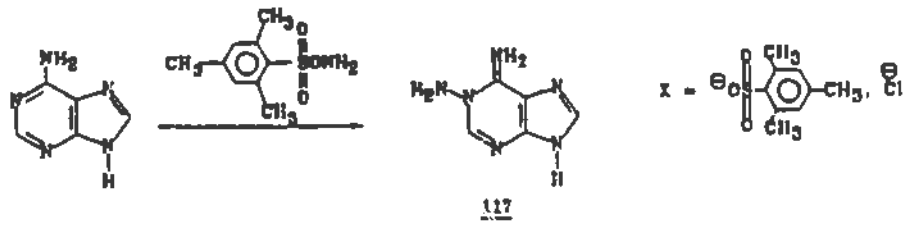
115a: R = H
115b: R = Et

114

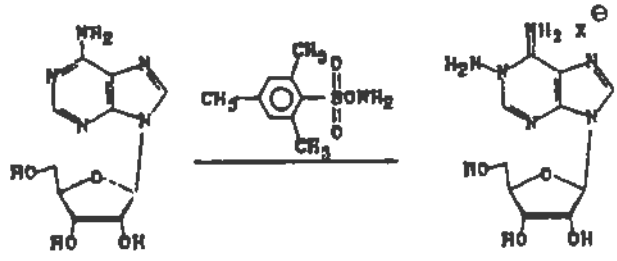


116

Scheme XXVIII

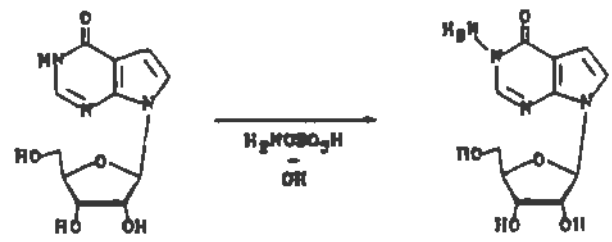


117



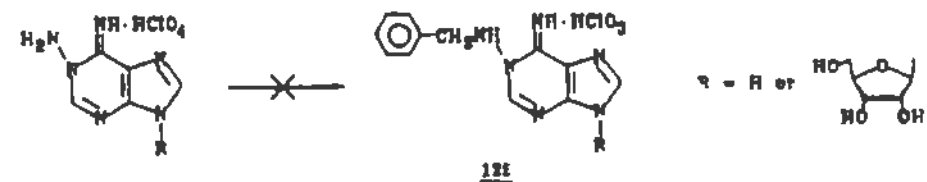
118

119 120



121 122

123 124



125

Dihydroquinolines and Tetrahydroquinolines

We also synthesized a number of dihydroquinolines and tetrahydroquinolines because of their structural analogy to the novel antibiotic virantmycin (**126**). Virantmycin had been isolated from *Streptomyces nitrosporeus*[42,43] and shown to have potent inhibitory activity against RNA and DNA viruses at very low concentrations. It was also found to exhibit weak antifungal activity against *Saccharomyces sake, Piricularia oryzae, Trichophyton interdigitale,* and *Aspergillus niger*. Since literature review showed little work with dihydroquinolines, we chose to pursue the development of analogs of this compound class. We specifically chose to simplify the side chains located at the 2-position, replacing the methoxymethyl and 2,3-dimethylpent-2-enyl sidechains with two methyl groups.

As shown in **Scheme XXIX**, the precursor for our analog series was dihydroquinoline **127**. This compound was prepared by refluxing ethyl 4-aminobenzoate with acetone in toluene and iodine.[44] Dihydroquinoline **127** was then formylated with formic acetic anhydride[45] to give derivative **128**. Unfortunately, we found that we could neither brominate nor epoxidize the 3- and 4-positions of either dihydroquinoline **127** or formylated dihydroquinoline **128**. We attempted these brominations under a number of different reaction conditions, and invariably, we were not able to halogenate the double bond. We similarly tried a number of reagents and reaction conditions but also could not epoxidize the double bond. We found that *m*-chloroperoxybenzoic acid added across the double bond of **128** to give adduct **130**, but the resulting ester alcohol would not collapse to the corresponding epoxide **131**.

However, we were able to obtain two more derivatives of these compounds. The 3,4-double bond of dihydroquinoline **129** was reduced by catalytic hydrogenation with palladium on carbon to give tetrahydorquinoline **132**. Furthermore, dihydroquinoline acid **133** was prepared from dihydroquinoline **129** by treating **129** with sodium hydroxide.

5-Bromo-3-nitro-1,2,4-triazole

5-Bromo-3-nitro-1,2,4-triazole (**135**)[46] was synthesized by direct bromination of 3-nitro-1,2,4-triazole (**134**) with bromine and sodium hydroxide, as shown in **Scheme XXX**.

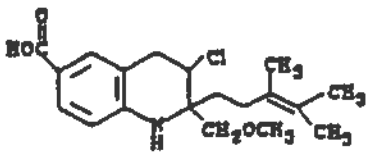
Ethyl 6-Amino 5-nitro-4-[(2-phenyl-2-oxoethyl)amino]pyridin-2-ylcarbamate oxime; Ethyl 5-Amino-3-(3′,4′-dimethoxyphenyl)-2*H*-pyrido[4,3-*b*][1,4]oxazin-7-ylcarbamate; Ethyl 5-Amino-1,2-dihydro-3-[(*N*-methylanilino)-methyl]pyrido[3,4-*b*]pyrazine-7-carbamate, Hemiethanolate; 9-Ribofuranosyl-2-methylthiopurine

These compounds, shown in the following figure (**Figure 3**) had been previously prepared at SRI. Since they had previously been shown to have biological activity, they were submitted as potential lead compounds.

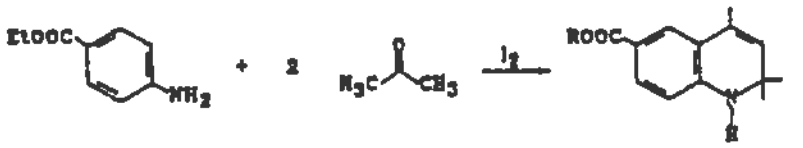
6-Ethylmercaptopurine Riboside [AVS-2700]; 6-Allylmercaptopurine Riboside; 6-Ethylsulfonyl-9-β-D-ribofuranosylpurine

These compounds were pursued since ribofuranosyl-6-ethylthiopurine had already been found to have activity against AD2, VV, JE, SF, and YF viruses. 6-Ethylmercaptopurine riboside [AVS-2700] (**137a**) and 6-allylmercaptopurine riboside (**137b**) were prepared as shown in **Scheme XXXI**. 6-Mercaptopurine riboside (**136**) was alkylated with either ethyl bromide or allyl bromide in DMAC and potassium carbonate, respectively, to give these nucleoside analogs.[47,48]

Scheme XXIX

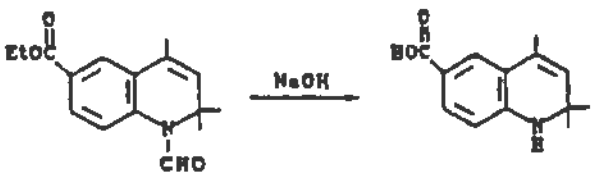


126



127

128



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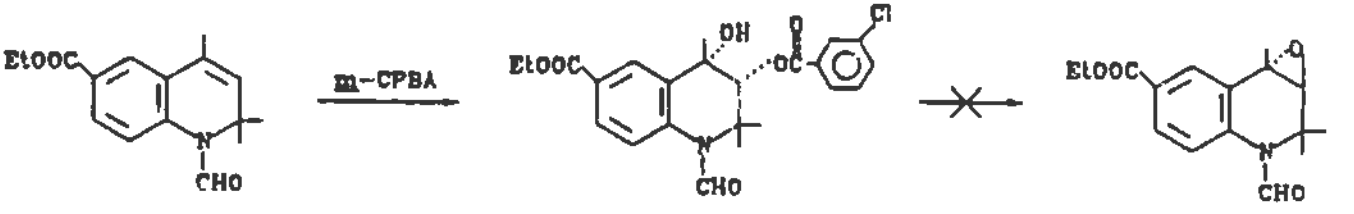
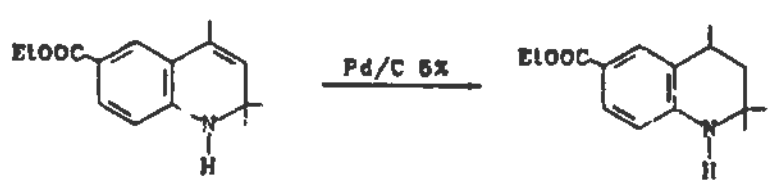
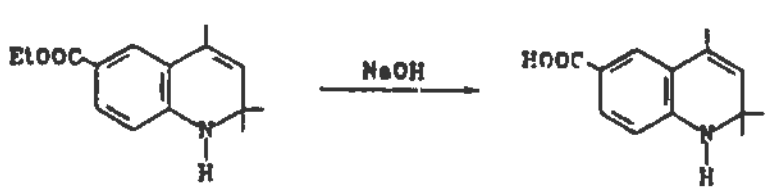


130

131

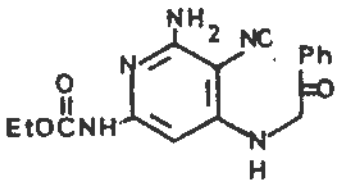


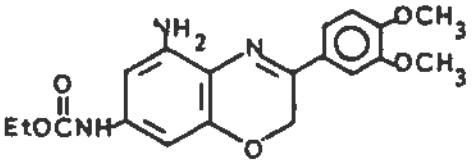
132

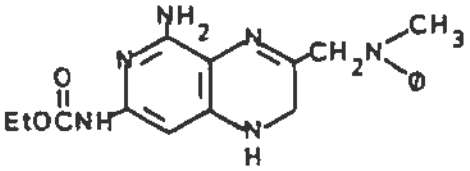


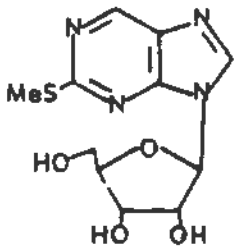
133

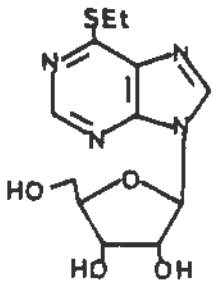
Figure 3. SoRI Compounds Submitted as Potential Lead Compounds



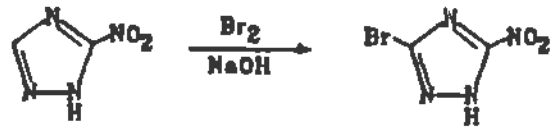






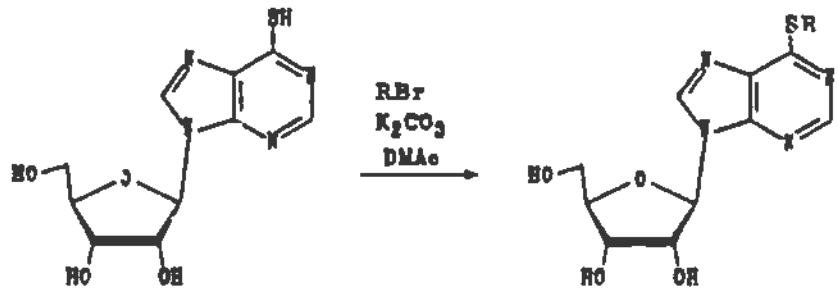


Scheme XXX



134 135

Scheme XXXI

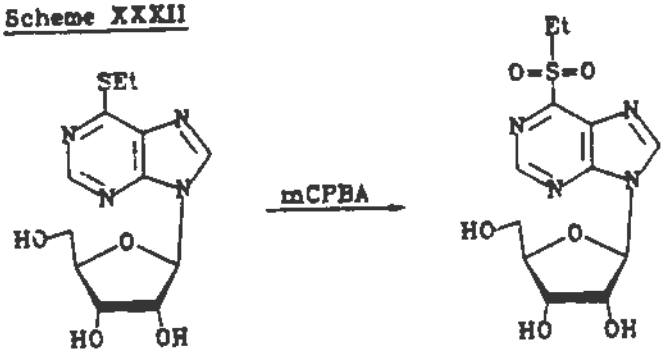


136 137

a: R = Et

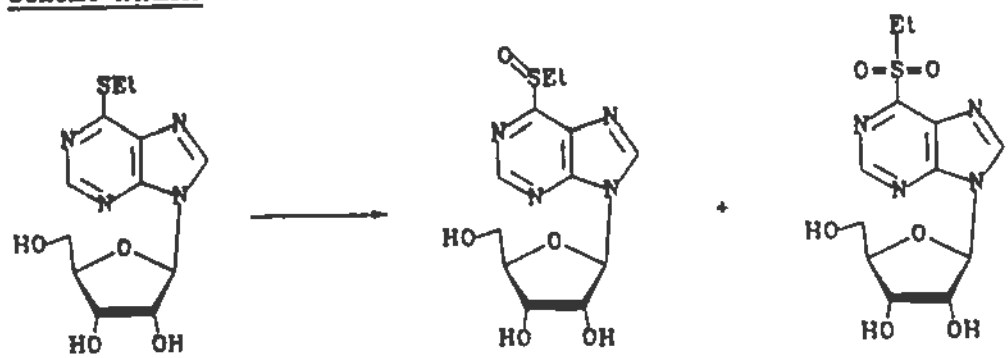
b: R = allyl

Scheme XXXII



138 139

Scheme XXXIII



138 140 139

We synthesized 6-ethylsulfonyl-9-β-D-ribofuranosylpurine (139) by the approach shown in Scheme XXXII. Oxidation of 6-ethylthiopurine riboside (AVS-2700) (138) with *m*-chloroperoxybenzoic acid in acetone[49] gave the corresponding sulfonyl compound 139.

We also synthesized 6-ethylsulfinylpurine riboside (140) by the almost identical route shown in Scheme XXXIII. This analog and potential metabolite of 6-ethylthiopurine riboside (AVS-2700) (138) was also made by oxidizing 6-ethylthiopurine riboside with *m*-chloroperbenzoic acid.[49] Analytical data for the product showed that our product was contaminated with the previously discussed sulfonyl analog 139. Our early attempts to separate these products chromatographically were not successful, and therefore, Dr. Gabrielsen decided that further pursuit of this compound was not necessary unless activity was found with previously submitted sulfonyl analog 139

1-Ribofuranosyl-7-cyanoimidazo[1,2-*b*]pyrazole

1-Ribofuranosyl-7-cyanoimidazo[1,2-b]pyrazole (147)[50,51] was made by the procedure shown in Scheme XXXIV. 2-Hydrazinoacetaldehyde diethylacetal (142) was made prepared hydrazine and chloroacetaldehyde diethylacetal (141) and was then reacted with ethoxymethylenemalononitrile to give 5-amino-1,3-(2,2-diethoxyethyl)-pyrazole-4-carbonitrile (143). Compound 143 was then cyclized to imidazolo[1,2-*b*]pyrazole-7-carbonitrile (144) by treatment with 1 *N* HCl, and pyrazolecarbonitrile 144 was then ribosylated with 1-*O*-acetyl-2,3,5-tribenzoyl-D-ribofuranose and HMDS, giving a product mixture containing both protected nucleoside 145 and the isomeric nucleoside 146. Chromatographic isolation of compound 145 followed by deprotection with methanolic ammonia gave the desired compound 147.

Tiazofurin 5′-Monophosphate (2-β-D-Ribofuranosyl-5′-phosphate-1,3-thiazole 4-carboxamide)

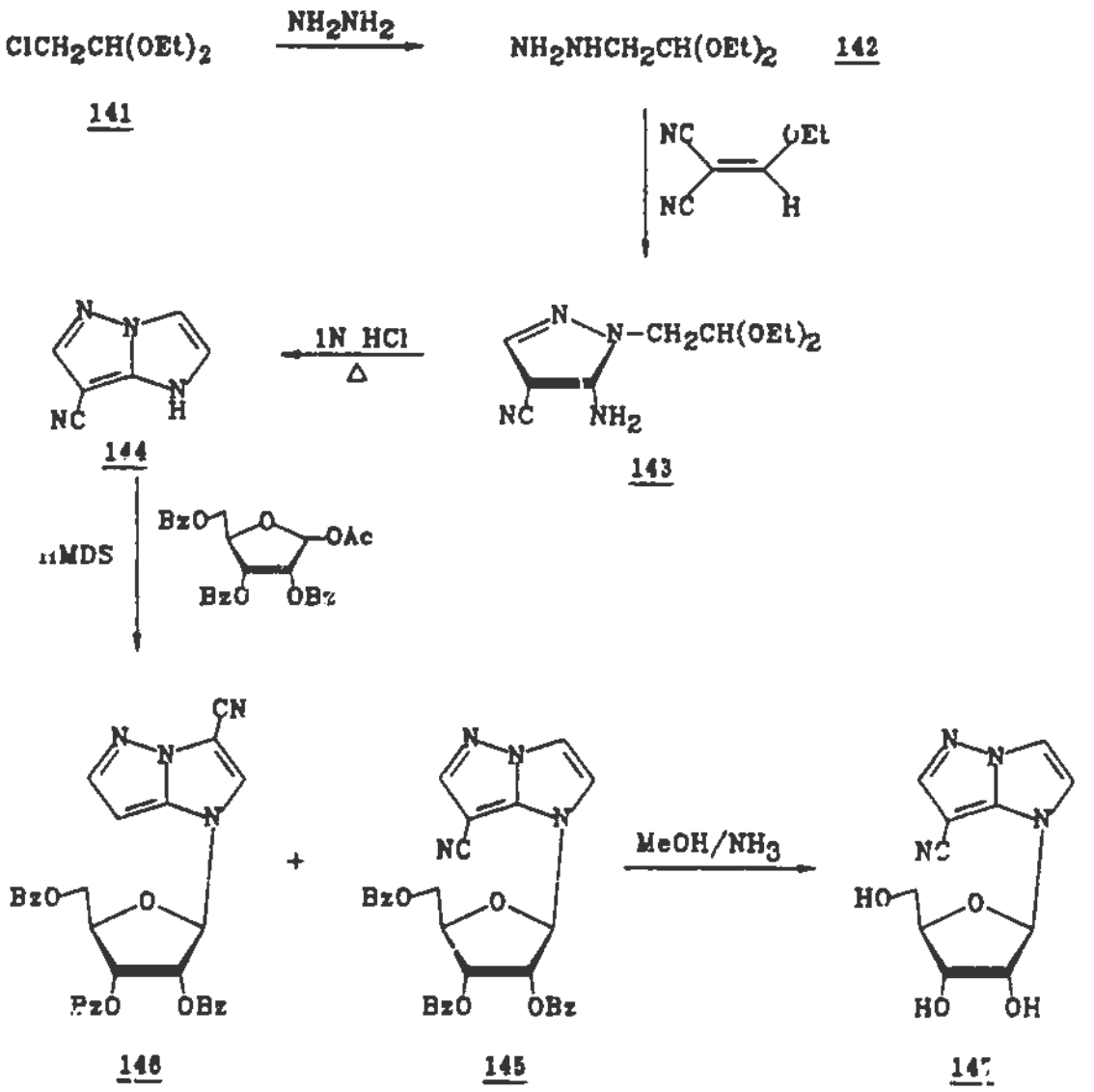
As shown in Scheme XXXV, tiazofurin 5′-phosphate (81)[52] was synthesized by treating tiazofurin with phosphorus oxychloride in pyridine.

Ribavirin 5′-Monophosphate, Ribavirin 5′-Methylphosphate, and Ribavirin 5′-Diphosphate; the Free Acid of Ribavirin Monophosphate

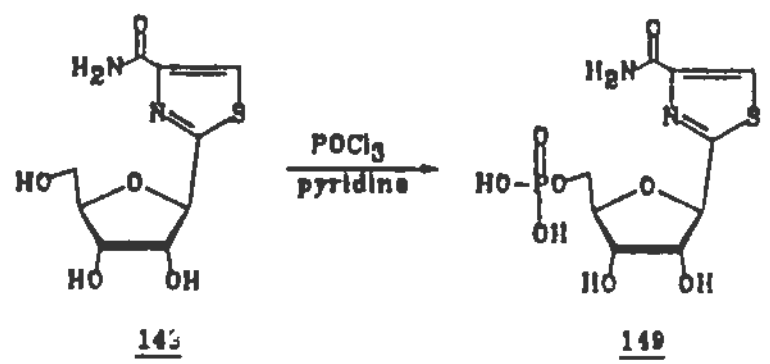
As shown in Scheme XXXVI, ribavirin 5′-phosphate (151) was made by treating ribavirin (150) with phosphoryl chloride and trimethylphosphate.[53] Treatment of phosphate 151 with MeOH, triethylamine, and dicyclohexylcarbodiimide gave ribavirin 5′-methylphosphate (152). Ribavirin 5′-phosphate (151) was also the precursor for ribevirin 5′-diphosphate (154). Phosphate (151) was first converted to its morpholidate 153. Subsequent treatment of the morpholidate with orthophosphoric acid, pyridine, and tributylamine then gave the desired ribavirin 5′-diphosphate (154).

Our efforts to synthesize ribavirin 5′-triphosphate (155) were complicated by the instability of the triphosphate compound during purification. According to thin-layer chromatographic and mass spectrometric data, we were cleanly synthesizing the desired triphosphate compound by treating morpholidate 153 in dry DMF (instead of pyridine as used in the syntheses of the other ribavirin nucleotides) with rigorously purified bis-tri-*n*-butylammonium pyrophosphate. The desired triphosphate compound was being obtained without contamination with di- and monophosphated nucleoside. However, our procedure for synthesizing ribavirin 5′-triphosphate (155) required a large excess (5X) of the pyrophosphate, and as a result the isolated product contained a significant amount of pyrophosphate in addition to the desired triphosphate, and unfortunately,

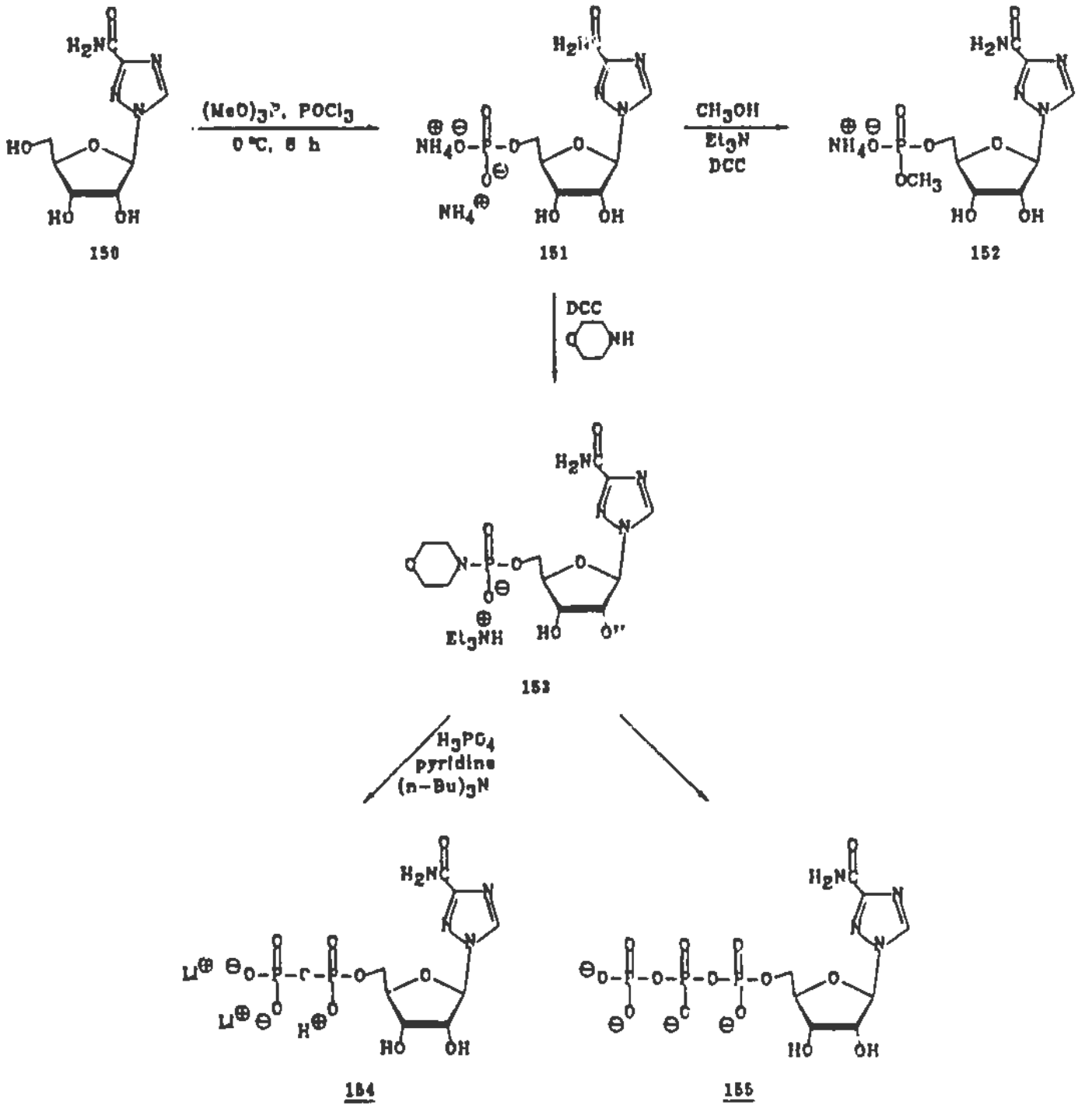
Scheme XXXIV



Scheme XXXV



Scheme XXXVI



150 151 152

153

154 155

the chromatographic systems that had effectively separated the other ribavirin nucleotides from their corresponding reaction sideproducts were now totally ineffective at separating ribavirin 5'-triphosphate from the residual pyrophosphate. When we tried other approaches to remove or reduce the level of pyrophosphate from the product mixture, none of our reaction condition modifications or chromatographic procedures provided pure ribavirin 5'-triphosphate. Since it was unlikely that pyrophosphate would cause any harmful effects in antiviral screenings, we felt that this compound could be tested as is. We then consulted with Dr. Gabrielsen, and he agreed to accept the obtained compound for screening, as obtained.

Formycin B, Formycin B 2',3',5'-Triacetate [AVS-0096]

Formycin B (**164**) was synthesized by the procedure shown in **Scheme XXXVII**.[54,55] Ribofuranose 1-acetate-2,3,5-tribenzoate was converted to intermediate **160** by the following series of reactions. Treatment of ribofuranose with HBr and $Hg(CN)_2$ gave 1-cyanosugar **156**. Hydrolysis of **156** followed by treatment with thionyl chloride gave acid chloride **157**. This intermediate was then treated with ylide **159**, giving cyanoester **160**. (Ylide **159** was generated from *t*-butylacetyltriphenylphosphorane (**158**) with 10% sodium hydroxide in chloroform. Triphenylphosphorane **158** was synthesized from chloroacetic acid and isobutene by treatment with sulfuric acid in benzene followed by triphenylphosphine.) Cyclization of cyanoester **160** with ethyl diazoacetate gave pyrazolediester **161**, thus forming the ribosylated pyrazole ring of Formycin B. Sequential treatment of this intermediate with formic acid followed by 2,2,2-trichloroethanol, triethylamine, and diphenylphosphoryl azide gave carbamoyl ester **162**. Treatment with zinc/acetic acid, and formamidine acetate effected cyclization, forming the necessary pyrimidine ring, thus giving 2',3',5'-tribenzoylated Formycin B (**163**). Deprotection was accomplished by using sodium methoxide in methanol to give Formycin B (**164**).

Formycin B 2',3',5'-triacetate (**165**) was then synthesized by adding acetic anhydride and pyridine to Formycin B (**164**).

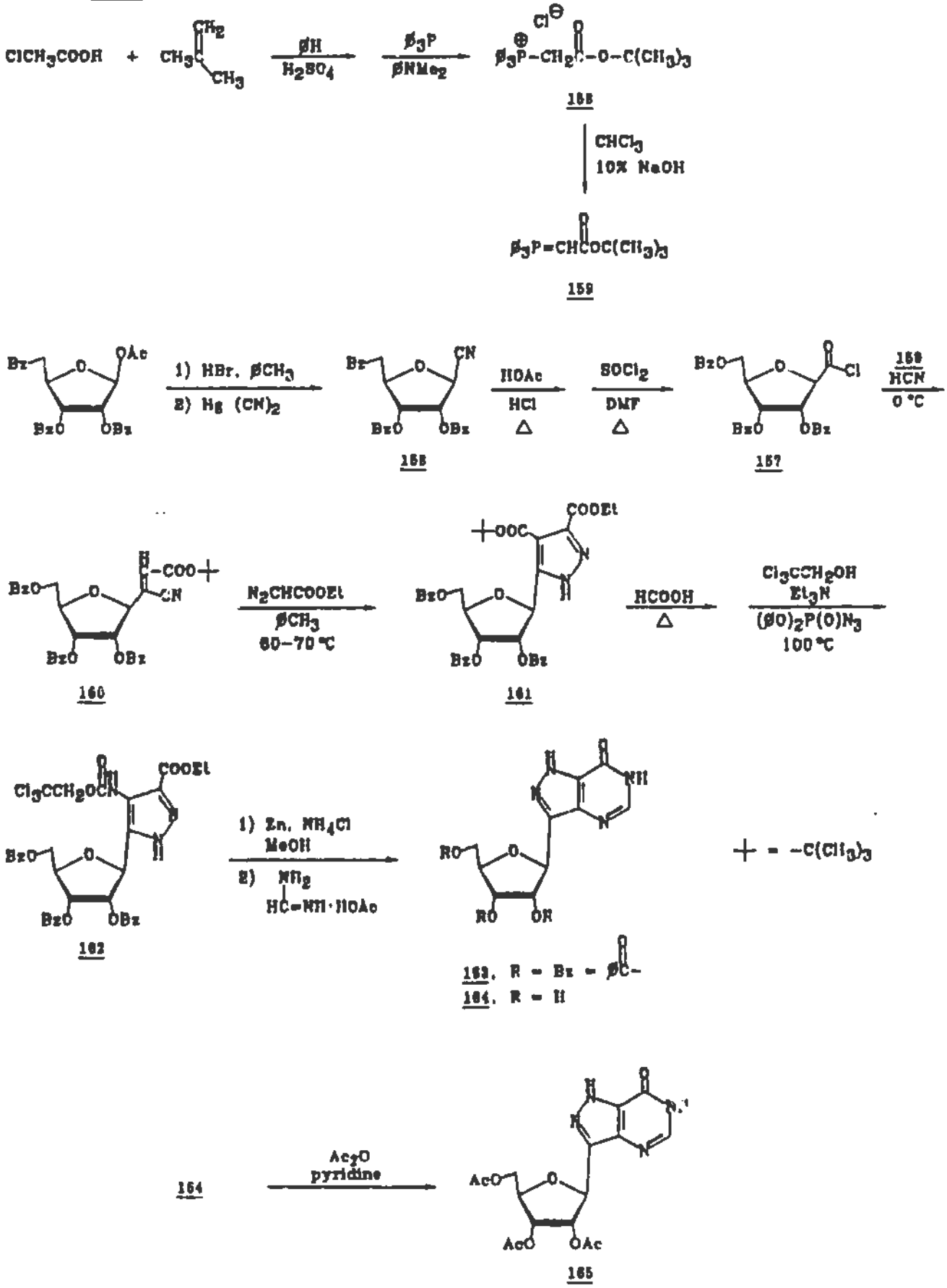
4-Acetyl-4-phenylpiperidine

Our activity with this 4-acetyl-4-phenylpiperidine was the chromatographic purification of a sample provided by USAMRIID. This compound was first eluted through silica gel with $CHCl_3$-MeOH (95:5) to remove 1-benzyl-4-acetyl-4-phenylpiperidine which was present as an impurity. When we later found that we could not consistently crystallize the purified compound, we treated the compound with HCl gas so that it could be isolated as its hydrochloride salt.

6-Benzyl-1,3-dioxoles (as Podophyllotoxin and Justicidin B Analogs)

We synthesized a number of 6-benzyl-1,3-benzodioxole derivatives as analogs of the biologically active natural products, podophyllotoxin (**166**) and Justicidin B (**167**). (Furthermore, we were especially interested in this series since Justicidin B was one of the USAMRIID requested compounds.) Our search of the literature yielded an antitumor activity study of benzodioxole derivatives against the *in vivo* i.p. P388 murine lymphocytic leukemia.[56] This study compared the activities of these benzodioxoles with that of podophyllotoxin and showed that the most active of these benzodioxoles were as effective as podophyllotoxin against P388 murine lymphocytic leukemia, although its effectiveness required higher dosage levels. Because of this demonstrated biological activity, we felt that these benzodioxole derivatives would be an excellent series of compounds for antiviral screening

Scheme XXXVII



Scheme XXXVIII shows the benzodioxole derivatives that we submitted as well as the synthetic routes used to make these compounds. Compounds **172a-c** were initially selected because they were among the most active antitumor agents in the previously mentioned study. Compounds **171a,b** were also submitted since they were intermediates leading to the synthesis of compounds **172a-c**. As shown in the scheme, compounds **171a,b** were made by condensing sesamol (**170**) in aqueous acidic media with the appropriately substituted benzyl alcohol (**169**) (obtained by sodium borohydride reduction of the corresponding substituted acetophenone). The resulting phenolic 1,3-benzodioxoles **171a,b** were then alkylated with either methyl iodide or ethyl iodide to give the corresponding alkylated 6-benzyl-1,3-benzodioxoles **172-c**. We then synthesized **171c-d** by following the same general sequence of first synthesizing the appropriately substituted benzyl alcohols from the corresponding acetophenones and then condensing sesamol with these benzyl alcohols. Derivatives **172d-g** were then also synthesized by alkylating with the appropriate alkyl bromides.

One other group of compounds were obtained from our pursuit of these benzodioxole derivatives. As shown in Scheme XXXIX, compound **174** was obtained instead of the expected benzyldioxole **176** when we condensed sesamol (**170**) with 3,4-dimethoxybenzyl alcohol (**173**). Ether derivatives **175a,b** were then obtained by alkylating with either methyl iodide or ethyl iodide.

<u>3-Phenyl-1,4-benzothiazin-2-one Oximes</u>

Our 3-phenyl-1,4-benzothiazin-2-one oximes were synthesized by the procedure shown in **Scheme XL**. We initially attempted to reproduce the methods in the literature[57-59] in which the appropriately substituted benzaldehydes were converted to the corresponding nitroacetophenones **178** via nitrostyrene intermediates **177**. According to the literature, the nitroacetophenone would then have been reacted with 2-aminothiophenol to give the desired benzothiazin-2-one oxime. Our efforts to prepare the nitroacetophenones were not successful, and therefore, we developed another approach to these compounds. The appropriately substituted α-chloroacetophenones **180a-c** were first treated with *n*-butylnitrite and HCl[60,61] to give chloronitroso compounds **181a-c**. These intermediates were then reacted with 2-aminothiophenol to give the target phenyl-benzothiazinone oximes **179a-c**.

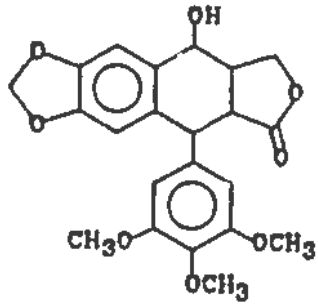
<u>Methanesulfonic Acid Derivatives</u>

We submitted four methanesulfonic acid derivatives **184a,b** and **189a,b**[62-65] which had been synthesized as analogs of busulfan (**182**), a compound that is biologically active against Friend Leukemia virus.[66] As shown in **Scheme XLI**, compounds **184a,b** were synthesized by reacting either the corresponding chloromethanesulfonyl chloride (**183a**) or (methylsulfonyl)methanesulfonyl chloride (**183b**) with 1,4-butanediol and triethylamine in ethyl acetate. Similarly, compounds **189a,b** were synthesized by reacting 4-benzyloxybutanol (**186**) (prepared by the method of Pistor[65]) with methanesulfonyl chloride to give common intermediate **187**. This intermediate was hydrogenated and debenzylated to give 4-methylsulfonyloxybutanol (**188**). Compound **188** was then immediately reacted with either chloromethanesulfonyl chloride or (methylsulfonyl)methanesulfonyl chloride to give **189a,b**.

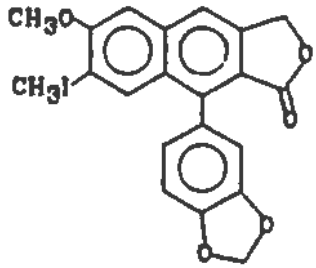
<u>9-(2-Phosphonylmethoxyethyl)adenine (PMEA); 9-[2-(Phosphonylmethoxy)ethyl]guanine (PMEG)</u>

9-[2-(Phosphonylmethoxy)ethyl]adenine or PMEA (**196**)[67,68] was synthesized by the reaction sequence shown in **Scheme XLII**. The key acyclosugar sidechain precursor **194** was synthesized by following a procedure

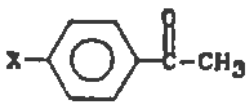
Scheme XXXVIII



166

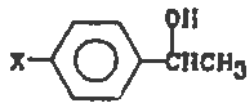


167



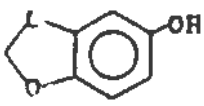
168

$NaBH_4$, EtOH



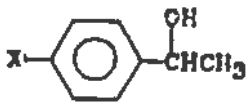
169

a) X = OEt
b) X = $-OCH_3$
c) X = $-CH_3$
d) X = F



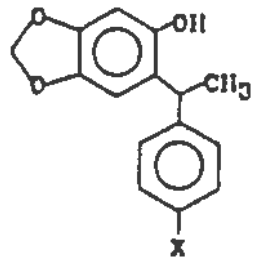
170

+



169

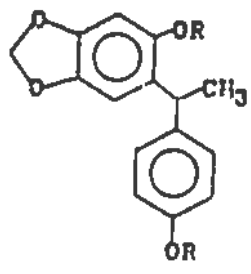
HOCCOH, AcOH



171

a) X = OEt
b) X = $-OCH_3$
c) X = $-CH_3$
d) X = F

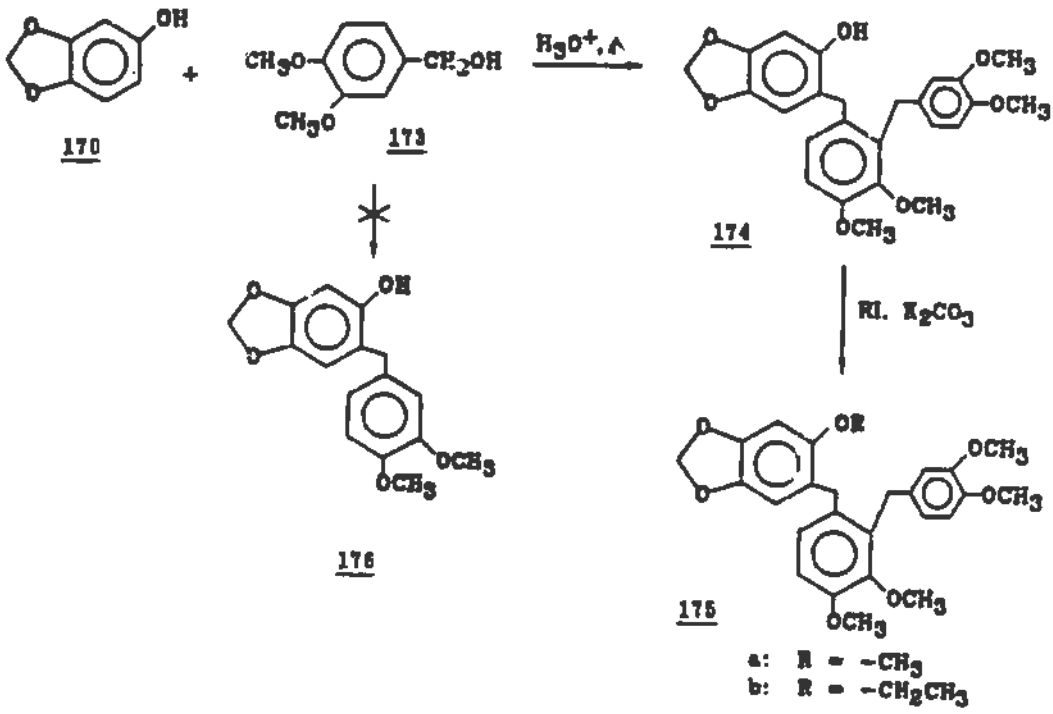
CH_3I or EtI
K_2CO_3



172

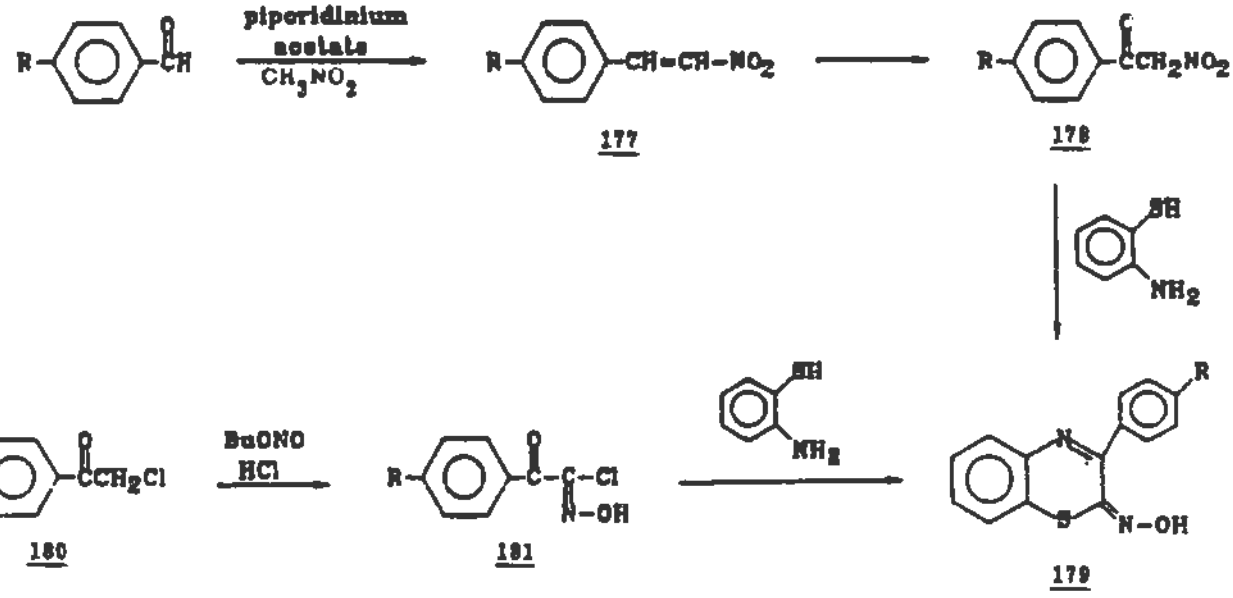
a) X = $-OCH_3$, R = $-CH_3$
b) X = -OEt, R = Et
c) X = -OEt, R = CH_3
d) X = $-OCH_3$, R = -Et
e) X = $-CH_3$, R = $-CH_3$
f) X = $-CH_3$, R = -Et
g) X = $-OCH_3$, R = $-CH_2-CH=CH_2$

Scheme XXXIX



170 173 174 175 176

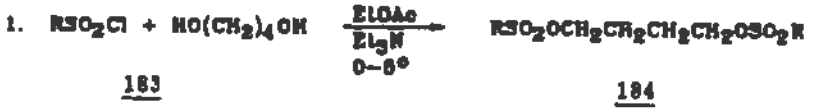
Scheme XL



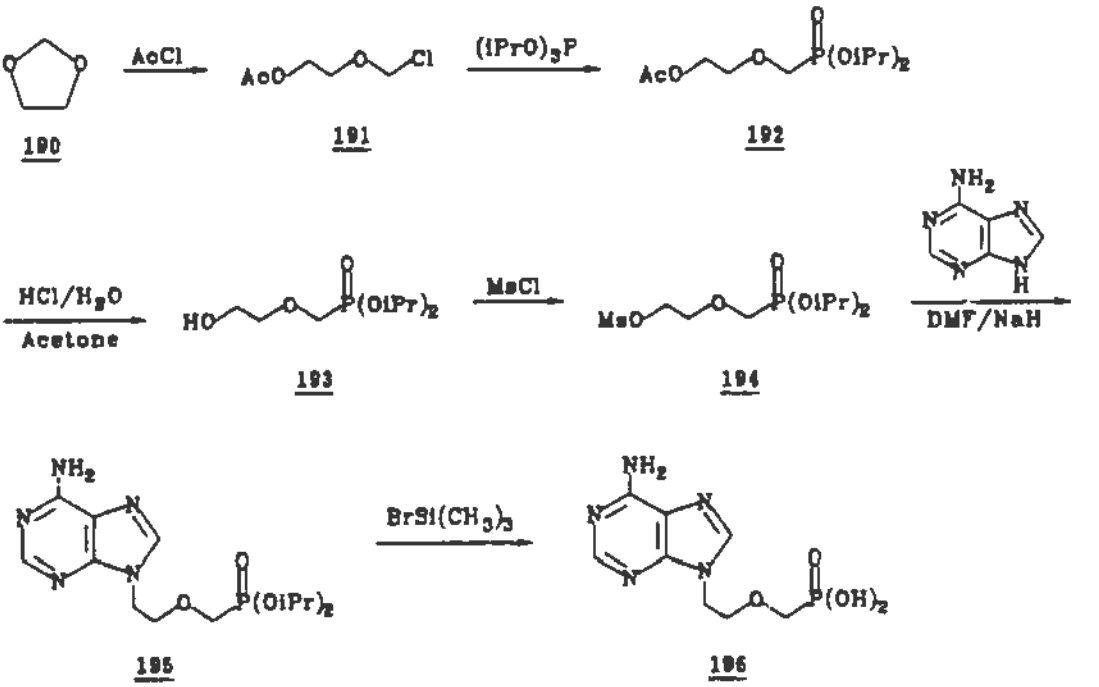
177 178 179 180 181

Scheme XLI

busulfan, 182



Scheme XLII



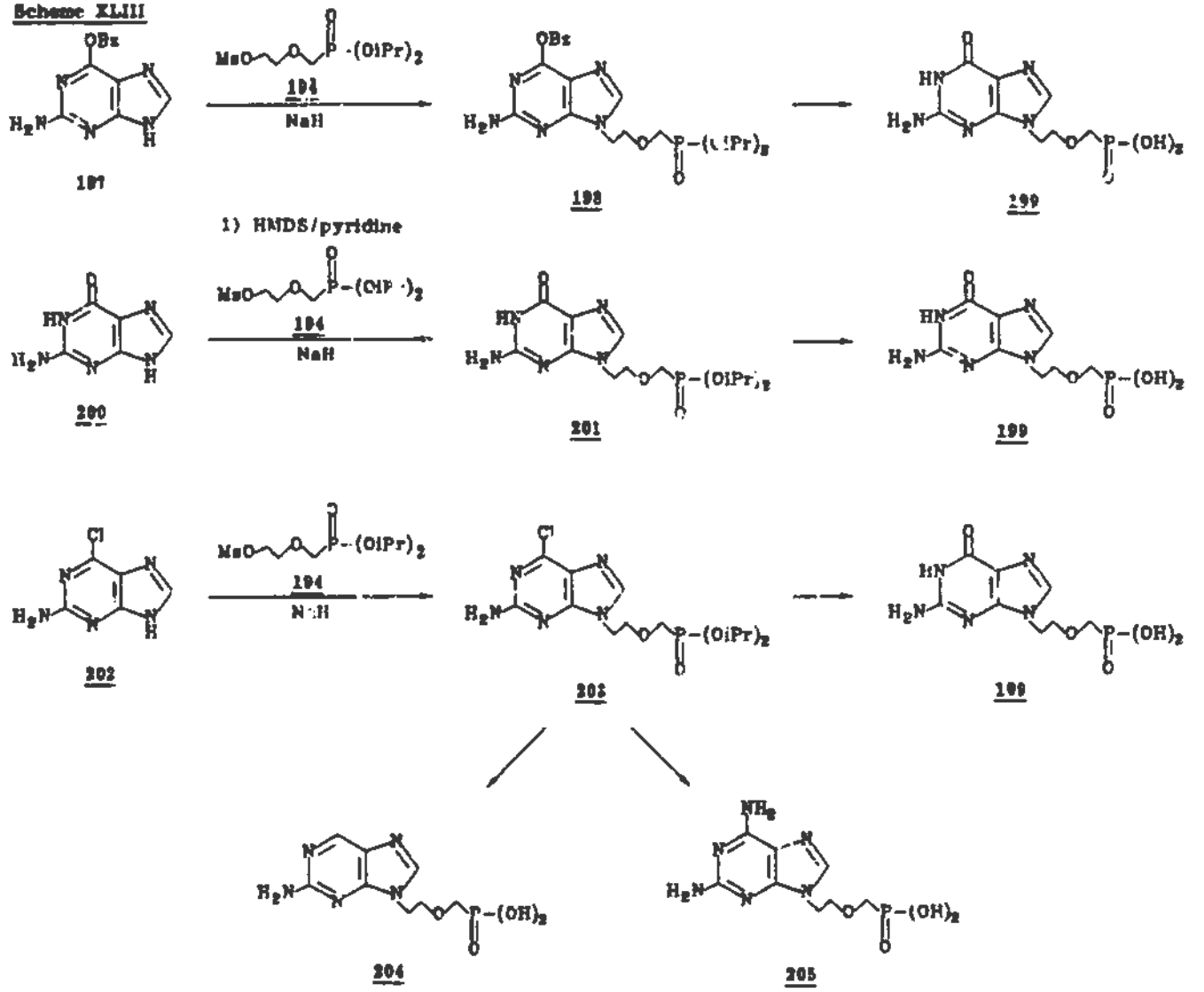
obtained from J. Bronson of Bristol-Myers. As shown in the scheme, dioxolane (**190**) was reacted with acetyl chloride and zinc chloride to give 2-(chloromethoxy)ethyl acetate (**191**). Treatment of **191** with triisopropylphosphite gave 2-(diisopropylphosphonylmethoxy)ethyl acetate (**192**). Hydrolysis of acetate **192** with HCl gave 2-(diisopropylphosphonylmethoxy)ethanol (**193**) which was then mesylated to give key intermediate **194**. Sodium hydride catalyzed coupling of **194** with adenine gave 9-(2-[diisopropylphosphonylmethoxy]ethyl)adenine (**195**), which gave PMEA **196** after hydrolysis with bromotrimethylsilane.

Schemes XLIII and **XLIV** show the synthetic methods that we pursued in our attempts to synthesize 9-[2-(phosphonylmethoxy)ethyl]guanine or PMEG (**199**), an analog of recently submitted 9-[2-(phosphonylmethoxy)ethyl]adenine or PMEA (**196**). We began our investigation of the synthesis of PMEG (**199**) by pursuing the three approaches shown in **Scheme XLIII**. The first mimicked the procedure for synthesizing PMEA (**196**).[67,68] As before, sidechain precursor **194** was first synthesized from dioxolane (**190**). We first tried the NaH-catalyzed coupling of 6-*O*-benzoylated guanine (**197**) with the sidechain precursor **194**. We also tried the HMDS-catalyzed alkylation of guanine (**200**) with sidechain precursor **194**, and we attempted the NaH-catalyzed coupling of 6-chloro-2-aminopurine (**202**) with the sidechain precursor **194**. We were especially interested in this third approach, because intermediate **203** could also be used directly in the synthesis of other USAMRIID-requested PMEA analogs 9-[2-(phosphonylmethoxy)ethyl]-2-aminopurine, PMEMAP (**204**) and 9-[2-(phosphonylmethoxy)ethyl]-2,6-diaminopurine, PMEDAP (**205**). Unfortunately, all of these early attempts met with little success, and therefore we decided to try the slightly different sidechain precursor **208** while also concurrently investigating milder reaction conditions. We had already synthesized modified sidechain precursor, diethylphosphonylmethoxyethyl tosylate **208**, more as a result of serendipity than rational strategy. As shown in **Scheme XLIV**, the procedure for preparing this precursor was almost identical to that for preparing **194**. In our earlier investigations into the synthesis of the sidechain precursor, we had synthesized a small amount of **206** by treating chloroacetate **191** with some triethylphosphite that was already on hand. We had not pursued the conversion of this intermediate to a useful sidechain precursor, because the literature had suggested that the 9-[2-(diisopropylphosphonylmethoxyethyl)purine offered a slight advantage in later conversions of 2-amino-6-chloropurine moiety of intermediate **203**. However, during an interim while we were waiting for more starting materials for synthesizing more **194**, we decided to proceed with **206** and to investigate a different leaving group in place of the mesyl group. Therefore, we hydrolyzed **206** with acetone-water (4:1) and concentrated HCl, and we treated the resulting diethylphosphonylmethoxyethanol (**207**) with tosyl chloride in methylene chloride and triethylamine to get precursor **208**.

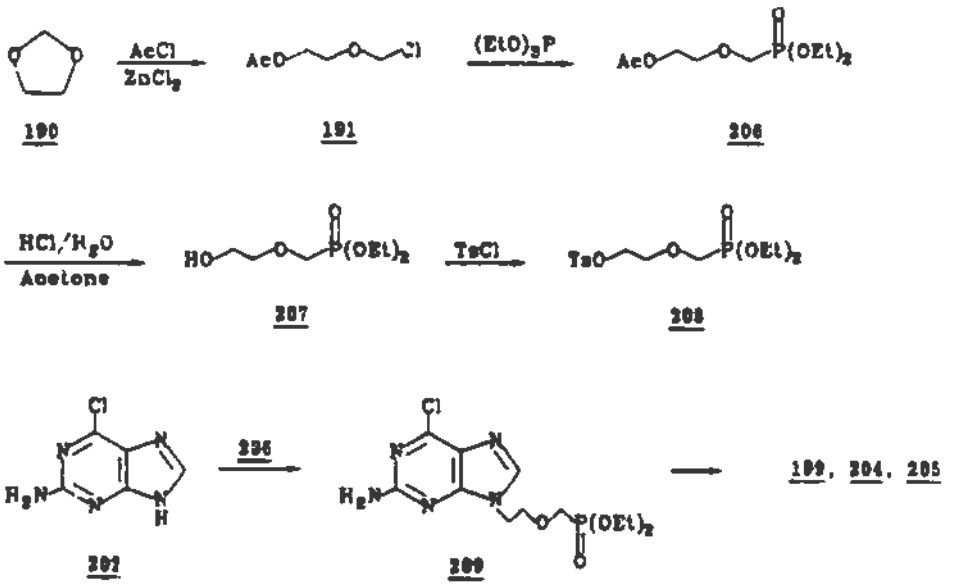
Using this new precursor **208** and 2-amino-6-chloropurine (**202**) under milder reaction conditions (potassium carbonate and anhydrous DMF at room temperature for 3 days under argon),[69] we were able to prepare intermediate **209**, the diethylester analog of **203**. PMEG (**199**) was then obtained from this intermediate after hydrolysis of the phosphonate ester with bromotrimethylsilane and hydrolysis of the 6-chloro group to the required 6-oxo group.

We were also able to convert intermediate **209** to PMEMAP (**204**) and PMEDAP (**205**) according to MS and ^{1}H NMR data. Unfortunately, we were unable to purify these compounds, and we directed our efforts to other compounds, as requested by Dr. Gabrielsen.

Scheme XLIII



Scheme XLIV



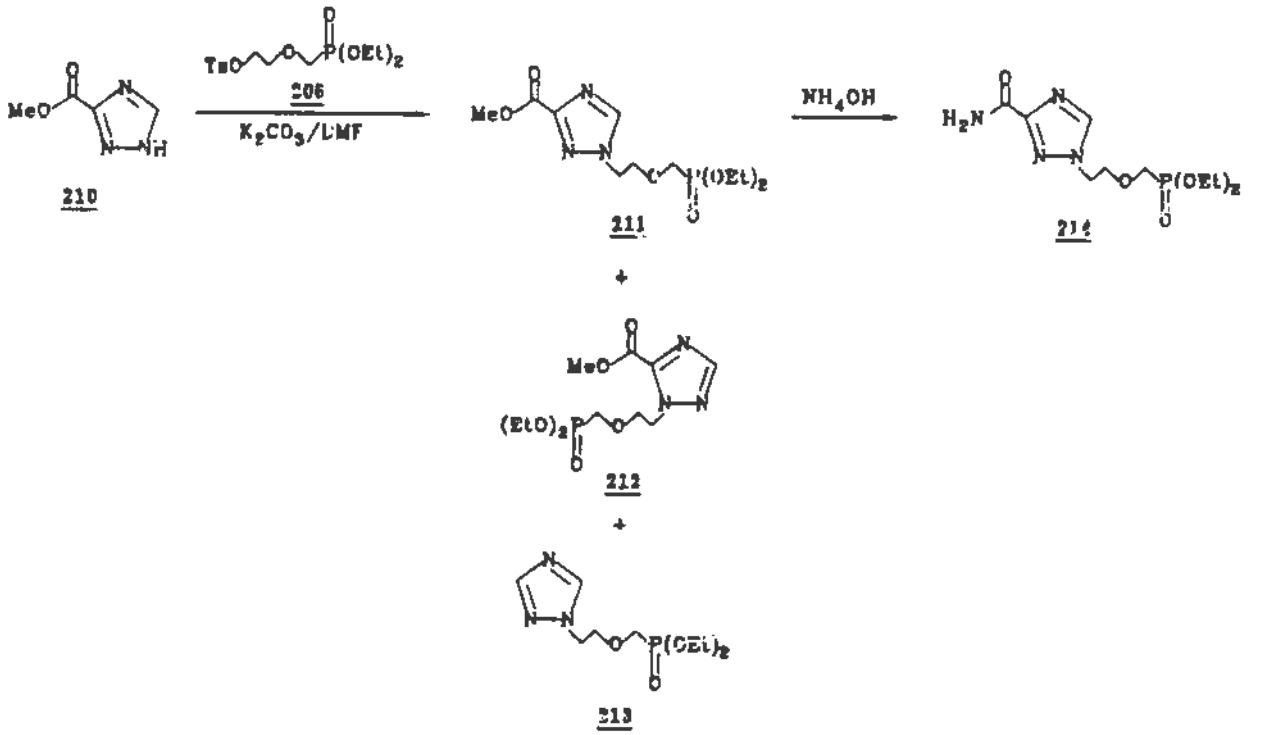
1-(2-Phosphonylmethoxyethyl)-1,2,4-triazole-3-carboxamide; the Diammonium Salt of 1-[(Phosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide (AVS-6469); 1-[2-(Diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide

Our approaches to the synthesis of ribavirin analog **215** are given in the following schemes. Our efforts to synthesize this PMEA analog used methyl 1,2,4-triazole-3-carboxylate (**210**) generously supplied by Dr. Gabrielsen. We initially investigated the alkylation of methyl 1,2,4-triazole-3-carboxylate (**210**) with the acyclosugar precursor **194** with a number of reagents and reaction conditions (bis-*p*-nitrophenylphosphate/130 °C[70], NaH/DMF/r.t. to 100 °C[34]; potassium carbonate/acetone or methanol; sodium methoxide/methanol or THF, etc.). Unfortunately, all of these early attempts were unsuccessful and consistently yielded hydrolyzed sidechain precursor along with some recovered methyl 1,2,4-triazole-3-carboxylate. We eventually developed the approach shown in **Scheme XLV**, which paralleled and was developed at the same time as the previously discussed PMEG work. This approach used the combination of milder reaction conditions and the modified sidechain precursor, 2-diethylphosphonylmethoxyethyl tosylate (**206**) instead of 2-diisopropylphosphonylmethoxyethyl mesylate **194**. We alkylated methyl 1,2,4-triazole-3-carboxylate with modified sidechain precursor **206** in anhydrous DMF with potassium carbonate at 90 °C under inert atmosphere[32] and obtained key intermediate **211** in addition to isomeric **212** and the decarboxylated analog **213**. **211** could not be easily isolated from **213**, and therefore, the mixture containing **211** and **213** were both treated with concentrated ammonium hydroxide to give **214** and **213**, which were easily separated by column chromatography. **214** was then deesterified with bromotrimethylsilane to desired target compound **215**, according to analytical data. Unfortunately, the isolated compound was not analytically pure, and therefore, the recrystallization procedure (from acetone/water) that had been effective for PMEA was ineffective for this compound probably due to the extreme water solubility of this compound. With multiple batches, we were inconsistently able to obtain a small yield the the desired **215** (<10% yield). Furthermore, TLC and MS analysis of the supernatant revealed that a significant amount of **215** was remaining in the supernatant. Therefore, we investigated a number of other purification methods until we determined that the treatment of **215** with dilute ammonium hydroxide followed by evaporation under vacuum gave a better yield of the desired compound as the diammonium salt **216**.

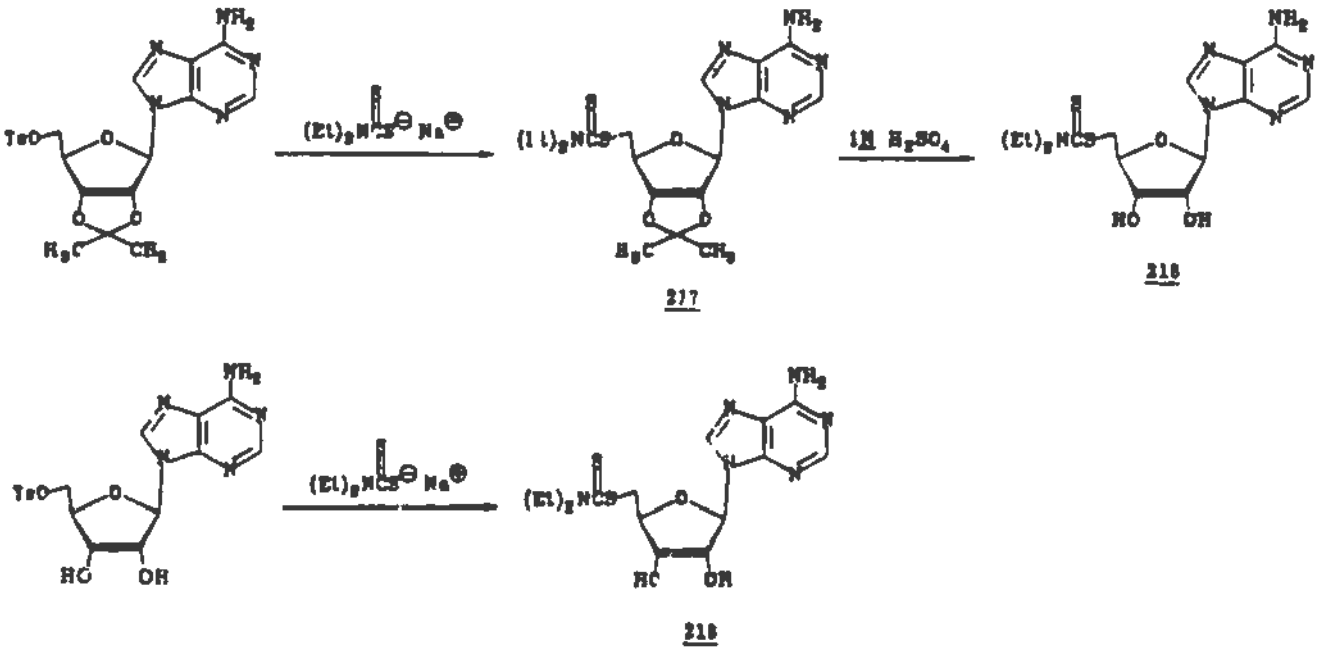
Adenosine 5′-Diethylthiocarbamate

We also investigated purine diethylthiocarbamates as possible lead compounds, because of the following reasons: several dithiocarbamates are well-known fungicides.[71-73] And, sodium diethyl dithiocarbamate (DTC or imuthiol) has been found to be an effective immune modulator in clinical trials;[74] in this study, AIDS and ARC patients treated with sodium diethyl dithiocarbamate were found to show more symptomatic improvement than untreated patients. A review of the literature showed that there have not been any detailed studies on dithiocarbamate-substituted nucleosides, and therefore, we initiated the exploration of this potential area by preparing 5′-deoxythioadenosine, 5′-*N*,*N*-diethylthiocarbamate (**218**). This thiocarbamate was made by refluxing commercially available sodium diethyldithiocarbamate trihydrate and 2′,3′-*O*-methylethylidene adenosine in DMF and then treating the reaction mixture with 1 *N* H_2SO_4 (**Scheme XLVI**). We also made **218** directly from commercially available 5′-tosyladenosine. By reacting 5′-tosyladenosine with sodium

Scheme XLV



Scheme XLVI



diethyldithiocarbamate under the same reaction conditions, we again obtained the desired 5′-*N*,*N*-diethylthiocarbamate-5′-deoxy-5′-thioadenosine (**218**) in good yield.

1,3-Bis-(morpholinomethyl)-tetrahydro-2(1*H*)pyrimidinone; 1-Morpholinomethyltetrahydro-2(1*H*)pyrimidinethione; 1-Morpholinomethyltetrahydro-2(1*H*)-pyrimidinone

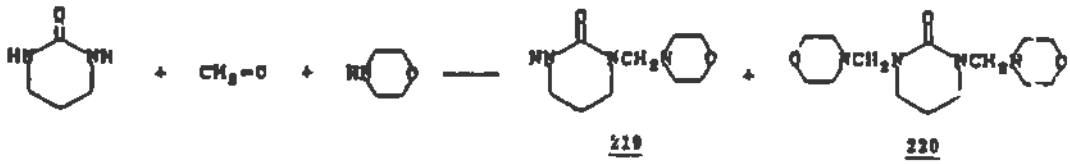
These Mannich condensation products were synthesized by similar routes.[75] As shown in **Scheme XLVII**, both 1-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**219**) and 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**220**) were synthesized by the condensation of tetrahydro-2(1*H*)-pyrimidinone with morpholine in formalin solution. Although the literature preparation for these compounds reported that the desired products could be isolated and sufficiently purified by recrystallizations from ethyl acetate, our efforts to duplicate this procedure immediately gave only the monomorpholinomethyl product **219** with sufficient purity. However, we were able to isolate pure 1,3-bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (**220**) after column chromatography (silica gel, $CHCl_3$-MeOH, 9:1, iodine) followed by recrystallization from ethyl acetate.

Scheme XLVIII shows that a similar route was used to synthesize 1-morpholinomethyltetrahydro-2(1*H*)-pyrimidinethione (**221**). Condensation of tetrahydro-2(1*H*)-pyrimidinethione with morpholine and formalin solution gave the desired compound, which was purified by numerous recrystallizations from ethanol.

5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (AVS-0124)

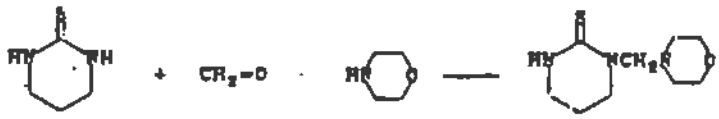
We synthesized 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**226**) by the approach shown in **Scheme XLIX**. Our synthesis started with the condensation and cyclization of diethylmalonate with 3-amino-1,2,4-triazole to give triazolopyrimidin-5,7-dione (**222**). This dione was converted to dichloro-triazolopyrimidine (**223**) by treatment with phosphorus oxychloride, and **223** was then hydrolyzed by treatment with NaOH to intermediate **224**.[76] The coupling[77] of **224** with 1,2,3,5-tetraacetylribofuranose gave protected nucleoside **225**, which was purified by flash chromatography (silica gel, 97:3 chloroform-methanol). Our difficulties in the synthesis of this compound occurred during the deprotection of **225**. In our early attempts, we determined that we were not only deblocking the sugar moiety but also opening of the triazole ring. Initially, we had been pursuing this deblocking by treating **225** with ethanolic ammonia.[78] Thin-layer chromatography seemed to indicate that the reaction was giving the usual mixture of completely and partially deacetylated products, and therefore, the mixture was further treated with ethanolic ammonia until only one product was present. Isolation and characterization of this product showed that it had the correct mass. However, the IR for this compound exhibited two bands at 2177 and 2245 cm^{-1} which were inconsistent for the target structure **226**, and which instead corresponded to the presence of nitriles in the compound. Also, the proton NMR showed only one aromatic proton, not the two different protons expected for a triazolopyrimidine such as **226**. These observations suggested that our conditions were rigorous enough to have opened the triazole ring to give compound **227**. We then reattempted the less rigorous deblocking of **225** with porcine esterase, and we obtained the properly deblocked desired product **226**. A comparison of this product with the compound mixture obtained from the exhaustive ethanolic ammonia attempts showed that the desired product had been forming in these earlier attempts, but that it had been misidentified as a partially deblocked intermediate. Therefore, the ethanolic ammonia procedure was an appropriate deblocking

Scheme XLVII



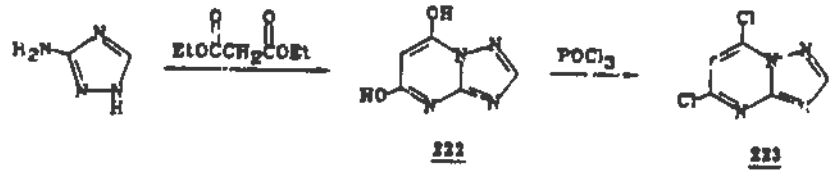
219 220

Scheme XLVIII

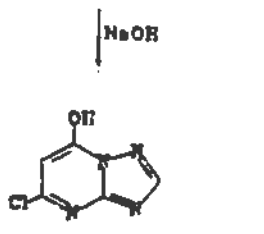


221

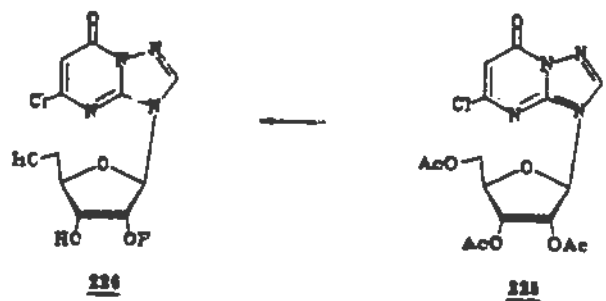
Scheme XLIX



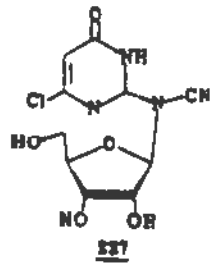
222 223



224



226 225



227

method, and it was used to prepare larger quantities of **226**. In the repeat synthesis, we determined that the undesired ring opening began after the deblocking reaction had proceeded for more than 16 h, and that several days were required for complete conversion of **226** to ring opened product **227**, which was consistent with our earlier observations. Therefore, by stopping the reaction after 16 h, the desired nucleoside **226** was obtained with only a trace of a partially deprotected product (by TLC, 12:1 chloroform-methanol).

6-Amino-2,4-dithiouracil

We synthesized 6-amino-2,4-dithiouracil (**229**)[79] by the procedure shown in **Scheme L** Commercially available 4-amino-6-hydroxy-2-mercaptopyrimidine (**228**) was dried and then treated with P_2S_5 in pyridine to give the desired product.

4-Thio-6-azauridine; 2',3',5'-Tri-*O*-acetyl-4-thio-6-azauridine

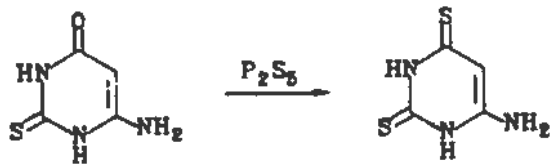
We synthesized 4-thio-6-azauridine (**232**) by the procedure shown in **Scheme LI**. 2',3',5'-Tri-*O*-acetyl-4-thio-6-azauridine (**231**) was first prepared by treating 2',3',5'-tri-*O*-acetyl-6-azauridine (**230**) with P_2S_5.[80] The crude thio compound **231** was then deblocked with Dowex 1 (OH^- form) to yield 4-thio-6-azauridine (**232**).

4-Amino-5-glucosylamino-2-thiouracil; 4-Amino-5-mannosylamino-2-thiouracil

We synthesized 4-amino-5-glucosylamino-2-thiouracil (**234**) by the route shown in **Scheme LII**, following a synthesis for 4-amino-5-*N*-glucosylaminouracil[81-83] in which a related compound was reportedly obtained by simply heating 4,5-diaminouracil with glucose in methanol. When we substituted 4,5-diamino-2-thiouracil (**233**) for 4,5-diaminouracil, we obtained a very low yield of what appeared to be product (identified primarily by mass spectrometric data). Therefore, to try to improve the yield, we investigated longer reaction times, and we also tried additional solvent as well as different solvents, since we had observed that 4,5-diamino-2-thiouracil was not especially soluble in methanol. We eventually discovered that using DMSO as the reaction solvent resulted in our obtaining an improved yield of a product with the expected MS (FAB) of 321 (M + 1). We then encountered another difficulty in our attempts to purify this product to analytical purity. Our attempts to monitor the reaction and to assess the purity of the reaction mixture by thin-layer chromatography had consistently indicated additional components. Further examination of this data led us to conclude that we were making the desired *N*-glucosaminouracil, but that this compound was somewhat unstable and subject to decomposition in the solvent systems of our thin-layer chromatography studies. We eventually determined that the reaction product could be recrystallized from EtOH/hexanes to give an analytically pure product. Unfortunately, a preliminary ^1H NMR spectrum of this product indicated that it was a mixture of any of the four possible isomers (**235-238**). When we notified Dr. Gabrielsen and Dr. Blough of this situation, we also told them that it was unlikely that we could develop a better synthesis for this compound, and they agreed to accept the product mixture that we had obtained.

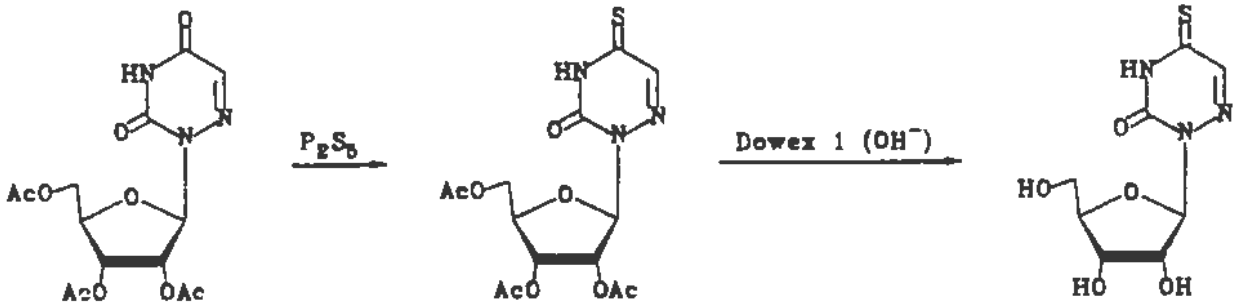
Since the submission of this compound, a closer inspection of the ^1H NMR data indicates that the probable structure of the obtained product is either β- or α-glucofuranosyl **237** or **238**. Such a glucofuranosyl configuration would form by the rearrangment of the imine resulting from the addition of the 5-amino group to the open chain aldehyde of the sugar. The assignment of the glucofuranosyl structure was based on the following ^1H NMR spectral assignments. A doublet at 5.32 ppm was assigned to H-1', while peaks between

Scheme L



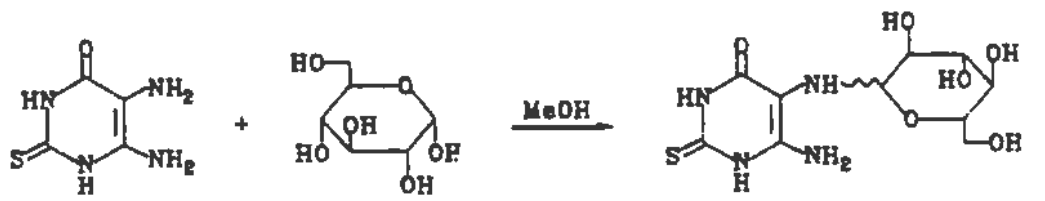
228 229

Scheme LI

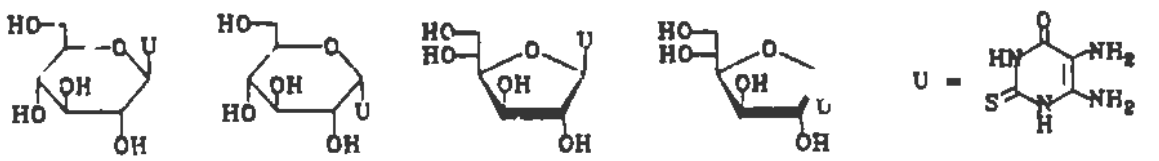


230 231 232

Scheme LII



233 234



235 236 237 238

4.2 and 5.0 ppm were assigned to the 6'-, 5'-, 3'-, and 2'-OH's. Decoupling experiments on the 6'-OH triplet (4.52 ppm) allowed the assignment of H-6'a and H-6'b to the signals at 3.34 and 3.66 ppm. The decoupling of the signal for H-1' allowed assignment of H-2' to the two-hydrogen multiplet between 3.00 and 2.85 ppm. The multiplet at 3.05-3.15 ppm was assigned to H-5' since it is coupled to H-6'a and H-6'b and furthermore it is coupled to the 2 hydrogen multiplet at 2.85 and 3.00 ppm. The signal for H-3', a doublet of doublets of doublets was coupled only to H-2' and H-4' at 2.85 and 3.00 ppm and to the 3'-OH at 4.29 ppm. Furthermore, the magnitude of the coupling constants of H-3' ($J_{2',3'} = J_{3',4'} = 4.0$ Hz) were small and were typical values found for xylo- and glucofuranose sugar rings. (Glucopyranose sugars and nucleotides typically have $J_{2',3'}$ and $J_{3',4'}$ of between 8-10 Hz.) Finally, the $J_{1',2'}$ of 3.2 Hz is typical of glucofuranoses in the β-configuration, suggesting that the obtained product may be **237**.

We also synthesized 4-amino-5-mannosylamino-2-thiouracil (**239**) by the same route, as shown in **Scheme** LIII, and as would be expected, we encountered the same difficulties. After recrystallization of the obtained product, we obtained an analytically pure product or product mixture. Unfortunately, the ^{1}H NMR spectrum of this product was more complex than that of the glucosylamino analog. Therefore, we can only state that its structure(s) may be any of **240-244**.

2,4-Dithio-6-azauridine; 2',3',5'-Tri-*O*-acetyl-2,4-dithio-6-azauridine

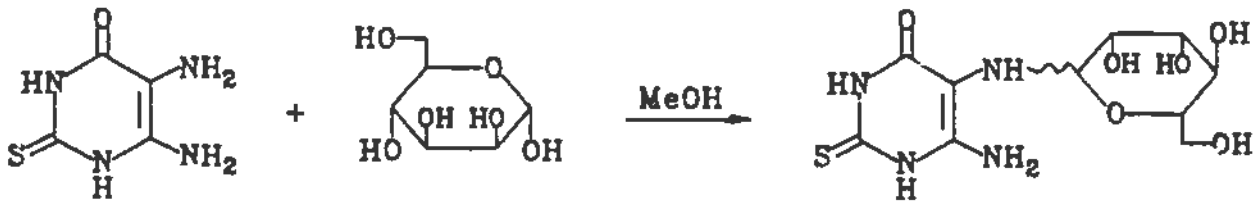
We also synthesized 2,4-dithio-6-azauridine (**246**, R = H) after evaluating a number of thiation reactions, including P_2S_5 and Lawessen's reagent.[84-87] As shown in **Scheme** LIV, our synthesis required the conversion of 2-thio-6-azauridine **245** (R = H) to its 2',3',5'-triacetate **245** (R = Ac). Treatment of this triacetate with P_2S_5 gave dithio **246** (R = Ac) which was then deprotected by treatment with Dowex 1 resin (OH^- form) to give **246** (R = H).

5'-*O*-[[[[2',3',4',6'-Tetra-*O*-benzyl-α-D-(glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-isopropylidene-6-azauridine

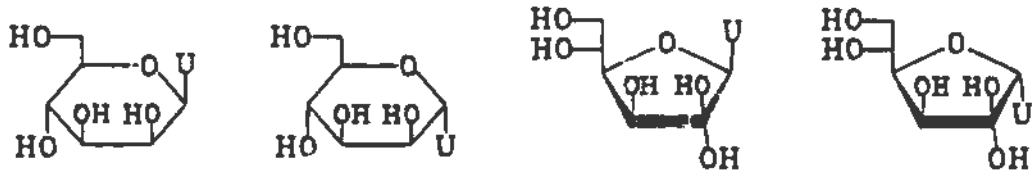
Scheme LV shows the route that we used to synthesize 5'-*O*-[[[[(2",3",4",6"-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-*O*-isopropylidene-6-azauridine (**249**) (X = O), a compound that we targeted after we were unsuccessful in our attempts to synthesize 5'-*O*-[[[[(2",3",4",6"-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-*O*-isopropylidene-2-thio-6-azauridine (**249**, X = S) by the literature synthesis for 5'-*O*-[[[[(2",3",4",6"-tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-*O*-isopropylideneuridine.[88] We synthesized the required 2',3'-*O*-isopropylidene-6-azauridine (**248**) by treatment of 6-azauridine with copper sulfate, acetone, and sulfuric acid.[89] Target compound **249** (X = O) was then obtained by the coupling sequence of adding the 2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranose (**247**) to chlorosulfonylisocyanate in methylene chloride at -20 to -15 °C, followed by the addition of 2',3'-*O*-isopropylidene-6-azauridine (**248**) in a solution of acetonitrile and pyridine.

We also attempted to synthesize the original target 5'-*O*-[[[[(2",3",4",6"-tetra-*O*-benzyl-α-D-(glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-*O*-isopropylidene-2-thio-6-azauridine (**249**) (X = S) again by using a slightly altered procedure. The literature procedure suggested that the nucleoside should be added in a solution of acetonitrile and pyridine. To minimize the suspected nucleophilicity of the 2-thione, we tried reducing the amount of pyridine as well as adding the pyridine later and in small increments. TLC indicated

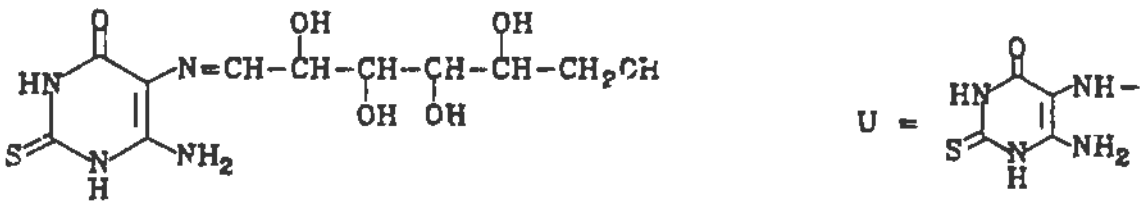
Scheme LII



233 239

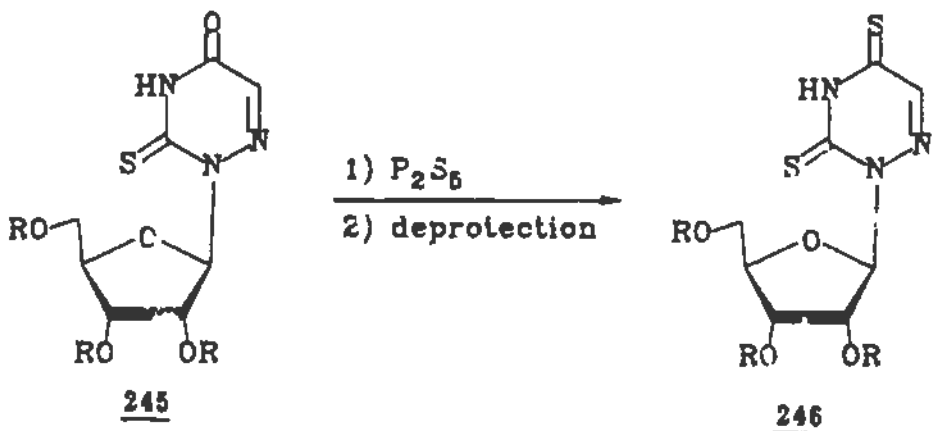


240 241 242 243



244

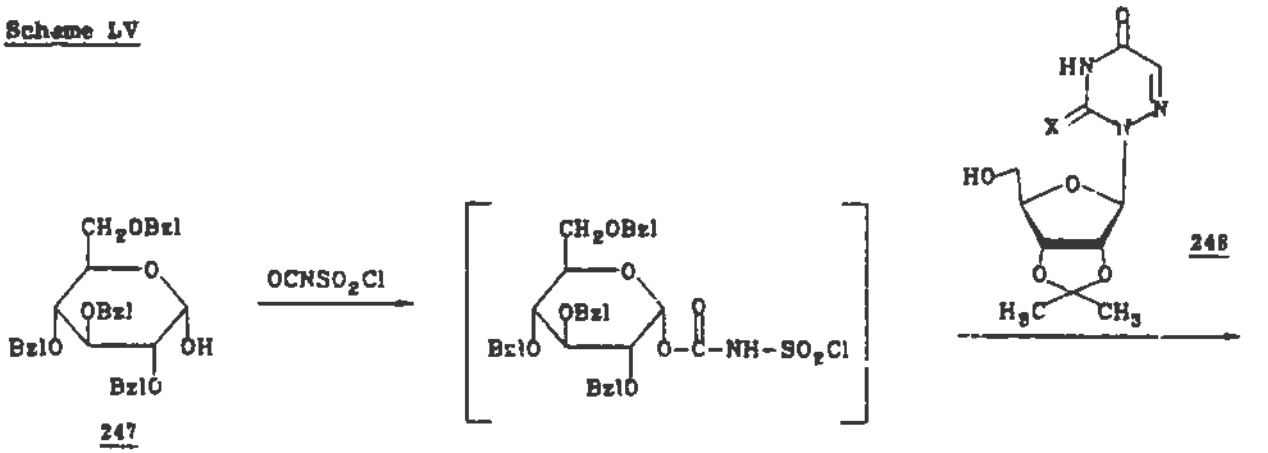
Scheme LIV



245 246

(R = H, Ac)

Scheme LV



247

248

249

250

251

R = $CONH_2$ or SO_2NH_2

252

Bzl = $-CH_2-C_6H_5$

X = O or S

253

that we were obtaining a mixture of products similar to those obtained with the previous attempts with 2',3'-*O*-isopropylidene-2-thio-6-azauridine and the successful synthesis with 2',3'-*O*-isopropylidene-6-azauridine. After chromatographic isolation of the reaction mixture components, we were again unable to detect the desired product by MS [expected MS (FAB) M + 1 = 946]. Instead, we had again obtained the mixture of products containing the expected byproducts **250** and **251** (X = S), as well as **252** and a high molecular weight product with a MS (FAB) M + 1 of 1063 whose structure is assumed to be **253**. Therefore, we still feel that the 2-thio group must be interfering with the coupling reaction or complicating the product isolation process.

3-Deazaadenosine; Carbocyclic 3-Deazaadenosine; Arabino-3-deazaadenosine; Carbocyclic 8-Azaadenosine; Carbocyclic 2'-Deoxy-8-azaadenosine; Carbocyclic 2'-Deoxy-8-azainosine; Carbocyclic 2,6-Diamino-8-azapurine-2'-deoxyribofuranoside; Carbocyclic 2'-Deoxy-8-azaguanosine; Carbocyclic 2'-Deoxy-8-aza-6-thioguanosine; and Carbocyclic 2-Amino-6-methoxy-8-azapurine-2'-deoxyribofuranoside

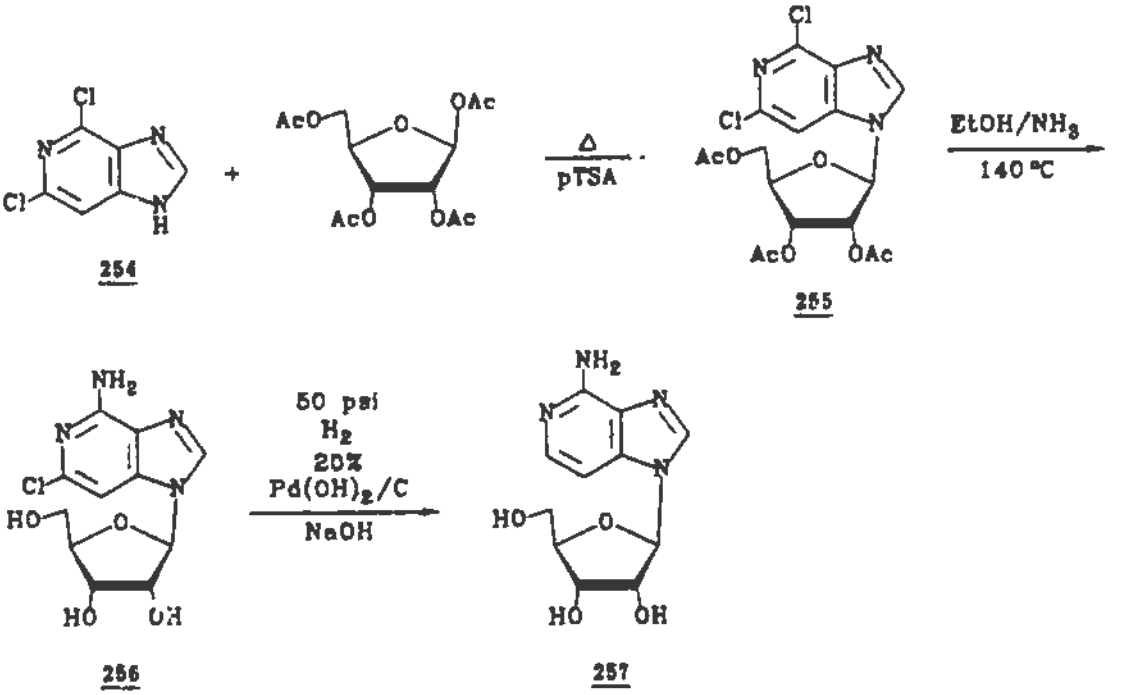
The following group of purine nucleoside analogs was also selected from the SRI compound archives. During the twentieth quarter, Dr. Gabrielsen expressed an interest in any SRI compounds which had been shown to be *S*-adenosylhomocysteine hydrolase inhibitors, since compounds with similar activity had been shown to be effective against the *Ebola* virus. In accordance to this request, we selected the following adenosine derivatives from our nucleoside analog archives: 3-deazaadenosine; arabino-3-deazaadenosine; and carbocyclic 3-deazaadenosine. The syntheses of these compounds are shown in **Schemes LVI-LVIX**. However, detailed synthetic procedures are not provided in the experimental section, because this information is available in the indicated references.

As shown in **Scheme LVI**, 3-deazaadenosine (**257**)[90] was synthesized by the following reaction sequence. The trimethylsilyl derivative of 4,6-dichloroimidazo[4,5-c]pyridine (**254**)[91] was generated and then treated with 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose to give **255**. The acetyl protecting groups and the 4-chloro group were simultaneously removed by treatment with ethanolic ammonia. Then, the remaining 6-chloro group of **256** was catalytically reduced to give 3-deazaadenosine (**257**).

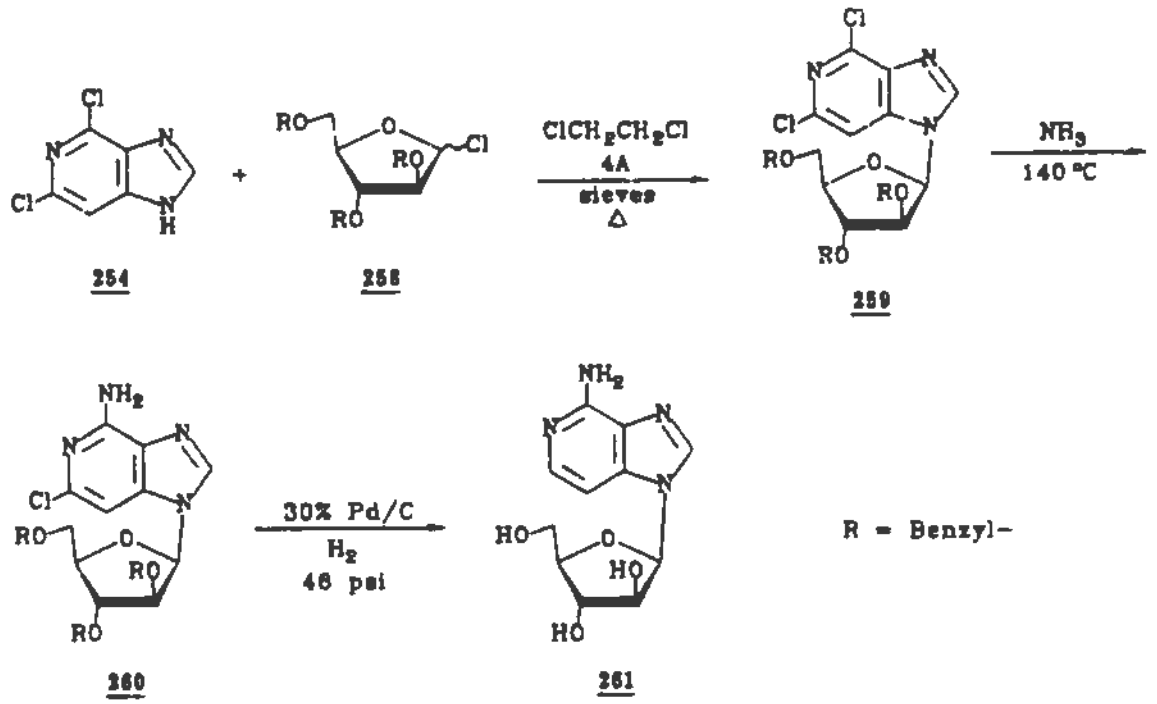
Scheme LVII shows that arabino-3-deazaadenosine (**261**)[92] was made similarly. 4,6-Dichloroimidazo[4,5-c]pyridine (**254**) was reacted with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**258**) in 1,2-dichloroethane and 4 A molecular sieves. The resulting protected nucleoside **259** was treated with ethanolic ammonia to aminate the 4-position to give **260**. Catalytic reduction then removed the benzyl groups while simultaneously removing the remaining 6-chloro group to give the target nucleoside **261**.

The synthesis of carbocyclic 3-deazaadenosine (**276**)[93] required the synthesis of (±)-4β-amino-2α,3α-dihydroxy-1-cyclopentanemethanol (**270**),[94,95] as shown in **Scheme LVIII**. Permanganate dihydroxylation of norbornadiene gave diol **262** which was then diacetylated to **263** by treatment with acetic anhydride. Diacetate **263** was then oxidized with sodium permanganate to diacetoxycyclopentanedicarboxylic acid **264**. This compound was converted to anhydride **265** with ethoxyacetylene and to diacetoxycarbamoylcyclopentanecarboxylic acid (**266**) by treatment with ammonia under anhydrous conditions. Hofmann hypobromite reaction of **266** followed by esterication of the carboxyl function, acetylation of the amino and hydroxyl groups to **268**, reduction of the ester with lithium borohydride, and hydrolysis of the resulting **269** gave 4-amino-2,3-dihydroxy-1-cyclopentanemethanol (**270**). Then, as shown in **Scheme LVIX**, 4-amino-2,3-

Scheme LVI



Scheme LVII



R = Benzyl-

dihydroxy-1-cyclopentanemethanol (270) was reacted with 2,4-dichloro-3-nitropyridine (271) in ethanol with triethylamine. The 3-nitro group of resulting adduct 272 was then reduced to the 3-amino compound 273 with Raney nickel and cyclized by treatment with triethylorthoformate in DMAC with an acid catalyst to give 274. This intermediate was converted to the final product 276 by displacement of the 4-chloro with hydrazine followed by refluxing with Raney nickel.

One other group of nucleoside analogs was also selected from our carbocyclic nucleoside archives. These compounds included: carbocyclic 8-azaadenosine; carbocyclic 2'-deoxy-8-azaadenosine; carbocyclic 2'-deoxy-8-azainosine; carbocyclic 2,6-diamino-8-azapurine-2'-deoxyribofuranoside; carbocyclic 2'-deoxy-8-azaguanosine; carbocyclic 2'-deoxy-8-aza-6-thioguanosine; and carbocyclic 2-amino-6-methoxy-8-azapurine-2'-deoxyribofuranoside. (We also tried to obtain a sample of carbocyclic adenosine for submission in this same screen). All of these compounds were previously prepared for evaluation as potential antitumor agents; they were requested by Dr. Gabrielsen as a result of the recently reported antiviral activity of other carbocyclic nucleoside analogs.[99,100] Their syntheses are given in **Schemes LX-LXIII**. However, as with the previous group of nucleoside analogs, detailed synthetic procedures are not provided in the experimental section since these procedures are available in the indicated references.

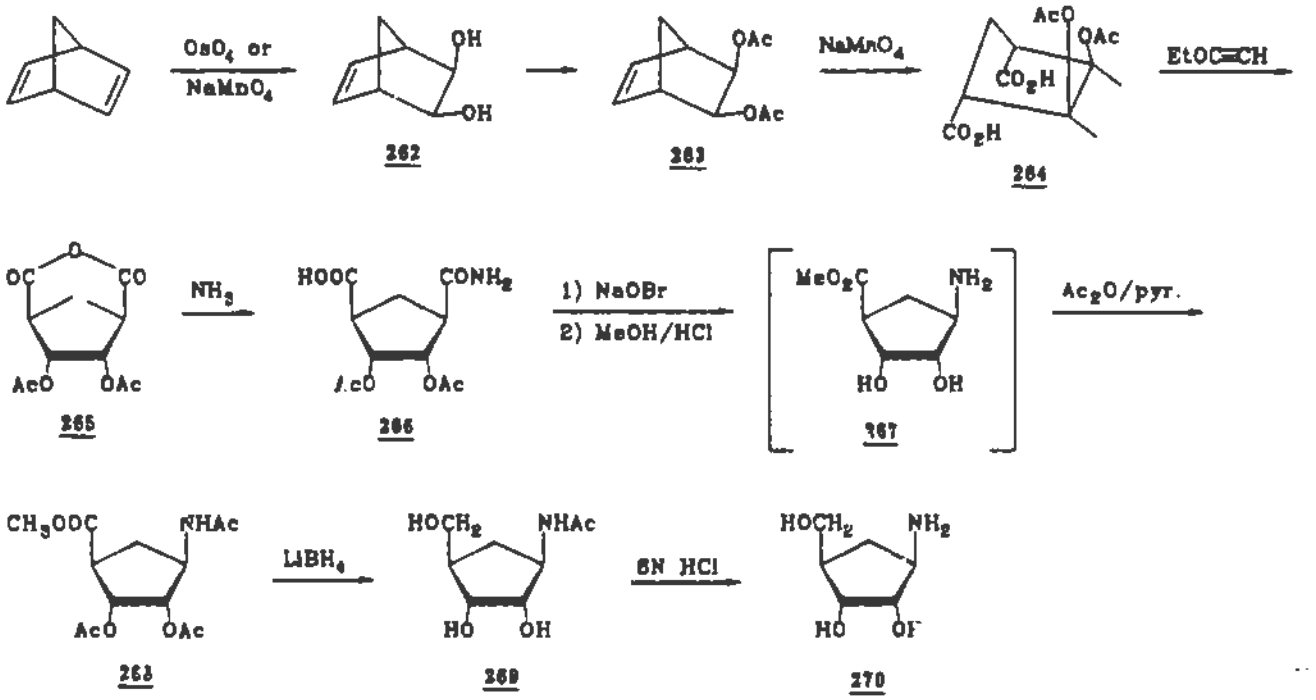
As shown in **Scheme LX**, carbocyclic 8-azaadenosine (**278**)[101] was synthesized by reacting previously mentioned (±)-4β-amino-2α,3α-dihydroxy-1-cyclopentanemethanol (**270**)[94,95] with 5-amino-4,6-dichloropyrimidine followed by cyclization with sodium nitrite and HCl and treatment with liquid ammonia at 60 °C.

The synthesis of all of the remaining nucleoside analogs of this group required the synthesis of (±)-*cis*-4-amino-*trans*-2-hydroxycyclopentanemethanol (**287**).[102] As shown in **Scheme LXI**, *exo*-5-norbornen-2-ol acetate was oxidized with sodium permanganate to dicarboxylic acid **280** and then cyclized to anhydride **281** by treatment with acetic anhydride. Treatment of **281** with methanol gave a mixture of monomethylesters **282**, which were then treated with thionyl chloride and ammonia to further convert them to easily separable carbamoylcyclopentanecarboxylates **283** and **284**. Reduction of **283** with lithium borohydride in tetrahydrofuran gave **285**. Hofmann hypobromite conversion of **285** to the methylcarbamate **286** was followed by hydrolysis to (±)-*cis*-4-amino-*trans*-2-hydroxycyclopentanemethanol (**287**).

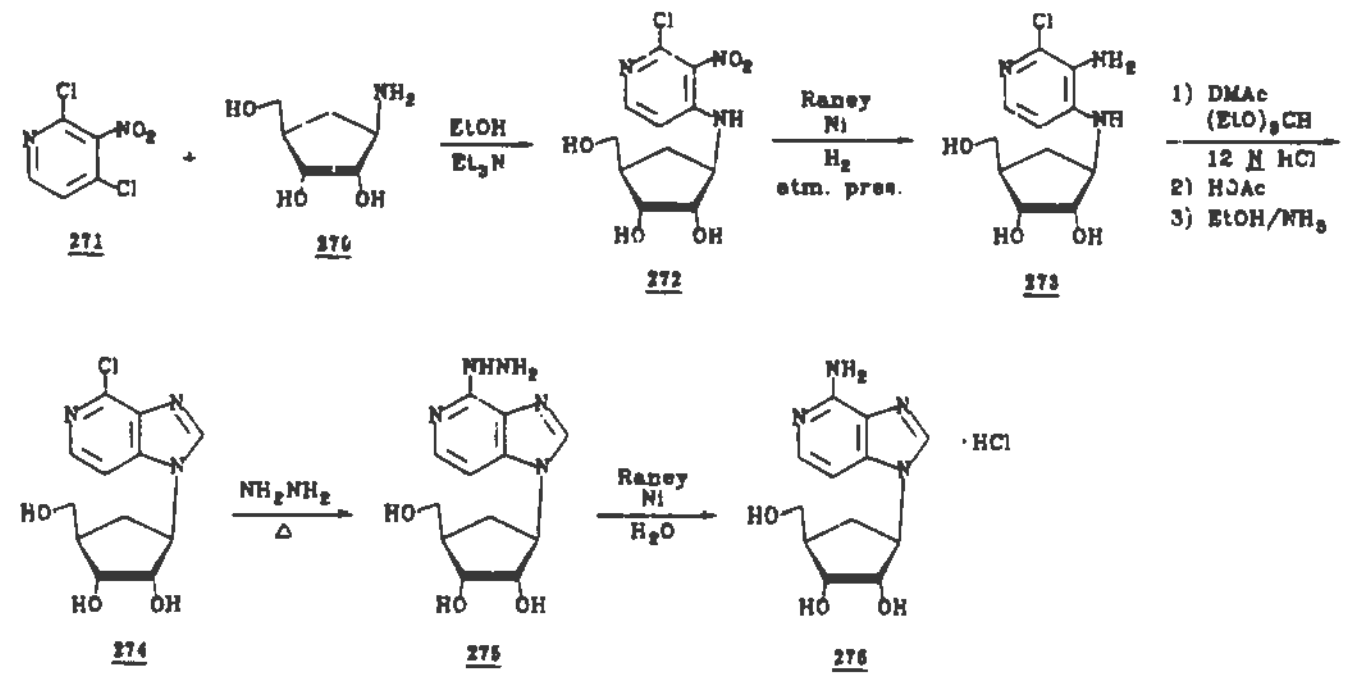
Scheme LXII shows that the synthetic route to carbocyclic 2'-deoxy-8-azaadenosine (**290**) and carbocyclic 2'-deoxy-8-azainosine (**291**)[101] next required the synthesis of **288**, from the reaction of 5-amino-4,6-dichloropyrimidine (**271**) with **287**. Cyclization of **288** by treatment with sodium nitrite and HCl gave 6-chloropurine nucleoside analog **289**. This intermediate was then either treated with ammonia at 60 °C to give carbocyclic 2'-deoxy-8-azaadenosine (**290**), or it was refluxed with additional HCl to give carbocyclic 2'-deoxy-8-azainosine (**291**).

As shown in **Scheme LXIII**, carbocyclic 2,6-diamino-8-azapurine-2'-deoxyribofuranoside (**297**),[103,104] carbocyclic 2'-deoxy-8-azaguanosine (**298**),[103,104] carbocyclic 2'-deoxy-8-aza-6-thioguanosine (**299**)[102] and carbocyclic 2-amino-6-methoxy-8-azapurine-2'-deoxyribofuranoside (**300**)[105] were all synthesized from intermediate **296**. This intermediate was synthesized by first reacting 2-amino-4,6-dichloropyrimidine with (±)-*cis*-4-amino-*trans*-2-hydroxycyclopentanemethanol (**287**).[102] This compound was then converted to the 5-aminopyrimidine **295** by coupling with 4-chlorobenzenediazonium chloride followed by reduction with zinc in

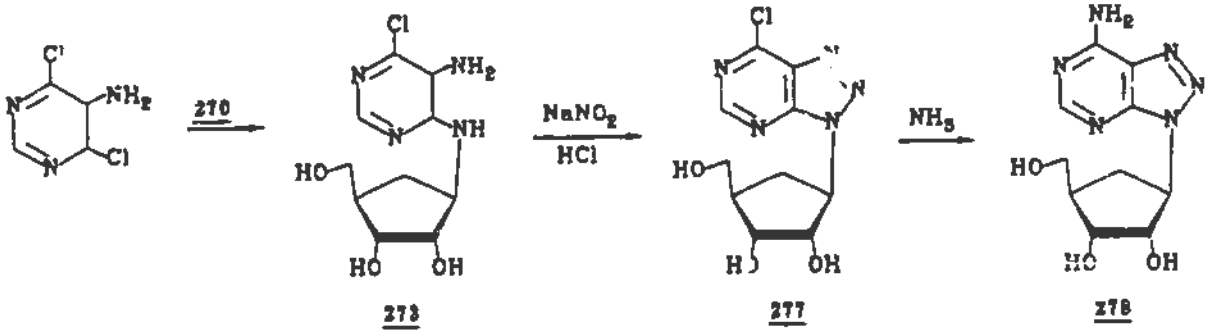
Scheme LVIII



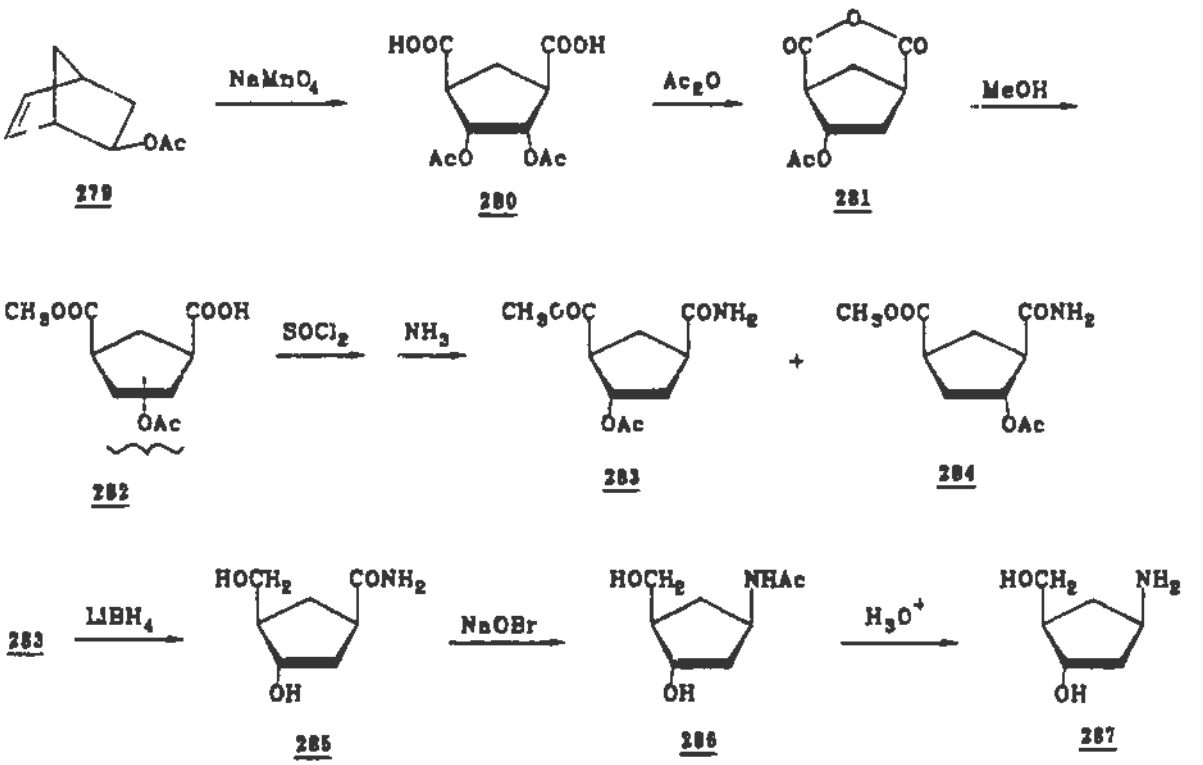
Scheme LVIX



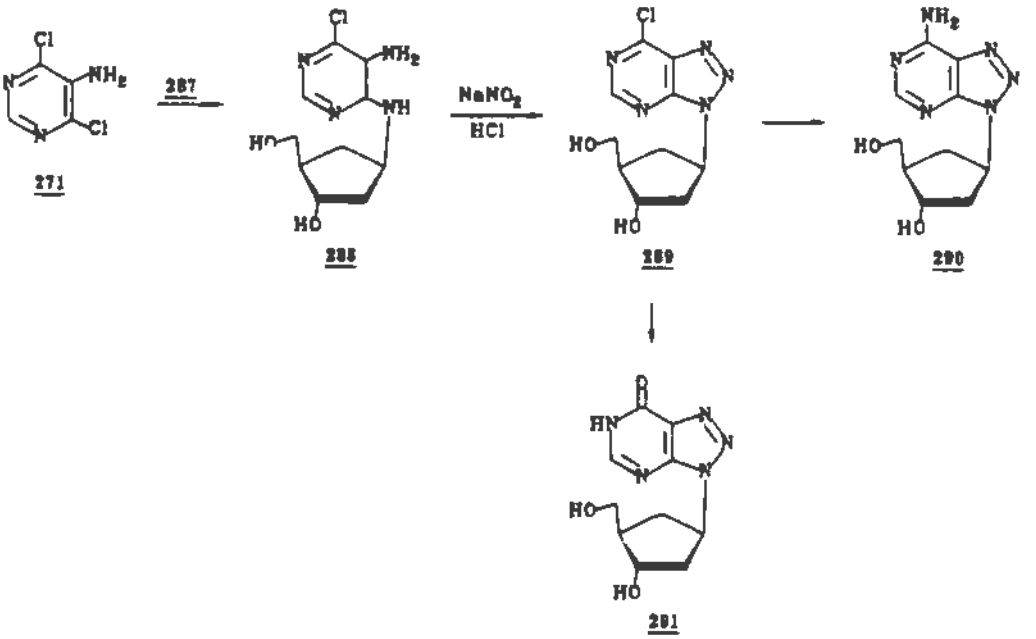
Scheme LX



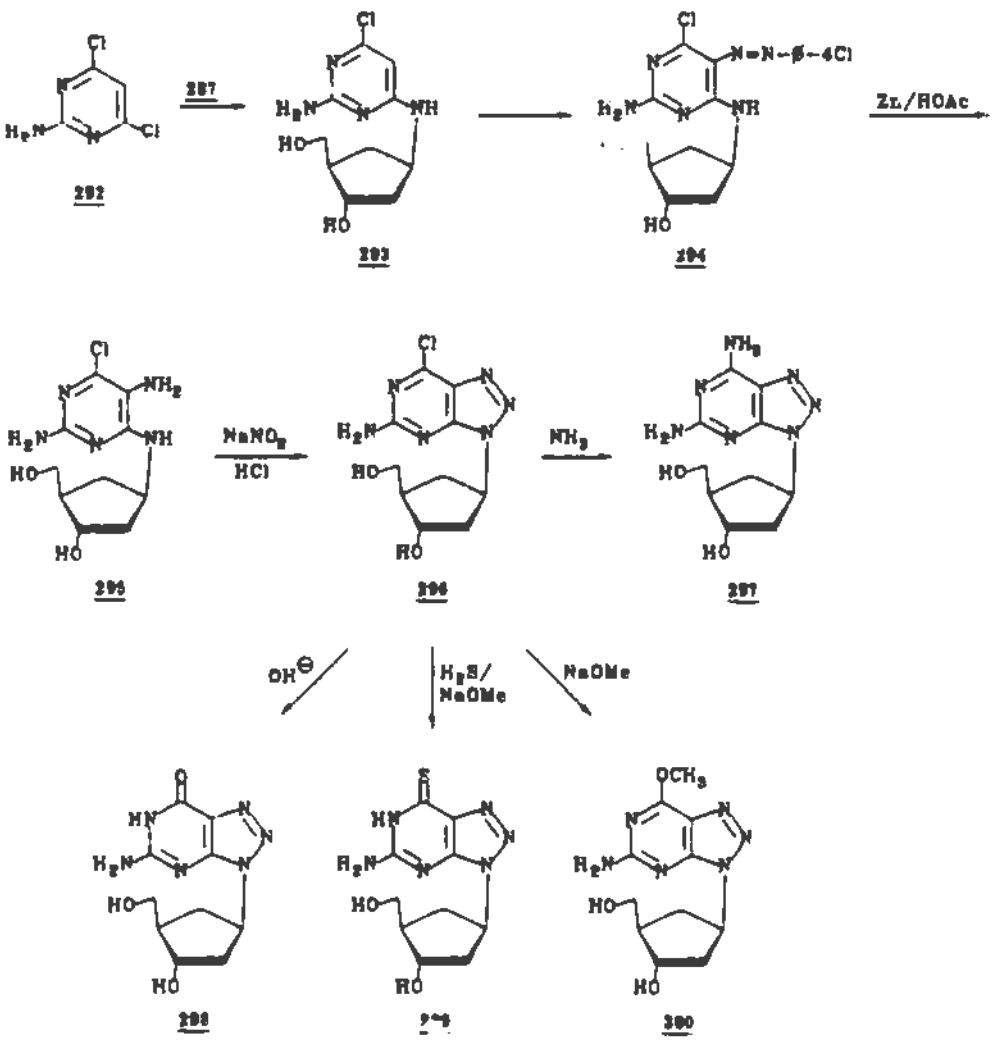
Scheme LXI



Scheme LXII



Scheme LXIII

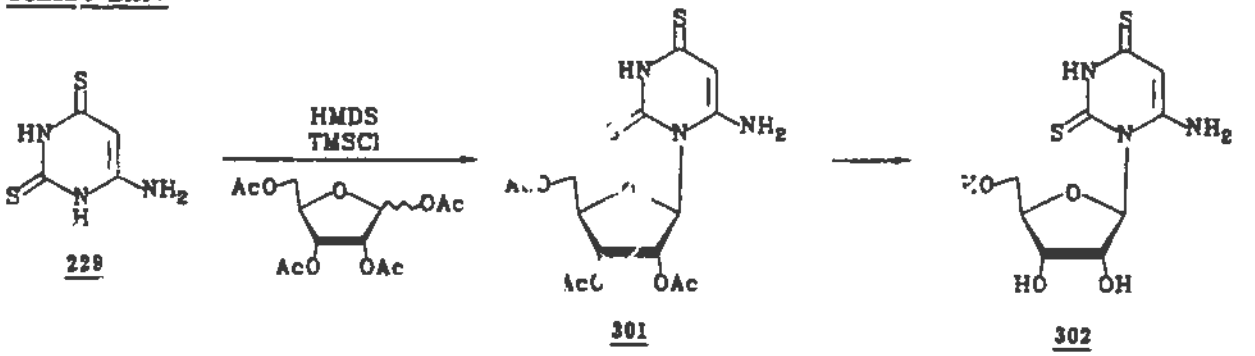


acetic acid. Cyclization with sodium nitrite in aqueous acetic acid then gave intermediate **296** which was easily converted to carbocyclic 2,6-diamino-8-azapurine-2′-deoxyribofuranoside (**297**) and carbocyclic 2′-deoxy-8-azaguanosine (**298**) by treatment with ammonia at 60 °C or dilute aqueous base, respectively. Carbocyclic 2′-deoxy-8-aza-6-thioguanosine (**299**) and carbocyclic 2-amino-6-methoxy-8-azapurine-2′-deoxyribofuranoside (**300**) were similarly obtained by treatment of **296** with H_2S/NaOMe or NaOMe, respectively.

Finally, we were not able to provide 1-β-D-ribofuranosyl-6-amino-2,4-dithiouridine (**302**), a compound that had been requested by Dr. Herbert Blough via USAMRIID. Early attempts to synthesize 1-β-D-ribofuranosyl-6-amino-2,4-dithiouridine (**302**) included: (1) the direct ribosylation of previously submitted 6-amino-2,4-dithiouridine (**229**) with 1,2,3,5-*O*-ribofuranose tetraacetate, as shown in Scheme LXIV; (2) the cyclization of **303** by refluxing with sodium ethoxide in ethanol followed by the treatment of the resulting cyclonucleoside **304** with NH_3/NH_4Cl to give 2′,3′-isopropylidine-6-aminouridine (**305**), as shown in Scheme LXV. Next, after blocking the 6-amino group as the corresponding acetamide, compound **305** would then be converted to the 2,5′-anhydro compound **306** by treatment with DEAD/triphenyl phosphine or by 5′-*O*-tosylation followed by treatment with potassium-*t*-butoxide. Treatment with P_2S_5 and H_2S would then be expected to give the desired 1-β-D-ribofuranosyl-6-amino-2,4-dithiouridine (**302**). Thus far, neither approach has been successful. The first approach was unsuccessful due to the undesired participation of the thiones, while the second approach is ongoing. The 2′,3′-isopropylidine-6-aminouridine was prepared as indicated. However, we have been unable to find a procedure that will selectively acetylate the 6-amino group. Other activity with this approach included investigating potentially quicker alternate routes to 6-aminouridine, since the conversion of cyclonucleoside **304** by treatment with NH_3/NH_4Cl was very slow and the yield was low.

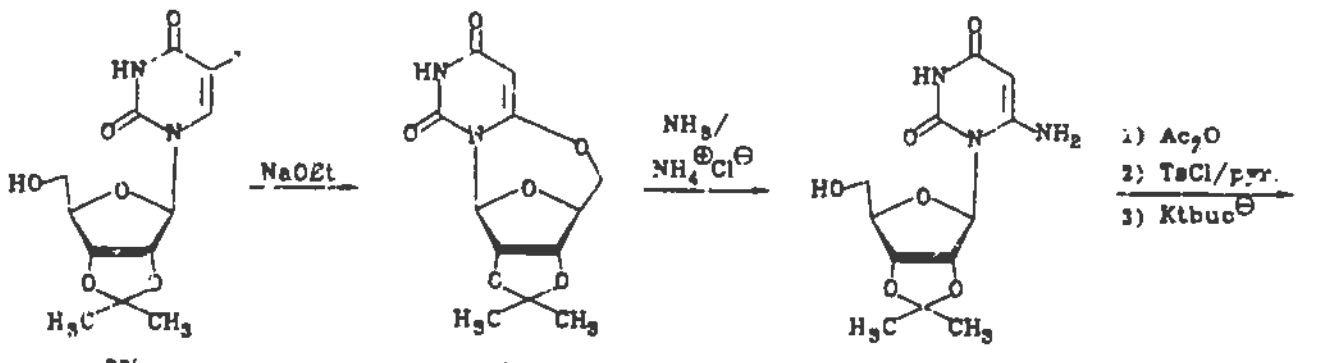
Also, we were unable to obtain a sample of carbocyclic adenosine. Since the time remaining in this contract was insufficient, we decided not to pursue the synthesis of this compound by the preparation in the literature.

Scheme LXIV

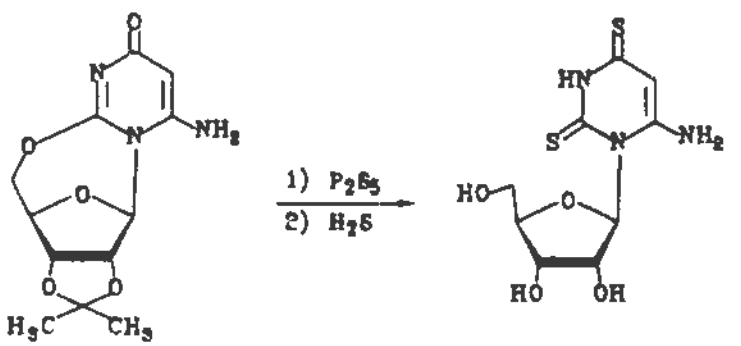


229 301 302

Scheme LXV



303 304 305



306 302

Experimental Section

All solvents and materials were reagent grade and were either used as received or purified as required. ^{1}H NMR and ^{13}C NMR spectra were run with a Nicolet NMC NT-300 NB spectrometer operating at 300.65 MHz with tetramethylsilane as an internal reference. Chemical shifts (δ) for multiplets were measured from the appropriate centers. The mass spectral data were obtained from a Varian MAT 311A mass spectrometer in fast atom bombardment (FAB) or electron-impact (EI) mode (direct probe temperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases, only strong or medium peaks in the 1800-600 cm^{-1} range were reported. UV absorption spectra were determined in the appropriate pH 1 (0.1 *N* HCl), pH 7 buffer, and pH 13 (0.1 *N* NaOH) solutions with either a Cary 17 spectrometer or a Perkin Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting Point apparatus, and all melting points were uncorrected. Elemental analysis data were obtained with an in-house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

Adenosine-N^1-oxide (1). In a 1-L round-bottomed flask protected with a calcium sulfate drying tube was placed 5.0 g (18.7 mmol) of adenosine and 500 mL of methanol. The mixture was stirred at room temperature and 4.85 g (22.5 mmol) of *m*-chloroperoxybenzoic acid (MCPBA, 80%) was added in 7-10 portions over 2 h. If thin-layer chromatography after 15-20 h of stirring indicates the presence of starting material, an additional 0.5 g (2.9 mmol) of MCPBA should be added and the reaction stirred an additional 4 h. If the TLC continues to show starting material, another portion of MCPBA must be added and the stirring continued overnight. After the TLC showed little or no starting material left, the reaction mixture was poured slowly into 2 L of ethyl acetate with good stirring. After having been stirred 2 h, the product was collected, washed with ethyl acetate, and dried *in vacuo* over phosphorus pentoxide: yield 5.6 g. This material was generally adequate for preparative purposes. One recrystallization from boiling ethanol usually provided analytically pure material. See Table 1 for the amounts of reactants used. The ratio of reactants and solvents was maintained.

Adenosine-N^1-oxide (1a). UV λ_{max} 212 nm (ϵ28,300), 257 (12,500), 265 (sh) at pH 1; 232 (41,900), 262 (8,300), 295 (2,400) at pH 7; 231 (24,900), 267 (8,800), 275 (sh), 307 (4,700) at pH 13; 235 (41,400), 263 (7,700), 304 (2,250) in EtOH; MS (FAB) *m/e* 284 (M + 1); IR (KBr) 1670, 1500, 1225, 1210, 1135 sh, 1125, 1085, 1060, 640 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.57, 3.69 (2 m, 2, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.96 (apparent q, 1, $J_{4',5'b}$ = 4.0 Hz, $J_{4',5'a}$ = 4.1 Hz, H-4'), 4.16 (apparent q, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.55 (apparent q, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.09 (apparent t, 1, OH-5'), 5.28 (apparent d, 1, OH-3'), 5.64 (apparent, d, 1, OH-2'), 5.89 (d, 1, H-1'), 8.55 (s, 1, H-2), 8.64 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6) δ 61.40 (C-5'), 70.31 (C-3'), 73.92 (C-2'), 84.83 (C-4'), 86.68 ($J_{C,H}$ = 163.77 Hz, C-1'), 99.46 ($J_{C,H}$ = 179.21 Hz, C-7), 102.28 (C-5), 124.59 (C-8), 141.64 (C-2), 142.17 (C-4), 148.29 (C-6).

2'-Deoxyadenosine-N^1-oxide (1b). UV λ_{max} 258 nm (12,520) at pH 1; 261 (8,490) at pH 7; 268 (8,600) at pH 13; MS (FAB) *m/e* 268 (M + 1); IR (KBr) 1680, 1499, 1380, 1233, 1213, 1091, 1075, 1070, 1025 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.32 (m, 1, $J_{2'a,3'}$ = 3.6 Hz, $J_{1',2'a}$ = 6.2 Hz, H-2'a), 2.70 (m, 1, $J_{2'b,2'}$ = 5.9 Hz, $J_{1',2'b}$ = 7.2 Hz, $J_{2'a,2'b}$ = 13.3 Hz, H-2'b), 3.52, 3.60 (2 m, 2, $J_{5'a,5'b}$ = 11.8 Hz, CH_2-5'), 3.87 (apparent

q, 1, $J_{4',5'_a} = J_{4',5'_b}$ = 4.7 Hz, H-4'), 4.41 (apparent q, 1, $J_{3',4'}$ = 2.7 Hz, $J_{2'_a,3'}$ = 3.6 Hz, $J_{2'_b,3'}$ = 5.9 Hz, H-3'), 4.98 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.0 Hz, OH-5'), 5.38 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 3.8 Hz, OH-3'), 6.33 (t, 1, $J_{1',2'_a}$ = 6.2 Hz, $J_{1',2'_b}$ = 7.2 Hz, H-1'), 8.51 (s, 1, H-2), 8.63 (s, 1, H-8).

9-Benzyladenine-N^1-oxide (1c). UV λ_{max} 259 (13,000) at pH 1; 262 (9,100), 233 (46,100) at pH 7; 308 (4,400), 269 (8,700), 232 (26,300) at pH 13; MS (FAB) *m/e* 241 (M), 225 (M − O); IR (KBr) 1669 broad, 1503, 1490, 1410, 1361, 1330, 1263, 1235, 1221, 1160, 1140, 713, 695 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.40 (s, 2, CH_2Ar), 7.33 (m, 5, Ar), 8.43 (s, 1, H-2), 8.63 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6) δ 46.29 (CH_2Ar), 127.37 (Ar-C-2,6), 127.71 (Ar-C-4), 128.57 (Ar-C-3,5), 136.43 (Ar-C-1), 141.80 (C-4), 143.09, 143.74 (C-2,8), 148.02 (C-6).

9-Methyladenine-N^1-oxide (1d). UV λ_{max} 259 nm (11,300) at pH 1; 262 (7,700) at pH 7; 268 (8,100) at pH 13; MS (FAB) *m/e* 166 (M + 1); IR (KBr) 1678, 1511, 1233, 1150, 1039, 692, 438 cm^{-1}; ^1H NMR (D_2O) δ 3.84 (s, 3, CH_3), 8.17 (s, 1, H-2), 8.57 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6) δ 30.80 (CH_3), 119.01 (C-5), 144.57 (C-2), 145.01 (C-4), 146.51 (C-6), 149.03 (C-6).

6-Methylamino-9-β-D-ribofuranosylpurine-N^1-oxide (1e).[8] UV λ_{max} 215 nm (25,800), 262 nm (13,900) at pH 1; 235 (37,900), 270 (9,800) at pH 7; 235 (38,000), 271 (9,500) at pH 13; MS (FAB) *m/e* 298 (M + 1); IR (KBr) 1656, 1580, 1500, 1425, 1215, 1090 (broad), 1050, 1025 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.45 (apparent d, 3, NCH_3), 3.54, 3.66 (2 m, 2, $J_{4',5'_a}$ = 4.0 Hz, $J_{4',5'_b}$ = 3.9 Hz, $J_{5'_a,5'_b}$ = 12.0 Hz, CH_2-5'), 3.93 (apparent q, 1, H-4'), 4.16 (apparent q, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.51 (apparent q, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.07 (t, 1, $J_{5',5'\text{-OH}}$ = 5.5 Hz, OH-5'), 5.24 (d, 1, $J_{3',3'\text{-OH}}$ = 5.1 Hz, OH-3'), 5.59 (d, 1, $J_{2',2'\text{-OH}}$ = 5.9 Hz, OH-2'), 5.88 (d, 1, $J_{1',2'}$ = 5.5 Hz, H-1'), 8.39 (br d, 1, CH_3NH), 8.55 (s, 1, H-2), 8.62 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6) δ 29.84 (NCH_3), 61.01 (C-5'), 70.00 (C-3'), 73.67 (C-2'), 85.33 (C-4'), 87.27 ($J_{C,H}$ = 166.57 Hz, C-1'), 118.29 (C-5), 141.66 (C-2), 142.47 (C-4,8), 147.52 (C-6).

9-β-D-Arabinofuranosyladenine-N^1-oxide (1f). UV λ_{max} 258 nm (12,600), 213 nm (28,300) at pH 1; 293 (2,200), 261 (8,500), 232 (42,200) at pH 13; MS (FAB) *m/e* 284 (M + 1); IR (KBr) 1669, 1505, 1425, 1385, 1216, 1135 (sh), 1130, 1115, 1083, 1040, 1035 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.66 (m, 1, CH_2-5'), 3.80 (apparent q, 1, H-4'), 4.12 (apparent q, 1, H-3'), 4.19 (apparent q, 1, H-2'), 5.10 (t, 1, OH-5'), 5.17 (d, 1, OH-3'), 5.59 (d, 1, OH-2'), 6.22 (d, 1, H-1'), 8.37 (s, 1, H-2), 8.63 (s, 1, H-8); ^{13}C NMR (Me_2SO-d_6) δ 60.61 (C-5'), 74.59 (C-3'), 75.54 (C-2'), 83.55 (C-1'), 84.14 (C-4'), 117.83 (C-5), 141.65 (C-4), 142.87, 142.95 (C-8,2), 148.02 (C-6).

8-Bromoadenosine-N^1-oxide (1g). UV λ_{max} 263 nm (15,300), 214 (27,700) at pH 1; 298 (7,700), 265 (10,500), and 237 (40,400) at pH 7; 315 (5,700), 278 (9,000), and 236 (23,100) at pH 13; MS (FAB) *m/e* 362 (M + 1); IR (KBr) 1678, 1466, 1295, 1275 (sh), 1270, 1142, 1100, 1075, 1070 (sh), 1057, 1051, 1025 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.49, 3.64 (2 m, 2, $J_{5'_a,5'_b}$ = 11.8 Hz, CH_2-5'), 3.91 (apparent q, 1, $J_{4',5'_a}$ = 5.7 Hz, $J_{4',5'_b}$ = 4.9 Hz, H-4), 4.21 (apparent q, 1, $J_{3',4'}$ = 3.4 Hz, H-3'), 4.83 (t, 1, $J_{5'_a,5'\text{-OH}}$ = 6.5 Hz, $J_{5'_b,5'\text{-OH}}$ = 5.4 Hz, OH-5'), 5.09 (q, 1, $J_{2',3'}$ = 5.3 Hz, H-2'), 5.26 (d, 1, $J_{3',3'\text{-OH}}$ = 5.0 Hz, OH-3'), 5.49 (d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.81 (d, 1, $J_{1',2'}$ = 6.1 Hz, H-1'), 8.65 (s, 1, H-2).

2,6-Diamino-9-β-D-ribofuranosylpurine-N^1-oxide (1h). UV λ_{max} 213 nm (26,200), 253 (11,100), 289 (10,200) at pH 1; 211 (16,200), 233 (33,700), 260 (9,000), 292 (6,900) at pH 7; 233 (31,700), 262 (9,200), 288 (7,200) at pH 13; MS (FAB) *m/e* 299 (M + 1); IR (KBr) 1672, 1633, 1618, 1420, 1225, 1125, 1105, 1055, 1040 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.56, 3.64 (2 m, 2, $J_{4',5'a}$ = 4.2 Hz, $J_{4',5'b}$ = 4.1 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'), 3.89 (apparent q, 1, H-4'), 4.10 (apparent q, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.45 (apparent q, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.02 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.5 Hz, OH-5'), 5.15 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 4.8 Hz, OH-3'), 5.43 (d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.75 (d, 1, $J_{1',2'}$ = 5.9 Hz, H-1'), 7.23 (br s, 2, H-NH_2), 8.15 (s, 1, H-8).

7-Deazaadenosine-N^1-oxide (1i). UV λ_{max} 210 nm (21,900), 223 (22,900), 272 (8,000) at pH 1; 234 (33,900), 271 (5,500), 303 (3,400) at pH 7; 234 (30,800), 273 (5,900), 305 (3,800) at pH 13; MS (FAB) *m/e* 283 (M + 1); IR (KBr) 1729, 1655, 1502, 1240, 1120, 1084, 1047, 1025, 1000, 800, 745, 645 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.52, 3.60 (2 m, 2, H-5'), 3.83 (apparent q, 1, H-4'), 4.07 (apparent d, 1, H-3'), 4.33 (apparent q, 1, H-2'), 5.10 (apparent t, 1, OH-5'), 5.17 (apparent d, 1, OH-3'), 5.43 (apparent d, 1, OH-2'), 6.00 (d, 1, H-1'), 6.68 (d, 1, H-7), 7.56 (d, 1, H-8), 8.05 (br s, 1, H-NH_2), 8.45 (s, 1, H-2); ^{13}C NMR (Me_2SO-d_6) δ 61.40 (C-5'), 70.31 (C-3'), 73.92 (C-2'), 84.83 (C-4'), 86.68 ($J_{C,H}$ = 163.77 Hz, C-1'), 99.46 ($J_{C,H}$ = 179.21 Hz, C-7), 102.28 (C-5), 124.59 ($J_{C,H}$ = 192.49 Hz, C-8), 141.64 (C-2), 142.17 (C-4), 148.29 ($J_{C_6H_2}$ = 5.03 Hz, C-6).

General Procedure for Synthesis of 1-Benzyloxyadenosines

1-(Substituted Benzyloxy)adenosines, Perchloric Acid Salt (2). In a 100-mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate drying tube was placed 2.5 g (8.83 mmol) of adenosine-N^1-oxide (**1a**), 50 mL of molecular sieve (4A) dried *N,N*-dimethylacetamide (DMAc), and 26.5 mmol of the appropriate benzyl bromide was added to the well-stirred suspension. The mixture was stirred for 2 h after complete solution was achieved. The reaction mixture was poured into 300-500 mL of anhydrous ether with slight swirling. After the product stuck to the walls of the flask the supernatant was decanted. The gummy residue was washed with 400 mL of ether, decanted, again covered with 400 mL of ether, and ground to a powder. The powder was allowed to settle, the ether was decanted, and the residue was dried in a stream of argon. The residue was dissolved in 25 mL of H_2O and added with stirring to a warm solution of 5 g (42.6 mmol) of ammonium perchlorate dissolved in 25 mL of H_2O. The product crystallized upon scratching and chilling. One recrystallization from H_2O and drying at either 56 or 78 °C for 16 h over phosphorus pentoxide usually yielded an analytical sample (see Table 2). See Table 2 for the amounts of the reactants used. The ratios of the reactants were maintained.

1-(3-Methylbenzyloxy)adenosine, Perchloric Acid Salt (2a-3). UV λ_{max} 258 nm (12,400) at pH 1; 258 (12,400) at pH 7; 257 (12,550) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1690, 1224, 1088 (broad), 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.35 (s, 3, CH_3), 3.58, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'b,5'a}$ = 12.0 Hz, CH_2-5'), 4.01 (apparent q, 1, H-4'), 4.15 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.48 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, OH-5'), 5.32 (m, 1, OH-3'), 5.36 (s, 2, OCH_2Ar), 5.56

(br s, 1, OH-2'), 5.93 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.38 (m, 4, Ar-H), 8.81 (s, 1, H-8), 8.95 (s, 1, H-2), 9.72, 10.40 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

1-(4-Methylbenzyloxy)adenosine, Perchloric Acid Salt (2a-4). UV λ_{max} 259 nm (12,900) at pH 1; 259 (12,600) at pH 7; 258 (12,510) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1679, 1505, 1425, 1220, 1100 (broad), 855, 623 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.34 (s, 3, ArCH_3), 3.59, 3.67 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.09, 5.32, 5.59 (3 br s, 3, OH-5',3',2'), 5.37 (s, 2, OCH_2Ar), 5.94 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.26 (d, 2, Ar-H-3,5), 7.54 (d, 2, Ar-H-2,6), 8.81 (s, 1, H-8), 8.92 (s, 1, H-2), 9.73, 10.39 (2 br s, 2, H-$\overset{\oplus}{N}H_2$).

1-(2-Methylbenzyloxy)adenosine, Perchloric Acid Salt (2a-2). UV λ_{max} 259 nm (13,420) at pH 1; 259 (13,260) at pH 7; 258 (13,210) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1687, 1510, 1415, 1227, 1127, 1083 (broad), 916, 880, 767, 690, 623 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.47 (s, 3, CH_3), 3.57, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.47 (br s, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, OH-5'), 5.32 (br s, 1, OH-3'), 5.46 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2'), 5.92 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.35 (m, 4, Ar-H), 8.61 (s, 1, H-2), 8.83 (s, 1, H-8), 9.79, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.64 (CH_3), 60.83 (C-5'), 69.92 (C=3'), 74.46 (C-2'), 79.56 (OCH_2Ar), 85.83 (C-4'), 87.74 (C-1'), 119.84 (C-5), 125.84 (Ar-C-3), 129.93 (Ar-C-6), 130.45 (Ar-C-4), 131.34 (Ar-C-2), 138.13 (Ar-C-1), 142.84 (C-8), 144.40 (C-2), 145.17 (C-4), 148.32 (C-6).

1-(2-Methoxybenzyl)adenosine, Perchloric Acid Salt (2b-2). The crude product (4.2 g) was dissolved in about 350 mL hot EtOH, treated with silica gel and filtered through a layer of silica gel. The clear solution was slowly diluted with benzene until cloudy, chilled overnight, and the precipitate was collected. This product still contained NH_4^+ according to the ^{1}H NMR spectrum. However, a second crop obtained from the filtrate which was washed with ether and dried at 56 °C over phosphorus pentoxide overnight was found to be free of NH_4^+. UV λ_{max} 259 nm (12,800) at pH 1; 259 (12,600) at pH 7; 259 (13,000) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR (KBr) 1684, 1605, 1505, 1500, 1250, 1225, 1100 (broad), 1025, 1015, 860, 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.65 (s, 3, OCH_3), 3.57, 3.68 (2 m, 2, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, H-3'), 4.47 (apparent q, 1, H-2'), 5.18 (apparent t, 1, OH-5'), 5.31 (apparent d, 1, OH-3'), 5.42 (s, 2, OCH_2Ar), 5.59 (apparent d, 1, OH-2'), 5.93 (d, 1, H-1'), 7.02 (m, 2, Ar-H-4,5), 7.48 (m, 2, Ar-H-3,6), 8.65 (s, 1, H-2), 8.80 (s, 1, H-8), 9.54, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 55.30 (OCH_3), 60.85 (C-5'), 69.95 (C-3'), 74.44 (C-2'), 76.67 (CH_2Ar), 85.38 (C-4'), 87.73 ($J_{C,H}$ = 166.63 Hz, C-1'), 111.01 (Ar-C-3), 119.16 (C-5), 119.67 (Ar-C-1), 120.49 (Ar-C-5), 132.12 (Ar-C-4), 132.96 (Ar-C-6), 142.89 (C-8), 144.59 (C-2), 145.23 (C-4), 148.39 (C-6), 158.15 (Ar-C-2).

1-(3-Methoxybenzyloxy)adenosine, Perchloric Acid Salt (2b-3). UV λ_{max} 260 nm (13,200) at pH 1; 260 (12,700) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR (KBr) 1683, 1605, 1510, 1495, 1435, 1270, 1100 (broad), 623 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.56, 3.68 (2 m, 2, CH_2-5'), 3.78 (s, 3, OCH_3), 3.98 (apparent q, 1, H-4'), 4.14 (apparent q, 1, H-3'), 4.47 (apparent q, 1, H-2'), 5.07 (apparent t, 1, OH-5'),

5.31 (apparent d, 1, OH-3′), 5.36 (s, 2, OCH_2Ar), 5.59 (apparent d, 1, OH-2′), 5.92 (d, 1, H-1′), 7.03 (m, 1, Ar-H-4), 7.19 (d, 1, Ar-H-6), 7.28 (apparent t, 1, Ar-H-2), 7.37 (t, 1, Ar-H-5), 8.76 (s, 1, H-8), 8.88 (s, 1, H-2), 9.95 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 55.14 (OCH_3), 60.90 (C-5′), 69.99 (C-3′), 74.44 (C-2′), 81.24 (CH_2Ar), 85.86 (C-4′), 87.73 ($J_{C_1',H_1'}$ = 167.6 Hz, C-1′), 115.47 (Ar-C-4), 115.93 (Ar-C-2), 119.67 (J_{C_5,H_8} = 11.8 Hz, C-5), 122.75 (Ar-C-6), 129.55 (Ar-C-5), 133.48 (Ar-C-1), 142.46 (J_{C_8,H_8} = 218.1 Hz, $J_{C_8,H_1'}$ = 4.1 Hz, C-8), 144.77 (J_{C_4,H_8} = 13.1 Hz, J_{C_4,H_2} = 5.3 Hz, $J_{C_4,H_1'}$ = 2.4 Hz, C-4), 144.84 (J_{C_2,H_2} = 221.5 Hz, C-2), 148.33 (J_{C_6,H_2} = 5.3 Hz, C-6), 159.18 (Ar-C-3).

1-(4-Methoxybenzyloxy)adenosine, Perchloric Acid Salt (2b-4). UV λ_{max} 258 nm (13,900) at pH 1; 259 (12,100) at pH 7; 259 (11,400) at pH 13; MS (FAB) *m/e* 404 (M + 1); IR (KBr) 1684, 1610, 1516, 1252, 1229, 1180, 1100 (broad), 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m, 2, CH_2-5′), 3.79 (s, 3, OCH_3), 3.99 (apparent q, 1, H-4′), 4.16 (apparent q, 1, H-3′), 4.49 (apparent q, 1, H-2′), 5.09 (apparent t, 1, OH-5′), 5.33 (apparent d, 1 OH-3′), 5.35 (s, 2, OCH_2Ar), 5.60 (d, 1, OH-2′), 5.93 (d, 1, H-1′), 6.99 (d, 2, Ar-H-3,5), 7.69 (d, 2, Ar-H-2,6), 8.80 (s, 1, H-8), 8.87 (s, 1, H-2), 10.02 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 55.14 (OCH_3), 60.85 (C-5′), 69.94 (C-3′), 74.41 (C-2′), 81.35 (CH_2Ar), 85.84 (C-4′), 87.70 ($J_{C_1',H_1'}$ = 167.7 Hz, C-1′), 113.80 (Ar-C-3,5), 119.33 (J_{C_5,H_8} = 11.7 Hz, C-5), 123.87 (Ar-C-1), 132.66 (Ar-C-2,6), 142.71 (J_{C_8,H_8} = 218.1 Hz, $J_{C_8,H_1'}$ = 4.2 Hz, C-8), 144.84 ($J_{C_4H_1'}$ = 2.6 Hz, J_{C_4,H_2} = 5.3 Hz, J_{C_4,H_8} = 13.2 Hz, C-4), 145.07 (J_{C_2,H_2} = 222.0 Hz, C-2), 148.35 (C-6), 160.35 (Ar-C-4).

1-(1-Phenylethyloxy)adenosine, Perchloric Acid Salt (2c). UV λ_{max} 259 nm (12,400) at pH 1; 259 (12,500) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1691, 1510, 1430, 1400, 1325, 1225, 1100 (broad), 875, 720, 705, 635, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (d, 3, CH_3), 3.55, 3.65 (2 m, 2, CH_2-5′), 3.95 (apparent q, 1, H-4′), 4.12 (apparent t, 1, H-3′), 4.43 (apparent t, 1, H-2′), 5.07, 5.31, 5.68 (apparent s, 3, OH-5′,3′,2′), 5.71 (apparent q, 1, O*CH*Ar), 5.90 (m, 1, H-1′), 7.42, 7.59 (2 m, 5, Ar-H), 8.77 (apparent t, 2, H-8,2), 9.53, 10.32 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.61 (*CH*CH_3), 60.80 (C-5′), 69.88 (C-3′), 74.39 (C-2′), 85.83 (C-4′), 87.65 (C-1′), 88.60 (O*CH*Ar), 118.97 (C-5), 128.49, 128.54 (Ar-C-2,3,5,6), 129.85 (Ar-C-4), 136.05 (Ar-C-1), 142.83 (C-8), 144.72 (C-2), 144.89 (C-4), 148.61 (C-6).

1-(2-Fluorobenzyloxy)adenosine, Perchloric Acid Salt (2d-2). UV λ_{max} 259 nm (13,400) at pH 1; 259 (13,100) at pH 7; 257 (12,500) at pH 13; MS (FAB) *m/e* 392 (M + 1), IR (KBr) 1686, 1515, 1415, 1227, 1100 (broad), 770, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.69 (2 m, 2, CH_2-5′), 3.99 (apparent q, H-4′), 4.15 (apparent t, 1, H-3′), 4.48 (apparent s, 1, H-2′), 5.09, 5.33 (2 br s, 2, OH-5′3′), 5.52 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2′), 5.94 (d, 1, H-1′), 7.30, 7.56, 7.69 (3 m, 4, Ar-H). 8.79 (s, 1, H-2), 8.82 (s, 1, H-8), 9.78, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.83 (C-5′), 69.92 (C-3′), 74.43 (C-2′), 74.95 ($J_{CH_2,F}$ = 2.3 Hz, CH_2Ar), 85.84 (C-4′), 87.71 ($J_{C_1',H_1'}$ = 168.2 Hz, C-1′), 115.51 ($J_{C_3,F}$ = 20.9 Hz, Ar-C-3), 119.33 (J_{C_5,H_8} = 12.3 Hz, C-5), 119.35 ($J_{C_1,F}$ = 14.3 Hz, Ar-C-1), 124.64 ($J_{C_5,F}$ = 14.3 Hz, Ar-C-5), 132.52 ($J_{C_4,F}$ = 8.4 Hz, Ar-C-4), 133.01 ($J_{C_6,F}$ = 2.7 Hz), 142.84 (J_{C_8,H_8} = 218.5 Hz, $J_{C_8,H_1'}$ = 4.0 Hz, C-8), 144.64 (J_{C_4,H_8} = 12.9 Hz, J_{C_4,H_2} = 5.3 Hz, $J_{C_4,H_1'}$ = 2.5 Hz, C-4), 148.36 (J_{C_6,H_2} = 5.2 Hz, C-6), 161.04 ($J_{C_2,F}$ = 249.1 Hz, Ar-C-2).

1-(3-Fluorobenzyloxy)adenosine, Perchloric Acid Salt (2d-3). UV λ_{max} 259 nm (13,700) at pH 1; 259 (13,700) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 392 (M + 1); IR (KBr) 1684, 1507, 1100 (broad), 625 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, CH_2-5′), 4.00 (apparent q, 1, H-4′), 4.16 (apparent t, 1, H-3′), 4.49 (apparent t, 1, H-2′), 5.43 (s, 2, OCH_2Ar), 5.97 (d, 1, H-1′), 7.34, 7.52, 7.63 (3 m, 4, Ar-H), 8.83 (s, 1, H-8), 9.05 (s, 1, H-2), 9.78, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.87 (C-5′), 69.97 (C-3′), 74.50 (C-2′), 80.67 (CH_2Ar), 85.90 (C-4′), 87.80 ($J_{C_1',H_1'}$ = 168.3 Hz, C-1′), 116.56, 117.36 ($J_{C_4,F}$ = 20.9 Hz, $J_{C_2,F}$ = 21.8 Hz, Ar-C-3,2), 119.37 (J_{C_5,H_8} = 12.3 Hz, C-5), 126.70 (Ar-C-6), 130.47 ($J_{C_5,F}$ = 7.7 Hz, Ar-C-5), 134.60 ($J_{C_1,F}$ = 7.5 Hz, Ar-C-1), 142.87 (J_{C_8,H_8} = 218.2, $J_{C_8,H_1'}$ = 4.5 Hz, C-8), 144.80 (J_{C_2,H_2} = 222.7 Hz, C-2), 145.22 (J_{C_4,H_8} = 12.5 Hz, J_{C_4,H_2} = 5.9 Hz, $J_{C_4,H_1'}$ = 2.5 Hz, C-4), 148.32 (J_{C_6,H_2} = 6.0

1-(4-Fluorobenzyloxy)adenosine, Perchloric Acid Salt (2d-4). UV λ_{max} 258 nm (12,500) at pH 1; 258 (12,300) at pH 7; 257 (12,400) at pH 13; MS (FAB) *m/e* 392 (M + 1); IR (KBr) 1690, 1511, 1226, 1110 (broad), 874, 855, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.70 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5′), 4.00 (apparent q, 1, H-4′), 4.17 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3′), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2′), 5.09 (br s, 1, OH-5′), 5.32 (br s, 1, OH-3′), 5.41 (s, 2, CH_2Ar), 5.59 (br d, 1, OH-2′), 5.95 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1′), 7.31 (t, 2, $J_{H,F}$ = 8.8 Hz, Ar-H-3,5), 7.75 (m, 2, $J_{H,F}$ = 5.6 Hz, Ar-H-2,6), 8.82 (s, 1, H-8), 9.00 (s, 1, H-2), 9.75, 10.39 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.85 (C-5′), 69.95 (C-3′), 74.45 (C-2′), 80.77 (CH_2Ar), 85.86 (C-4′), 87.75 ($J_{C-1'}$ = 166.8 Hz, C-1′), 115.35 (Ar-C-3,5), 119.32 (J_{C_5,H_8} = 12.2 Hz, C-5), 128.39 ($J_{C_1,F}$ = 2.5 Hz, Ar-C-1), 133.31 ($J_{C_2+C_6,F_1}$ = 8.7 Hz, Ar-C-1), 142.83 (J_{C_8,H_8} = 218.4 Hz, $J_{C_8,H_1'}$ = 3.9 Hz, C-8), 144.83 (J_{C_2,H_2} = 222.2 Hz, C-2), 145.20 (J_{C_4,H_8} = 13.1 Hz, J_{C_4,H_2} = 5.4 Hz, $J_{C_4,H_1'}$ = 2.2 Hz, C-4), 148.32 (J_{C_6,H_2} = 5.3 Hz, C-6), 162.85 ($J_{C_4,F}$ = 246.8 Hz, Ar-C-4).

1-(2,4-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2e-2,4). UV λ_{max} 259 nm (13,500) at pH 1; 259 (13,300) at pH 7; 257 (13,000) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR (KBr) 1690, 1620, 1508, 1100 (broad), and 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m, 2, $J_{4',5'a}$ = 3.7 Hz, $J_{4,5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5′), 3.99 (apparent q, 1, H-4′), 4.16 (apparent s, 1, $J_{3',4'}$ = 3.9 Hz, H-3′), 4.48 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2′), 5.09, 5.33 (2 apparent s, 2, OH-5′,3′), 5.47 (s, 2, OCH_2Ar), 5.60 (apparent d, 1, OH-2′), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1′), 7.22, 7.39 (2 m, 2, Ar-H-3,5), 7.76 (q, 1, Ar-H-6), 8.81 (s, 2, H-8,2), 9.79, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.86 (C-5′), 69.95 (C-3′), 74.36 (OCH_2Ar), 74.48 (C-2′), 85.89 (C-4′), 87.73 (C-1′), 104.24 (Ar-C-3), 111.85 (Ar-C-5), 117.00 (Ar-C-1), 119.39 (C-5), 134.60 (Ar-C-6), 142.87 (C-8), 144.55 (C-2), 145.25 (C-4), 148.41 (C-6), 161.55, 163.47 (Ar-C-2,4).

1-(2,5-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2e-2,5). UV λ_{max} 260 nm (13,800) at pH 1; 260 (13,800) at pH 7;258 (13,200) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR (KBr) 1691, 1510, 1500, 1435, 1240, 1230, 1195, 1100 (broad), 975, 880, 735, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.70 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5′), 4.01 (apparent q, 1, H-4′), 4.17 (apparent q, 1, $J_{3',4'}$ = 3.8 Hz, H-3′), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2′), 5.11 (t, 1, $J_{5',5'\text{-OH}}$ = 5.3 Hz, OH-5′), 5.35 (d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3′), 5.49 (s, 2, OCH_2Ar), 5.63 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2′), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1′), 7.40, 7.64 (2 m, 3, Ar-H), 8.83 (s, 1, H-8), 8.89 (s, 1, H-2); ^{13}C NMR (Me_2SO-

d_6) δ 60.85 (C-5'), 69.95 (C-3'), 74.24 (CH_2Ar), 74.45 (C-2'), 85.90 (C-4'), 87.71 ($J_{C_1',H_1'}$ = 164.5 Hz, C-1'), 117.20 (J_{C_6,F_5} = 24.34 Hz, J_{C_6,F_2} = 8.54 Hz, Ar-C-6), 118.96 (J_{C_3,F_2} = 27.44 Hz, J_{C_3,F_5} = 3.02 Hz, Ar-C-3), 119.39 (C-5), 121.20 (J_{C_1,F_2} = 17.39 Hz, J_{C_1,F_5} = 8.19 Hz, Ar-C-1), 142.87 (C-8), 144.55 (C-2), 145.25 (C-4), 148.36 (C-6), 155.90 (J_{C_2,F_2} = 48.54 Hz, Ar-C-2), 159.02 (J_{C_5,F_5} = 45.74 Hz, Ar-C-5).

1-(2,6-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2e-2,6). UV λ_{max}259 nm (14,000) at pH 1; 259 (13,900) at pH 7; 257 (13,400) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR (KBr) 1685, 1629, 1515, 1476, 1415, 1405, 1245, 1230, 1100 (broad), 920, 910, 800, 675, 622 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.58, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10 (br s, 1, OH-5'), 5.33 (br s, 1, OH-3'), 5.57 (s, 2, OCH_2Ar), 5.62 (apparent d, 1, OH-2'), 5.94 (d, 1, H-1'), 7.23 (t, 2, Ar-H-3,5), 7.63 (m, 1, Ar-H-4), 8.83 (s, 1, H-8), 8.87 (s, 1, H-2), 9.83, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.84 (C-5'), 68.78 (CH_2Ar), 69.94 (C-3'), 74.43 (C-2'), 85.90 (C-4'), 87.68 ($J_{C,H}$ = 167.91 Hz, C-1'), 108.44 ($J_{C_1,F}$ = 10.74 Hz, Ar-C-1), 111.88 ($J_{C,F}$ = 24.95 Hz, Ar-C-3,5), 119.29 (C-5), 133.57 ($J_{C,F}$ = 12.78 Hz, Ar-C-4), 142.95 (C-8), 144.43 (C-2), 145.24 (C-6), 161.47 (J_{C_1,F_1} = 251.15 Hz, J_{C_1,F_2} = 6.65 Hz, Ar-C-2,6).

1-(3,4-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2e-3,4). UV λ_{max} 259 nm (13,000) at pH 1; 259 (13,400) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR (KBr) 1687, 1522, 1440, 1294, 1100 (broad), and 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 3.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.17 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (br s, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10, 5.35, 5.60 (3 br s, 3, OH-5',3',2'), 5.38 (s, 2, OCH_2Ar), 5.95 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.55, 7.88 (2 m, 3, Ar-H-2,5,6), 8.82 (s, 1, H-8), 9.03 (s, 1, H-2), 9.76, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.88 (C-5'), 69.98 (C-3'), 74.45 (C-2'), 80.12 (CH_2Ar), 85.91 (C-4'), 87.75 (C-1'), 117.53 (Ar-C-5), 119.39 (J_{C_5,H_8} = 11.1 Hz, C-5), 120.04 (Ar-C-2), 128.16 (J_{C_6,F_4} = 6.8 Hz, J_{C_6,F_3} = 3.3 Hz, Ar-C-6), 129.72 (J_{C_1,F_3} = 6.2 Hz, J_{C_1,F_4} = 3.8 Hz, Ar-C-1), 142.86 (J_{C_8,H_8} = 218.5 Hz, $J_{C_8,H_1'}$ = 3.8 Hz, C-8), 144.89 (J_{C_2,H_2} = 222.5 Hz, C-2), 145.24 (J_{C_4,H_8} = 13.1 Hz, J_{C_4,H_2} = 5.2 Hz, $J_{C_4,H_1'}$ = 2.5 Hz, C-4), 148.32 (J_{C_6,H_2} = 5.2 Hz, C-6), 149.11, 150.24 (Ar-C-3,4).

1-(3,5-Difluorobenzyloxy)adenosine, Perchloric Acid Salt (2e-3,5). UV λ_{max} 259 nm (13,600) at pH 1; 259 (13,500) at pH 7; 257 (12,700) at pH 13; MS (FAB) *m/e* 410 (M + 1); IR (KBr) 1697, 1686 (sh), 1630, 1605, 1455, 1380, 1330, 1230, 1100 (broad), 870, 860 (sh), 845, 665, 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.59, 3.70 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.01 (apparent q, 1, H-4'), 4.17 (apparent d, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10 (br s, 1, OH-5'), 5.34 (apparent d, 1, OH-3'), 5.40 (s, 2, OCH_2Ar), 5.61 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.39 (m, 1, Ar-H-4), 7.50 (m, 2, Ar-H-2,6), 8.83 (s, 1, H-8), 9.07 (s, 1, H-2), 9.78, 10.47 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.87 (C-5'), 69.98 (C-3'), 74.45 (C-2'), 79.85 (CH_2Ar), 85.92 (C-4'), 87.76 ($J_{C,H}$ = 166.97 Hz, C-1'), 105.05 ($J_{C,F}$ = 25.55 Hz, Ar-C-4), 113.73 ($J_{C,F}$ = 25.33 Hz, Ar-C-2,6), 119.41 (C-5), 136.08 ($J_{C_1,F}$ = 9.93 Hz, Ar-C-1), 142.86 (C-8), 144.84 (C-2), 145.25 (C-4), 148.29 (C-6), 162.07 ($J_{C,F}$ = 233.31 Hz, Ar-C-3,5).

1-(2,4-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2f-2,4). UV λ_{max} 259 nm (13,300) at pH 1; 259 (13,400) at pH 7; 258 (13,200) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR (KBr) 1689, 1615, 1510, 1430, 1220, 1100 (broad), 895, 645, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.31, 2.42 (2 s, 6, Ar-CH_3), 3.57, 3.67 (2 m, 2, CH_2-5′), 3.98 (apparent q, 1, H-4′), 4.15 (apparent t, 1, H-3′), 4.48 (apparent t, 1, H-2′), 5.09 (br s, 1, OH-5′), 5.33 (br s, 1, OH-3′), 5.40 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2′), 5.91 (d, 1, $J_{1',2'}$ = 5.35 Hz, H-1′), 7.03, 7.15, 7.31 (m, 3, Ar-H), 8.52 (s, 1, H-2), 8.82 (s, 1, H-8), 9.76, 10.45 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.57 (Ar-CH_3), 20.73 (Ar-CH_3-4), 60.82 (C-5′), 69.92 (C-3′), 74.36 (C-2′), 79.42 (Ar-C-2), 85.84 (C-4′), 87.54 (C-1′), 119.37 (J_{C_5,H_8} = 12.2 Hz, C-5), 126.38 (Ar-C-5), 127.44 (Ar-C-1), 131.16, 131.70 (Ar-C-3,6), 138.16, 139.50 (Ar-C-2,4), 142.81 (C-8), 144.49 (C-2), 145.16 (C-4), 148.31 (C-6).

1-(2,5-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2f-2,5). UV λ_{max} 259 nm (13,100) at pH 1; 259 (13,200) at pH 7; 258 (13,200) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR (KBr) 1688, 1508, 1415, 1225, 1100 (broad), 915, 900, 880, 875, 825, 685, 655, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.26, 2.39 (2 s, 6 Ar-CH_3), 3.58, 3.68 (2 m, 2, $J_{4',5'_a}$ = $J_{4',5'_b}$ = 3.8 Hz, $J_{5'_a,5'_b}$ = 12.1 Hz, CH_2-5′), 3.99 (apparent q, 1, H-4′), 4.15 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3′), 4.48 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2′), 5.09 (br s, 1, OH-5′), 5.32 (br s, 1, OH-3′), 5.41 (s, 2, OCH_2Ar), 5.59 (apparent d, 1, OH-2′), 5.93 (d, 1, $J_{1',2'}$ = 5.37 Hz, H-1′), 7.18, 7.20, 7.30 (m, 3, Ar-H), 8.65 (s, 1, H-2), 8.82 (s, 1, H-8), 9.75, 10.45 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.15 (ArCH_3-2), 20.28 (ArCH_3-5), 60.84 (C-5′), 69.93 (C-3′), 74.43 (C-2′), 79.66 (CH_2Ar), 85.85 (C-4′), 87.75 (C-1′), 119.41 (J_{C_5,H_8} = 12.3 Hz, C-5), 130.22, 130.31, 130.38, 131.84, 134.82, 134.86 (Ar-C), 142.86 (J_{C_8,H_8} = 218.6 Hz, $J_{C_8,H_{1'}}$ = 3.9 Hz, C-8), 144.46 (J_{C_2,H_2} = 222.3 Hz, C-2), 145.17 (J_{C_4,H_8} = 130.0 Hz, J_{C_4,H_2} = 5.5 Hz, $J_{C_4,H_{1'}}$ = 2.6 Hz, C-4), 148.30 (J_{C_6,H_2} = 5.2 Hz, C-6).

1-(3,4-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2f-3,4). UV λ_{max} 259 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,600) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR (KBr) 1691, 1510, 1100 (broad), 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.25 (s, 6, Ar-CH_3) 3.58, 3.69 (2 m, 2, $J_{4,5'_a}$ = $J_{4,5'_b}$ = 3.87 Hz, $J_{5'_a,5'_b}$ = 12.1 Hz, CH_2-5′), 4.00 (apparent q, 1, H-4′), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.85 Hz, H-3′), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.88 Hz, H-2′), 5.09 (br s, 1, OH-5′), 5.33 (s, 2, OCH_2Ar), 5.60 (br d, 1, $J_{2',2'\text{-OH}}$ = 4.57 Hz, OH-2′), 5.94 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1′), 8.81 (s, 1, H-8), 8.91 (s, 1, H-2), 9.72, 10.41 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 19.17 (Ar-CH_3), 60.86 (C-5′), 69.96 (C-3′), 74.49 (C-2′), 81.71 (CH_2Ar), 85.87 (C-4′), 87.77 (C-1′), 119.30 (J_{C_5,H_8} = 11.6 Hz, C-5), 128.24 (Ar-C-6), 129.20 (Ar-C-1), 129.46 (Ar-C-5), 131.84 (Ar-C-2), 136.38, 138.08 (Ar-C-3,4), 142.83 (J_{C_8,H_8} = 218.4 Hz, $J_{C_8,H_{1'}}$ = 3.8 Hz, C-8), 144.78 (J_{C_2,H_2} = 222.0 Hz, C-2), 145.19 (J_{C_4,H_8} = 12.9 Hz, J_{C_4,H_2} = 5.2 Hz, $J_{C_4,H_{1'}}$ = 2.1 Hz, C-4), 148.29 (J_{C_6,H_2} = 5.2 Hz, C-6).

1-(3,5-Dimethylbenzyloxy)adenosine, Perchloric Acid Salt (2f-3,5). UV λ_{max} 259 nm (12,900) at pH 1; 259 (13,100) at pH 7; 258 (13,000) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR (KBr) 1693, 1510, 1225, 1100 (broad), 890, 853, 638, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.30 (s, 6, Ar-CH_3), 3.59, 3.69 (2 m, 2, $J_{4',5'_a}$ = 3.8 Hz, $J_{4',5'_b}$ = 3.9 Hz, $J_{5'_a,5'_b}$ = 12.0 Hz, CH_2-5′), 4.00 (apparent q, 1, H-4′), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3′), 4.49 (br s, 1, $J_{2',3'}$ = 4.9 Hz, H-2′), 5.09 (br s, 1, OH-5′), 5.32 (s, 2, OCH_2Ar), 5.60 (br

d, 1, OH-2'), 5.95 (d, 1, $J_{1',2'}$ = 5.38 Hz, H-1'), 7.11, 7.28 (2 s, 3, Ar-H), 8.82 (s, 1, H-8), 8.96 (s, 1, H-2), 9.72, 10.42 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 20.69 (Ar-CH_3), 60.85 (C-5'), 69.95 (C-3'), 74.50 (C-2'), 81.83 (CH_2Ar), 85.86 (C-4'), 87.78 (C-1'), 119.32 (J_{C_5,H_8} = 11.3 Hz, C-5), 128.32 (Ar-C-2,6), 130.99 (Ar-C-4), 131.78 (Ar-C-1), 137.54 (Ar-C-3,5), 142.84 (J_{C_8,H_8} = 218.2 Hz, $J_{C_8,H_{1'}}$ = 3.7 Hz, C-8), 144.82 (J_{C_2,H_2} = 222.2 Hz, C-2), 145.19 (J_{C_4,H_8} = 13.0 Hz, J_{C_4,H_2} = 5.1 Hz, C-4), 148.26 (J_{C_6,H_2} = 5.3 Hz, C-6).

1-(2-Trifluoromethylbenzyloxy)adenosine, Perchloric Acid Salt (2g). UV λ_{max} 258 nm (13,100) at pH 1; 258 (12,900) at pH 7; 257 (12,700) at pH 13; MS (FAB) *m/e* 442 (M + 1); IR (KBr) 1682, 1317, 1177, 1108 (broad), 778, 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.58, 3.68 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.17 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.32 (br s, 1, OH-3'), 5.60 (br s, 1, OH-2'), 5.61 (s, 2, OCH_2Ar), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.80 (m, 4, Ar-H), 8.68 (s, 1, H-2), 8.83 (s, 1, H-8), 9.81, 10.47 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.84 (C-5'), 69.93 (C-3'), 74.46 (C-2'), 77.11 (CH_2Ar), 85.86 (C-4'), 87.71 ($J_{C_1',H_1'}$ = 168.0 Hz, C-1'), 119.65 (J_{C_5,H_8} = 11.8 Hz, C-5), 123.94 ($J_{C,F}$ = 273.8 Hz, CF_3), 126.29 ($J_{C_{Ar}3,F}$ = 5.4 Hz, Ar-C-3), 127.39 ($J_{C_{Ar}2,F}$ = 30.5 Hz, Ar-C-2), 130.05, 132.77 (Ar-C-4,5), 132.11 (Ar-C-6), 142.80 (C-8), 144.34 (C-2), 148.43 (C-6).

1-[2,4-Bis(trifluoromethyl)benzyloxy]adenosine, Perchloric Acid Salt (2h-2,4). UV λ_{max} 259 nm (13,240) at pH 1; 259 (12,710) at pH 7; 257 (12,090) at pH 13; MS (FAB) *m/e* 510 (M + 1); IR (KBr) 1684, 1348, 1304, 1281, 1123 (broad), 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.60, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.6 Hz, $J_{5'a,5'b}$ = 12.3 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 5.0 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.33 (br s, 1, OH-3'), 5.60 (br s, 1, OH-2'), 5.71 (s, 2, OCH_2Ar), 5.93 (apparent d, 1, H-1'), 8.15 (m, 2, Ar-H-3,6), 8.27 (apparent d, 1, Ar-H-5), 8.84 (s, 1, H-8), 8.91 (s, 1, H-2), 9.84, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.94 (C-5'), 70.04 (C-3'), 74.58 (C-2'), 76.36 (OCH_2Ar), 85.99 (C-4'), 87.81 (C-1'), 119.77 (C-5), 123.08, 123.14, 123.21 (2 CF_3, Ar-C-3), 128.04, 129.71, 130.03, 132.35 (Ar-C-2,4,5,6), 135.91 (Ar-C-1), 142.86 (C-8), 144.53 (C-2), 145.31 (C-4), 148.53 (C-6).

1-[3,5-Bis(trifluoromethyl)benzyloxy]adenosine, Perchloric Acid Salt (2h-3,5). UV λ_{max} 259 nm (12,600) at pH 1; 259 (12,280) at pH 7; 257 (12,100) at pH 13; MS (FAB) *m/e* 510 (M + 1); IR (KBr) 1684, 1366, 1282, 1129 (broad), 684, and 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.61, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 11.9 Hz, CH_2-5'), 4.01 (apparent q, 1, H-4'), 4.18 (apparent t, 1, $J_{3',4'}$ = 3.8 Hz, H-3'), 4.52 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, OH-5'), 5.34 (br s, 1, OH-3'), 5.59 (br s, 1, OH-2'), 5.56 (s, 2, OCH_2Ar), 5.98 (apparent d, 1, $J_{1',2'}$ = 5.11 Hz, H-1'), 8.26 (s, 1, Ar-H-4), 8.52 (s, 1, Ar-H-6), 8.84 (s, 1, H-8), 9.30 (s, 1, H-2), 9.84, 10.51 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 61.02 (C-5'), 70.15 (C-3'), 74.62 (C-2'), 79.74 (OCH_2Ar), 86.08 (C-4'), 87.96 (C-1'), 119.55 (C-5), 123.21 (Ar-C-4), 123.23 (2 CF_3), 130.35 (Ar-C-3,5), 131.74 (Ar-C-2,6), 135.37 (Ar-C-1), 143.04 (C-8), 145.14 (C-2), 145.41 (C-4), 148.39 (C-6).

1-(2-Chlorobenzyloxy)adenosine, Perchloric Acid Salt (2i-2). UV λ_{max} 260 nm (12,690) at pH 1; 259 (12,550) at pH 7; 258 (12,510) at pH 13; MS (FAB) *m/e* 408 (M + 1); IR (KBr) 1689, 1509, 1220, 1100

(broad), 931, 860, 774, 769, 645, 640, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 4.0 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.6 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.31 (br s, 1, OH-3'), 5.54 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2'), 5.93 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.42-7.78 (m, 4, Ar-H), 8.70 (s, 1, H-2), 8.83 (s, 1, H-8), 9.82, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.82 (C-5'), 69.91 (C-3'), 74.45 (C-2'), 78.14 (OCH_2Ar), 85.84 (C-4'), 87.71 (C-1'), 119.44 (C-5), 127.42, 129.50, 131.70 (Ar-C-3,4,5), 129.99 (Ar-C-2), 132.94 (Ar-C-6), 134.02 (Ar-C-1), 142.84 (C-8), 144.33 (C-2), 145.19 (C-4), 148.39 (C-6).

1-(3-Chlorobenzyloxy)adenosine, Perchloric Acid Salt (2i-3). UV λ_{max} 259 nm (12,910) at pH 1; 259 (12,560) at pH 7; 258 (12,560) at pH 13; MS (FAB) *m/e* 408 (M + 1); IR (KBr) 1694 1620, 1575, 1510, 1430, 1415, 1380, 1220, 1075 (broad), 885, 785, 685, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.17 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.7 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.33 (br s, 1, OH-3'), 5.40 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.48-7.88 (m, 4, Ar-H), 8.82 (s, 1, H-8), 9.10 (s, 1, H-2), 9.78, 10.44 (2 br s, 1, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.85 (C-5'), 69.95 (C-3'), 74.46 (C-2'), 80.63 (OCH_2Ar), 85.87 (C-4'), 87.78 (C-1'), 119.34 (C-5), 129.23, 129.54, 130.41 (Ar-C-2,4,6), 130.24 (Ar-C-5), 133.00 (Ar-C-3), 134.32 (Ar-C-1), 142.84 (C-8), 144.82 (C-2), 145.20 (C-4), 148.26 (C-6).

1-(2-Nitrobenzyloxy)adenosine, Perchloric Acid Salt (2j-2). UV λ_{max} 259 nm (18,170) at pH 1; 259 (18,090) at pH 7; 257 (16,890) at pH 13; MS (FAB) *m/e* 419 (M + 1); IR (KBr) 1685, 1538, 1530, 1510, 1347, 1105 (broad), 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.7 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.08 (br s, 1, OH-5'), 5.32 (br s, 1, OH-3'), 5.60 (br s, 1, OH-2'), 5.76 (s, 2, OCH_2Ar), 5.95 (d, 1, $J_{1',2'}$ = 5.35 Hz, H-1'), 7.75 (m, 1, Ar-H-4), 7.90 (m, 1, Ar-H-5), 7.99 (apparent d, 1, Ar-H-3), 8.22 (apparent d, 1, Ar-H-6), 8.83 (s, 1, H-8), 8.94 (s, 1, H-2), 9.80, 10.46 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.83 (C-5'), 69.92 (C-3'), 74.46 (C-2'), 77.01 (OCH_2Ar), 85.84 (C-4'), 87.77 (C-1'), 119.54 (C-5), 124.81 (Ar-C-3), 128.32 (Ar-C-1), 130.29 (Ar-C-4), 131.11 (Ar-C-5), 134.03 (Ar-C-6), 142.79 (C-8), 144.45 (C-2), 145.21 (C-4), 147.54 (Ar-C-2), 148.36 (C-6).

1-(3-Nitrobenzyloxy)adenosine, Perchloric Acid Salt (2j-3). UV λ_{max} 259 nm (19,400) at pH 1; 259 (19,100) at pH 7; 258 (17,560) at pH 13; MS (FAB) *m/e* 419 (M + 1); IR (KBr) 1691, 1620, 1533, 1511, 1352, 1225, 1090 (broad), 900, 740, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60, 3.71 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.01 (apparent q, 1, H-4'), 4.18 (apparent t, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.51 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.10 (br s, 1, OH-5'), 5.34 (br s, 1, OH-3'), 5.55 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2'), 5.97 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.80 (t, 1, Ar-H-5), 8.17 (d, 1, Ar-H-6), 8.35 (m, 1, Ar-H-4), 8.67 (s, 1, Ar-H-2), 8.83 (s, 1, H-8), 9.17 (s, 1, H-2), 10.15 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.88 (C-5'), 69.99 (C-3'), 74.49 (C-2'), 80.11 (OCH_2Ar), 85.92 (C-4'), 87.79 (C-1'), 119.42 (C-5), 124.40 (Ar-C-5), 125.45 (Ar-C-4), 129.95 (Ar-C-2), 134.13 (Ar-C-6), 137.25 (Ar-C-1), 142.87 (C-8), 144.95 (C-2), 145.24 (C-4), 147.64 (Ar-C-3), 148.31 (C-6).

1-(4-Nitrobenzyloxy)adenosine, Perchloric Acid Salt (2j-4). UV λ_{max} 260 nm (22,270) at pH 1; 260 (21,970) at pH 7; 265 (18,550) at pH 13 (slowly decreased); MS (FAB) *m/e* 419 (M + 1); IR (KBr) 1686, 1524, 1348, 1220, 1090 (broad), 854, 750, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.57, 3.70 (2 m, 2, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H-4'), 4.16 (apparent q, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.09 (t, 1, $J_{5',5'\text{-OH}}$ = 5.3 Hz, OH-5'), 5.34 (d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.55 (s, 2, OCH_2Ar), 5.60 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.95 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.97 (d, 2, Ar-H-2,6), 8.34 (d, 2, Ar-H-3,5), 8.83 (s, 1, H-8), 9.11 (s, 1, H-2), 10.15 (broad, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.87 (C-5'), 69.97 (C-3'), 74.53 (C-2'), 80.03 (OCH_2Ar), 85.89 (C-4'), 87.84 (C-1'), 119.43 (C-5), 123.38 (Ar-C-3,5), 131.38 (Ar-C-2,6), 139.45 (Ar-C-1), 142.88 (C-8), 144.76 (C-2), 145.24 (C-4), 148.01 (Ar-C-4), 148.33 (C-6).

1-(2-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2k-2). UV λ_{max} 260 nm (12,700) at pH 1; 259 (12,560) at pH 7; 257 (12,160) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR (KBr) 2250, 1684, 1505, 1222, 1100 (broad), 772, and 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.09 (br s, 1, OH-5'), 5.33 (br s, 1, OH-3'), 5.60 (br, 1, OH-2'), 5.60 (s, 2, OCH_2Ar), 5.94 (apparent d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.70 (t, 1, Ar-H, 4), 7.87, 7.90 (2 m, 2, Ar-H, 3,5), 7.99 (d, 1, Ar-H-6), 8.81 (s, 1, H-2), 8.83 (s, 1, H-8), 9.54, 10.48 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.81 (C-5'), 69.89 (C-3'), 74.44 (C-2'), 78.56 (OCH_2Ar), 85.83 (C-4'), 87.74 (C-1'), 112.53 (Ar-C-2), 117.12 (C≡N), 119.58 (C-5), 130.50, 131.71, 133.20, 133.38 (Ar-C-3,4,5,6), 135.16 (Ar-C-1), 142.81 (C-8), 144.23 (C-2), 145.16 (C-4), 148.38 (C-6).

1-(3-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2k-3). UV λ_{max} 259 nm (13,500) at pH 1; 259 (12,900) at pH 7; 257 (12,980) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR (KBr) 2230, 1694, 1510, 1235, 1215, 1090 (broad), 892, 690, 655, 640, and 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.8 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.00 (apparent q, 1, H- 4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.7 Hz, H-2'), 5.12 (br s, 1, OH-5'), 5.34 (br s, 1, OH-3'), 5.45 (s, 2, OCH_2Ar), 5.60 (br s, 1, OH-2'), 5.96 (apparent d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.69 (t, 1, Ar-H-5), 7.96, 8.02 (2 m, 2, Ar-H-4,6), 8.25 (s, 1, Ar-H-2), 8.83 (s, 1, H-8), 9.13 (s, 1, H-2), 9.78, 10.45 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.87 (C-5'), 69.97 (C-3'), 74.50 (C-2'), 80.26 (OCH_2Ar), 85.90 (C-4'), 87.82 (C-1'), 111.44 (Ar-C-3), 118.31 (C≡N), 119.41 (C-5) 129.64 (Ar-C-5), 133.18 (Ar-C-4), 133.60 (Ar-C-1), 134.32 (Ar-C-2), 135.33 (Ar-C-6), 142.87 (C-8), 144.84 (C-2), 145.25 (C-4), 148.28 (C-6).

1-(4-Cyanobenzyloxy)adenosine, Perchloric Acid Salt (2k-4). UV λ_{max} 259 nm (13,800) at pH 1; 259 (13,620) at pH 7; 258 (sh) at pH 13; MS (FAB) *m/e* 399 (M + 1); IR (KBr) 2240, 1687, 1510, 1420, 1385, 1225, 1215, 1075 broad, 825, 621 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.61, 3.73 (2 m, 2, $J_{4',5'a}$ = 3.9 Hz, $J_{4',5'b}$ = 5.6 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 4.02 (apparent q, 1, H-4'), 4.19 (apparent q, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.51 (apparent q, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.11 (t, 1, $J_{5',5'\text{-OH}}$ = 5.3 Hz, OH-5'), 5.35 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.51 (s, 2, OCH_2Ar), 5.62 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.97

(apparent d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.90 (d, 2, Ar-H-3,5), 7.99 (d, 2, Ar-H-2,6), 8.83 (s, 1, H-8), 9.10 (s, 1, H-2), 10.15 (broad, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 60.84 (C-5'), 69.94 (C-3'), 74.51 (C-2'), 80.44 (OCH_2Ar), 85.85 (C-4'), 87.83 (C-1'), 112.16 (Ar-C-4), 118.38 (C≡N), 119.39 (C-5), 131.03 (Ar-C-2,6), 132.26 (Ar-C-3,5), 137.43 (Ar-C-1), 142.85 (C-8), 144.71 (C-2), 145.21 (C-4), 148.29 (C-6).

1-(2-Methoxy-5-nitrobenzyloxy)adenosine, Perchloric Acid Salt (2l). UV λ_{max} 259 nm (14,550) and 310 (10,620) at pH 1; 259 (14,510) and 310 (10,870) at pH 7; 311 (11,800) at pH 13; MS (FAB) *m/e* 449 (M + 1); IR (KBr) 1681, 1595, 1510, 1500, 1490, 1332, 1261, 1212, 1127, 1090 (broad), 1036, 900, 640, and 620 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.59, 3.68 (2 m, 2, $J_{4',5'_a}$ = 3.5 Hz, $J_{4',5'_b}$ = 3.5 Hz, $J_{5'_a,5'_b}$ = 12.0 Hz, CH_2-5'), 3.86 (s, 3, CH_3OAr), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 4.0 Hz, H-3'), 4.49 (apparent t, 1, $J_{2',3'}$ = 4.1 Hz, H-2'), 5.09 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 4.9 Hz, OH-5'), 5.33 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.0 Hz, OH-3'), 5.50 (s, 2, OCH_2Ar), 5.59 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.95 (d, 1, $J_{1',2'}$ = 5.34 Hz, H-1'), 7.31 (d, 1, Ar-H-3), 8.40 (apparent q, 1, Ar-H-4), 8.56 (d, 1, Ar-H-6), 8.84 (s, 2, H-2,8), 9.74, 10.35 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 56.78 ($ArOCH_3$), 60.86 (C-5'), 69.96 (C-3'), 74.59 (C-2'), 75.61 (OCH_2Ar), 85.89 (C-4'), 87.89 (C-1'), 111.80 (Ar-C-3), 119.35 (C-5), 121.12 (Ar-C-1), 127.77, 128.24 (Ar-C-6,4), 140.31 (Ar-C-5), 142.93 (C-8), 144.52 (C-2), 145.25 (C-4), 148.39 (C-6), 163.21 (Ar-C-2).

1-(3-Methoxycarbonylbenzyloxy)adenosine, Perchloric Acid Salt (2m). UV λ_{max} 259 nm (12,670) at pH 1; 259 (12,670) at pH 7; 257 (13,410) at pH 13; MS (FAB) *m/e* 432 (M + 1); IR (KBr) 1710, 1684, 1435, 1315, 1294, 1214, 1100 (broad), 895, 765, and 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.59, 3.69 (2 m, 2, $J_{4',5'_a}$ = 3.7 Hz, $J_{4',5'_b}$ = 3.9 Hz, $J_{5'_a,5'_b}$ = 12.1 Hz, CH_2-5'), 3.89 (s, 3, $ArCO_2CH_3$), 4.00 (apparent q, 1, H-4'), 4.16 (apparent t, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.50 (apparent t, 1, $J_{2',3'}$ = 4.8 Hz, H-2'), 5.10, 5.34, 5.61 (3 br s, 3, OH-5',3',2'), 5.49 (s, 2, OCH_2Ar), 5.96 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.64 (t, 1, Ar-H-5), 7.99, 8.06 (d, 2, Ar-H-6,4), 8.33 (s, 1, Ar-H-2), 8.83 (s, 1, H-8), 9.03 (s, 1, H-2), 9.82, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 52.21 ($ArCO_2CH_3$), 60.88 (C-5'), 69.99 (C-3'), 74.56 (C-2'), 81.02 (OCH_2Ar), 85.90 (C-4'), 87.87 (C-1'), 119.38 (C-5), 128.94 (Ar-C-5), 129.81 (Ar-C-3), 130.32, 131.40, 135.49 (Ar-C-6,4,2), 132.78 (Ar-C-1), 142.87 (C-8), 144.88 (C-2), 145.23 (C-4), 148.33 (C-6), 165.80 ($ArCO_2CH_3$).

1-Benzyloxyadenosine, Perchloric Acid Salt (2n). UV λ_{max} 259 nm (13,100) at pH 1; 259 (13,300) at pH 7; 257 (13,100) at pH 13; MS (FAB) *m/e* 374 (M + 1); IR (KBr) 1686, 1515, 1415, 1230, 1100 (broad), 755, 622 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.58, 3.68 (2 m, 2, $J_{4',5'_a}$ = 3.9 Hz, $J_{4',5'_b}$ = 3.9 Hz, $J_{5'_a,5'_b}$ = 12.1 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.49 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-4'), 5.18 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.1 Hz, OH-5'), 5.33 (d, 1, $J_{3',3'\text{-OH}}$ = 5.1 Hz, OH-3'), 5.42 (s, 2, OCH_2Ar), 5.60 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.4 Hz, H-1'), 7.48, 7.66 (2 m, 5, Ar-H), 8.82 (s, 1, H-8), 8.97 (s, 1, H-2); ^{13}C NMR (Me_2SO-d_6) δ 60.84 (C-5'), 69.93 (C-3'), 74.42 (C-2'), 81.63 (CH_2Ar), 85.85 (C-4'), 87.70 (C-1'), 119.28 (C-5), 128.42 (Ar-C-3,5), 129.73 (Ar-C-4), 130.69 (Ar-C-2,6), 131.97 (Ar-C-1), 142.81 (C-8), 144.78 (C-2), 145.17 (C-4), 148.29 (C-6).

1-(2-Phenylethyloxy)adenosine, Perchloric Acid Salt (2o). UV λ_{max} 259 nm (12,100) at pH 1; 259 nm (13,000) at pH 7; 257 nm (12,700) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1691, 1505, 1225, 1100 broad, 760, 705, 625 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.23 (t, 2, OCH_2CH_2Ar), 3.58, 3.68 (2 m, 2, $J_{4',5'_a}$ = 3.8

Hz, $J_{4',5'b}$ = 3.8 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.7 Hz, H-3'), 4.48 (apparent q, 1, $J_{2',3'}$ = 5.01 Hz, H-2'), 4.60 (t, 2, OCH_2CH_2Ar), 5.09 (apparent t, 1, OH-5'), 5.34 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.0 Hz, OH-3'), 5.60 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.25, 7.36 (2 m, 5, Ar-H), 8.80 (s, 1, H-8), 9.06 (s, 1, H-2), 9.65, 10.39 (br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 32.91 (OCH_2CH_2Ar), 60.83 (C-5'), 69.91 (C-3'), 74.46 (C-2'), 80.41 (OCH_2CH_2Ar), 85.82 (C-4'), 87.80 (C-1'), 119.37 (C-5), 126.55 (Ar-C-4), 128.40 (Ar-C-2,6), 128.78 (Ar-C-3,5), 136.08 (Ar-C-1), 142.75 (C-8), 144.45 (C-2), 145.21 (C-4), 148.21 (C-6).

2'-Deoxy-1-(2-methylbenzyloxy)adenosine, Perchloric Acid Salt (2p-2). UV λ_{max} 259 nm (13,400) at pH 1; 259 (13,100) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 372 (M + 1); IR (KBr) 1684, 1505, 1220, 1100 (broad), 765, 750, 635, 625 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.37, 2.64 (2 m, 2, CH_2-2'), 2.47 (s, 3, CH_3Ar), 3.52, 3.61 (2 m, 2, CH_2-5'), 3.90 (apparent q, 1, H-4'), 4.41 (m, 1, H-3'), 4.95 (br s, 1, OH-5'), 5.39 (br s, 1, OH-3'), 5.46 (s, 2, OCH_2Ar), 6.38 (t, 1, H-1'), 7.24, 7.36, 7.45 (3 m, 4, Ar-H), 8.59 (s, 1, H-2), 8.78 (s, 1, H-8), 9.76, 10.44 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.64 (CH_3), 39.84 (C-2'), 61.20 (C-5'), 70.26 (C-3'), 79.54 (OCH_2Ar), 83.99 (C-1'), 88.21 (C-4'), 119.43 (J_{C_5,H_8} = 11.7 Hz, C-5), 125.85 (Ar-C-5), 129.92 (Ar-C-4), 130.45, 130.50, 131.36 (Ar-C-1,3,6), 138.12 (Ar-C-2), 142.90 (J_{C_8,H_8} = 218.3 Hz, $J_{C_8,H_{1'}}$ = 3.8 Hz, C-8), 144.28 (J_{C_2,H_2} = 222.2 Hz, C-2), 144.83 (J_{C_4,H_8} = 13.0 Hz, J_{C_4,H_2} = 5.4 Hz, $J_{C_4,H_{1'}}$ = 2.5 Hz, C-4), 148.30 (J_{C_6,H_2} = 5.4 Hz, C-6).

2'-Deoxy-1-(3-methylbenzyloxy)adenosine, Perchloric Acid Salt (2p-3). UV λ_{max} 260 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,400) at pH 13; MS (FAB) *m/e* 372 (M + 1); IR (KBr) 1691, 1507, 1425, 1218, 1100 (broad), 933, 624 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.35 (s, 3, CH_3Ar), 2.39, 2.65 (2 m, 2, CH_2-2'), 3.54, 3.61 (2 m, 2, CH_2-5'), 3.92 (apparent q, 1, H-4'), 4.42 (m, 1, H-3'), 4.97 (br s, 1, OH-5'), 5.37 (s, 2, OCH_2Ar), 5.39 (m, 1, OH-3'), 6.38 (t, 1, H-1'), 7.28, 7.34, 7.43, 7.49 (m, 4, Ar-H-2,4,5,6), 8.76 (s, 1, H-8), 8.93 (s, 1, H-2), 9.74, 10.37 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 20.78 (CH_3Ar), 39.84 (C-2'), 61.20 (C-5'), 70.26 (C-3'), 81.74 (OCH_2Ar), 84.02 (C-1'), 88.20 (C-4'), 119.31 (C-5), 127.72, 128.30, 130.30, 131.23, 131.87, 137.71 (Ar-C-1,2,3,4,5,6), 142.86 (C-8), 144.59 (C-4), 144.83 (C-2), 148.24 (C-6).

2'-Deoxy-1-(4-methylbenzyloxy)adenosine, Perchloric Acid Salt (2p-4). UV λ_{max} 259 nm (13,300) at pH 1; 259 (13,300) at pH 7; 258 (13,300) at pH 13; MS (FAB) *m/e* 372 (M + 1); IR (KBr) 1692, 1505, 1425, 1380, 1220, 1100 (broad), 931, 855, 815, 641, 623 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.34 (s, 3, CH_3Ar), 2.39, 2.64 (2 m, 2, CH_2-2'), 3.53, 3.61 (2 m, 2, CH_2-5'), 3.91 (apparent q, 1, H-4'), 4.42 (br m, 1, H-3'), 4.97 (br s, 1, OH-5'), 5.36 (s, 2, OCH_2Ar), 6.37 (t, 1, H-1'), 7.26, 7.53 (2 d, 4, Ar-H), 8.76 (s, 1, H-8), 8.89 (s, 1, H-2), 9.70, 10.36 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 20.84 (CH_3), 39.87 (C-2'), 61.22 (C-5'), 70.28 (C-3'), 81.54 (OCH_2Ar), 84.00 (C-1'), 88.22 (C-4'), 119.27 (C-5), 129.00 (Ar-C-3,5,1), 130.83 (Ar-C-2,6), 139.39 (Ar-C-4), 142.86 (J_{C_8,H_8} = 218.6 Hz, $J_{C_8,H_{1'}}$ = 3.7 Hz, C-8), 144.59 (J_{C_2,H_2} = 221.9 Hz, C-2), 144.84 (J_{C_4,H_8} = 13.1 Hz, J_{C_4,H_2} = 5.4 Hz, $J_{C_4,H_{1'}}$ = 2.5 Hz, C-4), 148.28 (J_{C_6,H_2} = 5.3 Hz, C-6).

2'-Deoxy-1-(2-fluorobenzyloxy)adenosine, Perchloric Acid Salt (2q-2). UV λ_{max} 259 nm (13,700) at pH 1; 259 (13,600) at pH 7; and 258 (13,300) at pH 13; MS (FAB) *m/e* 376 (M + 1); IR (KBr) 1680, 1645, 1508, 1240, 1220, 1205, 1100 (broad), 990, 941, 930, 915, 875, 870, 755, 622 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ

2.39, 2.65 (2 m, 2, CH_2-2′), 3.53, 3.61 (2 m, 2, CH_2-5′), 3.91 (apparent q, 1, H-4′), 4.42 (apparent s, 1, H-3′), 4.97 (br s, 1, OH-5′), 5.39 (apparent s, 1, OH-3′), 5.50 (s, 2, OCH_2Ar), 6.37 (t, 1, H-1′), 7.30, 7.56, 7.69 (3 m, 4, Ar-H), 8.77 (2 apparent s, 2, H-8,2), 9.76 10.42 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 39.83 (C-2′), 61.18 (C-5′), 70.24 (C-3′), 74.90 (J_{CH_2F} = 2.9 Hz, OCH_2Ar), 83.96 ($J_{C_1',H_1'}$ = 169.8 Hz, C-1′), 88.20 (C-4′), 115.52 ($J_{Ar_{C3}F}$ = 21.0 Hz, Ar-C-3), 119.32 (J_{C_5,H_8} = 11.8 Hz, C-5), 119.39 ($J_{Ar_{C1}F}$ = 13.8 Hz, Ar-C-1), 124.63 ($J_{Ar_{C5}F}$ = 3.3 Hz, Ar-C-5), 132.50 ($J_{Ar_{C4}F}$ = 8.6 Hz, Ar-C-4), 133.02 ($J_{Ar_{C6}F}$ = 2.7 Hz, Ar-C-6), 142.90 (J_{C_8,H_8} = 218.5 Hz, $J_{C_8,H_{1'}}$ = 4.1 Hz, C-8), 144.33 (J_{C_2,H_2} = 222.3 Hz, C-2), 144.85 (J_{C_4,H_8} = 13.1 Hz, J_{C_4,H_2} = 5.3 Hz, $J_{C_4,H_{1'}}$ = 2.6 Hz, C-4), 148.32 (J_{C_6,H_2} = 5.4 Hz, C-6), 161.05 ($J_{Ar_{C2}F}$ = 248.9 Hz, Ar-C-2).

2′-Deoxy-1-(3-fluorobenzyloxy)adenosine, Perchloric Acid Salt (2q-3). UV λ_{max} 259 nm (13,700) at pH 1; 259 (13,500) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 376 (M + 1); IR (KBr) 1690, 1505, 1425, 1260, 1225, 1100 (broad), 932, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.39, 2.65 (2 m, 2, CH_2-2′), 3.54, 3.61 (2 m, 2, CH_2-5′), 3.91 (apparent q, 1, H-4′), 4.42 (m, 1, H-3′), 4.97 (m, 1, OH-5′), 5.41 (s, 2, OCH_2Ar), 5.41 (m, 1, OH-3′), 6.39 (t, 1, H-1′), 7.32, 7.50, 7.62 (3 m, 4, Ar-H), 8.78 (s, 1, H-8), 9.03 (s, 1, H-2) 9.76, 10.40 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 39.86 (C-2′), 61.20 (C-5′), 70.28 (C-3′), 80.63 (OCH_2Ar), 84.03 (C-1′), 88.22 (C-4′), 116.55 ($J_{Ar_{C4}F}$ = 20.9 Hz, Ar-C-4), 117.38 ($J_{Ar_{C2}F}$ = 21.9 Hz, Ar-C-2), 119.34 (J_{C_5,H_8} = 12.1 Hz, C-5), 126.72 ($J_{Ar_{C6}F}$ = 2.2 Hz, Ar-C-6), 130.45 ($J_{Ar_{C5}F}$ = 8.2 Hz, Ar-C-5), 134.59 ($J_{Ar_{C1}F}$ = 7.8 Hz, Ar-C-1), 142.89 (J_{C_8,H_8} = 217.9 Hz, $J_{C_8,H_{1'}}$ = 3.7 Hz, C-8), 144.67 (J_{C_2,H_2} = 222.3 Hz, C-2), 144.86 (J_{C_4,H_8} = 13.1 Hz, J_{C_4,H_2} = 5.4 Hz, $J_{C_4,H_{1'}}$ = 2.5 Hz, C-4), 148.25 (J_{C_6,H_2} = 5.4 Hz, C-6), 161.83 ($J_{Ar_{C3}F}$ = 243.8 Hz, Ar-C-3).

2′-Deoxy-1-(4-fluorobenzyloxy)adenosine, Perchloric Acid Salt (2q-4). UV λ_{max} 259 nm (13,000) at pH 1; 259 (12,900) at pH 7; 258 (12,900) at pH 13; MS (FAB) *m/e* 376 (M + 1); IR (KBr) 1683, 1514, 1508, 1385, 1229, 1218, 1100 (broad), 925, 622 cm^{-1}, ^1H NMR (Me_2SO-d_6) δ 2.38, 2.65 (2 m, 2, CH_2-2′), 3.53, 3.61 (2 m, 2, CH_2-5′), 3.91 (apparent 1, H-4′), 4.42 (m, 1, H-3′), 4.97 (br s, 1, OH-5′), 5.39 (s, 2, OCH_2Ar), 6.38 (t, 1, H-1′), 7.30 (m, 2, Ar-H-3,5), 7.74 (m, 2, Ar-H-2,6), 8.77 (s, 1, H-8), 8.98 (s, 1, H-2), 9.72, 10.39 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 39.92 (C-2′), 61.24 (C-5′), 70.31 (C-3′), 80.81 (OCH_2Ar), 84.08 (C-1′), 88.25 (C-4′), 115.36 ($J_{Ar_{C3,C5}F}$ = 21.5 Hz, Ar-C-3,5), 119.34 (J_{C_5,H_8} = 11.8 Hz, C-5), 128.41 ($J_{Ar_{C1}F}$ = 3.0 Hz, Ar-C-1), 133.32 ($J_{Ar_{C2}F}$ = 8.7 Hz, Ar-C-2), 142.89 (J_{C_8,H_8} = 28.2 Hz, $J_{C_8,H_{1'}}$ = 3.7 Hz, C-8), 144.64 (J_{C_2,H_2} = 222.1 Hz, C-2), 144.89 (J_{C_4,H_2} = 5.3 Hz, $J_{C_4,H_{1'}}$ = 2.5 Hz, C-4), 148.31 (J_{C_6,H_2} = 5.2 Hz, C-6), 162.88 ($J_{Ar_{C4}F}$ = 246.8 Hz, Ar-C-4).

9-Benzyl-1-(2-methylbenzyloxy)adenine, Perchloric Acid Salt (2r-2). UV λ_{max} 262 nm (13,500) at pH 1; 261 (13,400) at pH 7; 259 (13,600) at pH 13; MS (FAB) *m/e* 346 (M + 1); IR (KBr) 1691, 1514, 1220, 1100 (broad), 764, 725, 706, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.45 (s, 3, CH_3Ar), 5.45, 5.50 (2 s, 4, OCH_2Ar, NCH_2Ar), 7.17-7.46 (m, 9, Ar-H), 8.57 (s, 1, H-2), 8.72 (s, 1, H-8), 9.73, 10.40 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.63 (Ar-CH_3), 47.01 (NCH_2Ar), 79.40 (OCH_2Ar), 119.06 (C-5), 125.81 (OCH_2Ar-C-5), 127.62 (NCH_2Ar-C-2,6), 128.07 (NCH_2Ar-C-4), 128.67 (NCH_2Ar-C-3,5), 129.88 (OCH_2Ar-C-4), 130.42 (OCH_2Ar-C-3),

130.51 (OCH_2Ar-C-1), 131.33 (OCH_2Ar-C-6), 135.63 (NCH_2Ar-C-1), 138.11 (OCH_2Ar-C-2), 144.31 (J_{C_2,H_2} = 222.0 Hz, C-2), 144.84 (J_{C_8,H_8} = 217.2 Hz, C-8), 1[illegible]31 (C-4), 148.25 (J_{C_6,H_2} = 5.1 Hz, C-6).

9-Benzyl-1-(3-methylbenzyloxy)adenine, Perchloric Acid Salt (2r-3). UV λ_{max} 261 nm (13,500) at pH 1; 261 (13,300) at pH 7; 259 (13,600) at pH 13; MS (FAB) *m/e* 346 (M + 1); IR (KBr) 1695, 1575, 1375, 1100 broad, 795, 765, 729, 645, 640, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3, CH_3Ar), 5.37, 5.50 (s, 4, CH_2Ar), 7.35 (m, 9, Ar-H), 8.71, 8.89 (s, 2, H-8,2), 9.68, 10.34 (br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Benzyl-1-(4-methylbenzyloxy)adenine, Perchloric Acid Salt (2r-4). UV λ_{max} 261 nm (12,900) at pH 1; 261 (13,100) at pH7; 259 (13,600) at pH 13; MS (FAB) *m/e* 346 (M + 1); IR (KBr) 1689, 1620, 1514, 1425, 1100 (broad), 725, 710, 622 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3, CH_3Ar), 5.35 (s, 2, OCH_2Ar), 5.49 (s, 2, NCH_2Ar), 7.22-7.52 (3 m, 9, Ar-H), 8.69 (s, 1, H-8), 8.85 (s, 1, H-2), 9.67, 10.34 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 20.84 (CH_3), 47.01 (NCH_2Ar), 81.44 (OCH_2Ar), 118.91 (J_{C_5,H_8} = 12.2 Hz, C-5), 127.65 (NCH_2Ar-C-2,6), 128.08 (NCH_2Ar-C-4), 128.68 (NCH_2Ar-C-3), 128.98 (CCH_2Ar-C-3,5), 129.02 (OCH_2Ar-C-1), 130.83 (OCH_2Ar-C-2), 135.64 (NCH_2Ar-C-1), 139.36 (OCH_2Ar-C-4), 144.64 (J_{C_2,H_2} = 221.9 Hz, C-2), 144.81 (J_{C_8,H_8} = 217.5 Hz, C-8), 145.32 (J_{C_4,H_8} = 12.9 Hz, J_{C_4,H_2} = 6.0 Hz, C-4), 148.24 (J_{C_6,H_2} = 5.6 Hz, C-6).

9-Benzyl-1-(2-fluorobenzyloxy)adenine, Perchloric Acid Salt (2s-2). UV λ_{max} 261 nm (13,800) at pH 1; 261 (13,800) at pH 7; 259 (14,000) at pH 13; MS (FAB) *m/e* 350 (M + 1); IR (KBr) 1684, 1620, 1580, 1514, 1490, 1455, 1415, 1100 (broad), 754, 697, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.49 (s, 4, OCH_2Ar, NCH_2Ar), 7.25-7.70 (m, 9, Ar-H), 8.70 (s, 1, H-8), 8.74 (s, 1, H-2), 9.73, 10.39 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 47.02 (NCH_2Ar), 74.84 ($J_{CH_2,F}$ = 2.6 Hz, OCH_2Ar), 115.48 (OCH_2Ar-C-3), 118.99 (J_{C_5,H_8} = 11.9 Hz, C-5), 119.42 ($J_{Ar_{C1}F}$ = 14.2 Hz, OCH_2Ar-C-1), 124.62 ($J_{Ar_{C5}F}$ = 3.3 Hz, CH_2Ar-C-5), 127.62 (NCH_2Ar-C-2,6), 128.09 (NCH_2Ar-C-4), 128.70 (NCH_2Ar-C-3,5), 132.48 ($J_{Ar_{C4}F}$ = 8.5 Hz, OCH_2Ar-C-4), 133.02 ($J_{Ar_{C6}F}$ = 2.8 Hz, OCH_2Ar-C-6), 135.62 (NCH_2Ar-C-1), 144.32 (J_{C_2,H_2} = 222.0 Hz, C-2), 144.87 (J_{C_8,H_8} = 217.0 Hz, C-8), 145.36 (C-4), 148.29 (J_{C_6,H_2} = 5.4 Hz, C-6), 161.06 ($J_{Ar_{C2}F}$ = 248.9 Hz, OCH_2Ar-C-2).

9-Benzyl-1-(3-fluorobenzyloxy)adenine, Perchloric Acid Salt (2s-3). UV λ_{max} 262 nm (13,700) at pH 1; 261 (13,900) at pH 7, 259 (13,900) at pH 13; MS (FAB) *m/e* 350 (M + 1); IR (KBr) 1692, 1672, 1510, 1456, 1100 (broad), 713, 702, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.40 (s, 2, OCH_2Ar), 5.50 (s, 2, NCH_2Ar), 7.30-7.61 (3 m, 9, Ar-H), 8.72 (s, 1, H-8), 8.98 (s, 1, H-2), 9.71, 10.38 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 47.05 (NCH_2Ar), 80.58 (OCH_2Ar), 116.53 ($J_{Ar_{C4}F}$ = 20.9 Hz, OCH_2Ar-C-4), 117.37 ($J_{Ar_{C2}F}$ = 21.7 Hz, OCH_2Ar-C-2), 119.00 (J_{C_5,H_8} = 12.0 Hz, C-5), 126.71 ($J_{Ar_{C6}F}$ = 2.6 Hz, OCH_2Ar-C-6), 127.70 (NCH_2Ar-C-2,6), 128.10 (NCH_2Ar-C-4), 128.70 (NCH_2Ar-C-3,5), 130.45 ($J_{Ar_{C5}F}$ = 8.2 Hz, OCH_2Ar-C-5), 134.35 ($J_{Ar_{C1}F}$ = 7.9 Hz, OCH_2Ar-C-1), 135.64 (NCH_2Ar-C-1), 144.67 (J_{C_2,H_2} = 222.0 Hz, C-2), 144.84 (J_{C_8,H_8} = 217.0 Hz, $J_{C_8Ar_1}$ = 4.1 Hz, C-8), 145.37 (J_{C_4,H_8} = 13.3 Hz, J_{C_4,H_2} = 6.0 Hz, C-4), 148.23 (J_{C_6,H_2} = 5.2 Hz, C-6), 161.85 ($J_{Ar_{C3}F}$ = 244.1 Hz, OCH_2Ar-C-3).

9-Benzyl-1-(4-fluorobenzyloxy)adenine, Perchloric Acid Salt (2s-4). UV λ_{max} 261 nm (13,000) at pH 1; 261 (13,000) at pH 7; 259 (13,500) at pH 13; MS (FAB) *m/e* 350 (M + 1); IR (KBr) 1692, 1615, 1600, 1575, 1513, 1495, 1425, 1355, 1228, 1162, 1100 (broad), 860, 845, 725, 710, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.39

(s, 2, OCH_2Ar), 5.51 (s, 2, NCH_2Ar), 7.34, 7.73 (2 m, 9, Ar-H), 8.72 (s, 1, H-8), 8.95 (s, 1, H-2), 9.70, 10.36 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 47.03 (NCH_2Ar), 80.68 (OCH_2Ar), 115.34 ($J_{Ar_{C3,C5}F}$ = 21.7 Hz, OCH_2Ar-C-3,5), 118.95 (J_{C_5,H_8} = 10.8 Hz, C-5), 127.67 (NCH_2Ar-C-2,6), 128.09 (NCH_2Ar-C-4), 128.69 (NCH_2Ar-C-3,5), 128.46 ($J_{Ar_{C1}F}$ = 2.9 Hz, OCH_2Ar-C-1), 133.30 ($J_{Ar_{C2,C4}F}$ = 8.7, OCH_2Ar-C-2,4), 135.62 (NCH_2Ar-C-1), 144.70 (J_{C_2,H_2} = 222.0 Hz, C-2), 144.81 (J_{C_8,H_8} = 217.0 Hz, $J_{C_8Ar_{C1}}$ = 4.5 Hz, C-8), 145.36 (J_{C_4,H_8} = 1.8 Hz, J_{C_4,H_2} = 5.2 Hz, $J_{C_4Ar_{C1}}$ = 3.1 Hz, C-4), 162.84 ($J_{Ar_{C4}F}$ = 246.8 Hz, OCH_2Ar-C-4).

9-Benzyl-1-ethoxyadenine, Perchloric Acid Salt (2t). UV λ_{max} 261 nm (12,500) at pH 1; 260 (12,700) at pH 7; 258 (13,100) at pH 13; MS (FAB) *m/e* 270 (M + 1); IR (KBr) 1701, 1620, 1515, 1455, 1425, 1415, 1225, 1100 broad, 1000, 735, 707, 650, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.43 (t, 3, OCH_2CH_3), 4.42 (q, 2, OCH_2CH_3), 5.51 (s, 2, CH_2Ar), 7.38 (m, 5, Ar-H), 8.71 (s, 1, H-8), 9.11 (s, 1, H-2), 9.56, 10.28 (br s, 2, H-$\overset{\oplus}{N}H_2$).

9-Methyl-1-(2-methylbenzyloxy)adenine, Perchloric Acid Salt (2u-2). UV λ_{max} 261 nm (12,400) at pH 1; 261 (12,000) at pH 7; 259 (12,300) at pH 13; MS (FAB) *m/e* 270 (M + 1); IR (KBr) 1689, 1526, 1410, 1100 (broad), 768, 749, 654, 622 cm^{-1}, ^1H NMR (Me_2SO-d_6) δ 2.46 (s, 3, CH_3Ar), 3.83 (s, 3, CH_3-9), 5.45 (s, 2, OCH_2Ar), 7.20-7.44 (3 m, 4, Ar-H), 8.49 (s, 1, H-2), 8.51 (s, 1, H-8), 9.71, 10.36 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 18.62 (Ar-CH_3), 30.15 (N^9-CH_3), 79.39 (CH_2), 118.67 (J_{C_5,H_8} = 12.5 Hz, C-5), 125.85 (Ar-C-5), 129.92 (Ar-C-4), 130.45 (Ar-C-1,3), 131.38 (Ar-C-6), 138.15 (Ar-C-2), 143.98 (J_{C_2,H_2} = 221.9 Hz, C-2), 145.57 (J_{C_8,H_8} = 216.7 Hz, J_{C_8,NCH_3} = 3.4 Hz, C-8), 145.68 (C-4), 148.04 (J_{C_6,H_2} = 5.3 Hz, C-6).

9-Methyl-1-(3-methylbenzyloxy)adenine, Perchloric Acid Salt (2u-3). UV λ_{max} 261 nm (12,300) at pH 1; 260 (12,700) at pH 7; 258 (12,800) at pH 13; MS (FAB) *m/e* 270 (M + 1); IR (KBr) 1686, 1525, 1410, 1385, 1230, 1100 (broad), 793, 692, 644, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.34 (s, 3, CH_3Ar), 3.83 (s, 3, CH_3-9), 5.37 (s, 2, OCH_2Ar), 7.28-7.42 (m, 3, Ar-H-4,5,6), 7.48 (s, 1, Ar-H-2), 8.50 (s, 1, H-8), 8.89 (s, 1, H-2), 9.64, 10.29 (2 br s, 2, H-$\overset{\oplus}{N}H_2$); ^{13}C NMR (Me_2SO-d_6) δ 20.78 ($ArCH_3$), 30.16 (CH_3-9), 81.63 (CH_2Ar), 118.55 (J_{C_5,H_8} = 11.5 Hz, C-5), 127.71, 128.30, 130.29, 131.22, 131.88 (Ar-C), 137.71 (Ar-C-3), 144.30 (J_{C_2,H_2} = 222.0 Hz, C-2), 145.54 (J_{C_8,H_8} = 216.6 Hz, $J_{C_8,9\text{-}CH_3}$ = 3.4 Hz, C-8), 145.71 (C-4), 148.00 (J_{C_6,H_2} = 5.1 Hz, C-6).

6-Methylamino-1-(3-methylbenzyloxy)-9-β-D-ribofuranosylpurine, Perchloric Acid Salt (2v-3). UV λ_{max} 263 nm (13,500) at pH 1; 263 (13,600) at pH 7; 261 (12,600) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR (KBr) 1662, 1595, 1509, 1425, 1350, 1220, 1100 (broad), 975, 870, 690, 665, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.35 (s, 3, CH_3Ar), 3.56 (s, 3, CH_3N), 3.56, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.0 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.48 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.10 (apparent t, 1, OH-5'), 5.43 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.47 (s, 2, OCH_2Ar), 5.62 (d, 1, $J_{2',2'\text{-OH}}$ = 6.0 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.27-7.47 (m, 4, Ar-H), 8.83 (s, 1, H-8), 8.95 (s, 1, H-2), 9.82 (br s, 1, CH_3NH); ^{13}C NMR (Me_2SO-d_6) δ 20.76 ($ArCH_3$), 31.32 (NCH_3), 60.78 (C-5'), 69.89 (C-3'), 74.41 (C-2'), 81.83 (CH_2Ar), 85.86 ($J_{C,H}$ = 170.63 Hz, C-1'), 119.15 (C-5), 127.68 (Ar-C-6), 128.33 (Ar-C-5), 130.35 (Ar-C-4), 131.16 (Ar-C-2), 131.78 (Ar-C-1), 137.75 (Ar-C-3), 142.21 (C-8), 145.05 (C-2), 146.14 (C-4), 146.76 (C-6).

6-Methylamino-1-(2-methylbenzyloxy)-9-β-D-ribofuranosylpurine, Perchloric Acid Salt (2v-2). UV λ_{max} 263 nm (12,900) at pH 1; 263 (13,200) at pH 7; 260 (11,700) at pH 13; MS (FAB) *m/e* 402 (M + 1); IR (KBr) 1667, 1595, 1505, 1425, 1100 (broad), 1020, 985, 895, 620 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.46 (s, 3, CH_3Ar), 3.59 (s, 3, CH_3N), 3.59, 3.68 (2 m, 2, $J_{4',5'a}$ = 3.8 Hz, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'), 3.98 (apparent q, 1, H-4'), 4.14 (apparent q, 1, $J_{3',4'}$ = 4.4 Hz, H-3'), 4.47 (apparent q, 1, $J_{2',3'}$ = 5.1 Hz, H-2'), 5.10 (apparent t, 1, OH-5'), 5.33 (apparent d, 1, OH-3'), 5.46 (s, 2, OCH_2Ar), 5.61 (apparent d, 1, $J_{2',2'\text{-OH}}$ = 5.9 Hz, OH-2'), 5.94 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.20-7.46 (3 m, 4, Ar-H), 8.62 (s, 1, H-2), 8.85 (s, 1, H-8), 9.89 (br s, 1, CH_3NH); ^{13}C NMR (Me_2SO-d_6) δ 18.61 ($ArCH_3$), 31.37 (NCH_3), 60.75 (C-5'), 69.87 (C-3'), 74.33 (C-2'), 79.60 (CH_2Ar), 85.84 (C-4'), 87.53 ($J_{C_1',H_1'}$ = 168.0 Hz, C-1'), 119.21 (C-5), 125.81 (Ar-C-5), 129.93 (Ar-C-4), 130.43 (Ar-C-1,3), 131.23 (Ar-C-6), 138.12 (Ar-C-2), 142.19 (C-8), 144.74 (C-2), 146.09 (C-4), 146.75 (C-6).

6-Methylamino-1-(2,4-difluorobenzyloxy)-9-β-D-ribofuranosylpurine, Perchloric Acid Salt (2w). UV λ_{max} 263 nm (14,400) at pH 1; 263 (14,300) at pH 7; 260 (12,600) at pH 13; MS (FAB) *m/e* 424 (M + 1); IR (KBr) 1671, 1595, 1510, 1505, 1100 (broad), 985, 860, 623 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.56 (s, 3, CH_3N), 3.56, 3.66 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 11.9 Hz, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.15 (apparent q, 1, $J_{3',4'}$ = 3.9 Hz, H-3'), 4.50 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.11 (apparent t, 1, $J_{5',5'\text{-OH}}$ = 5.2 Hz, OH-5'), 5.84 (apparent d, 1, $J_{3',3'\text{-OH}}$ = 5.2 Hz, OH-3'), 5.49 (s, 2, OCH_2Ar), 5.62 (d, 1, $J_{2',2'\text{-OH}}$ = 6.1 Hz, OH-2'), 5.96 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 7.23, 7.42 (2 m, 2, Ar-H-3,5), 7.73 (m, 1, Ar-H-6), 8.85 (apparent d, 2, H-8,2), 9.90 (br s, 1, CH_3NH); ^{13}C NMR (Me_2SO-d_6) δ 31.30 (NCH_3), 60.77 (C-5'), 69.88 (C-3'), 74.39 (C-2'), 74.46 (OCH_2Ar), 85.87 (C-4'), 87.59 ($J_{C,H}$ = 167.83 Hz, C-1'), 104.33 ($J_{C,F}$ = 21.17 Hz, Ar-C-3), 111.88 (J_{C_5,F_4} = 21.47 Hz, J_{C_5,F_2} = 3.10 Hz, Ar-C-5), 116.03 (J_{C_1,F_2} = 14.60 Hz, J_{C_1,F_4} = 3.48 Hz, Ar-C-1), 119.24 (C-5), 134.46 ($J_{C,F}$ = 10.36 Hz, $J_{C,F}$ = 4.38 Hz, Ar-C-6), 142.23 (C-8), 144.84 (C-2), 146.16 (C-4), 146.81 (C-6), 160.82 (J_{C_4,F_4} = 148.93 Hz, J_{C_4,F_2} = 12.25 Hz, Ar-C-4), 164.34 (J_{C_2,F_2} = 147.20 Hz, J_{C_2,F_4} = 12.50 Hz, Ar-C-2).

2,6-Diamino-1-(3-methylbenzyloxy)-9-β-D-ribofuranosylpurine, Perchloric Acid Salt (2x). UV λ_{max} 256 nm (10,900), 295 nm (9,200) at pH 1; 256 (11,200), 295 (9,300) at pH 7; 268 (16,000) at pH 13; MS (FAB) *m/e* 403 (M + 1); IR (KBr) 1696, 1644, 1634, 1594, 1420, 1100 (broad), 860, 624 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.30 (s, 3, CH_3Ar), 3.55, 3.64 (2 m, 2, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.1 Hz, $J_{5'a,5'b}$ = 12.0 Hz, H-5'). 3.91 (apparent q, 1, H-4'), 4.10 (apparent q, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.40 (apparent q, 1, $J_{2',3'}$ = 4.9 Hz, H-2'), 5.13 (apparent t, 1, OH-5'), 5.18-5.28 (2 m, 2, OCH_2Ar), 5.23 (apparent d, 1, OH-3'), 5.47 (apparent d, 1, OH-2'), 5.71 (d, 1, $J_{1',2'}$ = 5.8 Hz, H-1'), 7.22-7.43 (m, 4, Ar-H), 8.19 (br s, 2, NH_2-2), 8.35 (s, 1, H-8), 9.03, 9.81 (2 br s, 2, NH_2-6).

8-Bromo-1-(3-methylbenzyloxy)adenosine, Perchloric Acid Salt (2y). UV λ_{max} 265 nm (16,500) at pH 1; 264 (15,800) at pH 7; 260 (13,700) at pH 13; MS (FAB) *m/e* 466 (M + 1); IR (KBr) 1685, 1475, 1410, 1300, 1100 (broad), 985, 890, 880, 765, 623, 610 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.35 (s, 3, CH_3Ar), 3.51, 3.67 (2 m, 2, $J_{4',5'a}$ = 5.6 Hz, $J_{4',5'b}$ = 5.4 Hz, $J_{5'a,5'b}$ = 11.7 Hz, CH_2-5'), 3.96 (apparent q, 1, H-4'), 4.22

(apparent t, 1, $J_{3',4'}$ = 3.5 Hz, H-3'), 4.96 (t, 1, $J_{2',3'}$ = 5.3 Hz, H-2'), 5.36 (s, 2, OCH_2Ar), 5.90 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1'), 7.28-7.50 (m, 4, Ar-H), 9.01 (s, 1, H-2), 9.89, 10.57 (br s, 2, H-$\overset{\oplus}{N}$H); ^{13}C NMR (Me_2SO-d_6) δ 20.76 (CH_3), 61.51 (C-5'), 70.10 (C-3'), 71.31 (C-2'), 81.85 (CH_2Ar), 86.30 (C-4'), 90.65 ($J_{C,H}$ = 162.78 Hz, C-1'), 120.22 (C-5), 127.76 (Ar-C-6), 128.28 (Ar-C-5), 130.32 (Ar-C-2), 130.71 (C-8), 131.29 (Ar-C-4), 131.77 (Ar-C-3), 137.67 (Ar-C-1), 144.82 (C-2), 146.02 (C-4), 147.36 (C-6).

***p,p'*-Dicyanoterephthalanilide or [*N,N'*-Bis(4-cyanophenyl)-1,4-phenyldicarboxamide] (4).** Two grams of [2807-49-A*] (SRI-1W) (NSC D73449) were recrystallized from DMF, washed with EtOH, and dried: (D685-35-5D) 1.7 g; mp 320 °C cap; MS (FAB) *m/e* 367 (M + 1); IR (KBr) 2230, 1675, 1597, 1532, 1506, 1403, 1321, 1261, 845 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.84 (d, 4, H-3',3'',5',5''), 8.01 (d, 4, H-2',2'',6',6''), 8.10 (s, 4, H-2,3,5,6), 10.78 (s, 2, NH). *Anal.* Calcd for $C_{22}H_{14}N_4O_2 \cdot 0.25H_2O$: C, 71.25; H, 3.94; N, 15.20. Found: C, 71.30; H, 3.97; N, 15.20. *This sample was originally synthesized by Dr. J. L. Greene, Jr.

4',4''-Bis[5-methyl-1,4,5,6-tetrahydropyrimidin-2-yl]-2,5-pyridinedicarboxanilide, Dihydrochloride or *N,N'*-Bis-[4-(5-methyl-1,3,4,5-tetrahydropyrimidin-2-yl)phenyl]-2,5-pyridinedicarboxamide, Dihydrochloride (5). Compound 3377-133A* (SRI-89W) (NSC D84442) (2.6 g) was dissolved in hot water, filtered, cooled, and diluted with acetonitrile. The product was collected by filtration, washed with acetonitrile, and dried at 78 °C over P_2O_5: yield 1.9 g; mp >320 °C; MS (FAB) *m/e* 510 (M + 1); IR (KBr) 1675, 1643, 1614, 1597, 1516, 1465, 1415, 1390, 1328, 1310, 1284, 1260 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.05 (d, 6, CH_3), 2.11 (br s, 2, pyrimidin-H-5,5'), 3.12 (apparent q, 4, pyrimidin-H-4,4',6,6'), 3.56 (d d, 4, pyrimidin-H-4,4',6,6'), 7.84 (apparent q, 4, Ar-H-2',6',3'',5''), 8.10, 8.19 (d d, 4, Ar-H-3',5',2'',6''), 8.34 (d, 1, H-3), 8.68 (d d, 1, pyridyl-H-4), 9.32 (d, 1, pyridyl-H-6), 10.06 (s, 2, pyrimidin-H-3,3'), 11.19, 11.30 (2 s, 2, CONH). *Anal.* Calcd for $C_{29}H_{33}Cl_2N_7O_2 \cdot 0.5H_2O$: C, 58.01; H, 5.90; N, 16.63. Found: C, 58.02; H, 5.78; N, 16.61. *This sample was originally synthesized by Dr. J. L. Greene, Jr.

***N,N'*-Bis[4-(4,5-dihydro-4(or 5)-methyl-1H-imidazo-2-yl)phenyl]-1,4-cyclohexanedicarboxamide, dihydrochloride (6).** Compound (NSC D88689) (SRI-116W) [NB 3519-73*] (2.8 g) was dissolved in 175 mL hot water, filtered, cooled, and diluted wiht 175 mL acetonitrile. The first crop of crystals was only 1.05 g, so the volume acetonitrile was reduced under reduced pressure. About 500 mL of acetone was added and a second crop of 1.16 was obtained. The two crops were combined and recrystallized from 150 mL hot water. After crystallization was well established and the mixture had cooled, 400 mL of acetone was added. The product was collected and dried 20 h at 75 °C over P_2O_5: yield 2.05 g; mp 280 °C; MS (FAB) *m/e* 487 (M + 1); IR (KBr) 1680, 1605, 1575, 1511, 1350, 1325, 1305, 1260, 1170 cm^{-1}; ^{1}H NMR (D_2O) δ 1.14 (d, 6, CH_3), 1.31 (br t, 4, H-2,3,5,6 axial), 1.77 (d, 4, H-2,3,5,6-equatorial), 2.22 (br s, 2, Ar-H-1,4-axial), 3.37, 3.89 (q, t, 4, imidazoyl-H-5), 4.25 (s, 2, imidazoyl-H-1,4-axial), 7.48 (q, 8, Ar-H-2,2',3,3',5,5',6,6'). *Anal.* Calcd for $C_{28}H_{36}Cl_2N_6O_2 \cdot 1.75H_2O$: C, 56.90; H, 6.74; N, 14.22. Found: C, 56.92; H, 6.76; N, 14.21. *This sample was originally synthesized by Dr. J. L. Greene, Jr.

***N,N*-Bis[4-(5-hydroxy-1,4,5,6-tetrahydro-pyrimidin-2-yl)phenyl]-1,4-cyclohexanedicarboxamide, dihydrochloride (7).** Compound (NSC D87183) (SR1-95W) [NB-368-93A*], 2.9 g, was dissolved in 1600 mL of hot water, filtered, cooled, and acidified with 30-40 mL of 2 *N* HCl. The product was collected, washed with

2 *N* HCl and acetone. It was dried at 78 °C for 16 h over phosphorus pentoxide: yield, 2.75 g; mp ~260 °C; MS (FAB): *m/e* 519 (M + 1); IR (KBr) 1668, 1646, 1619, 1595, 1520, 1413, and 849 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.50 (apparent t, 4, H-2,3,5,6 axial), 1.96 (apparent d, 4, H-2,3,5,6 equatorial), 2.46 (br m, 2, H-1,4 axial), 3.33, 3.52 (2 d, 8, pyrimidyl-H-4′,4″,6′,6″ axial, 4′,4″,6′,6″ equatorial), 4.22 (apparent d, 2, pyrimidyl-H-5′,5″), 5.59 (d, 2, OH), 7.71, 7.85 (2 d, 8, H-2′,2″,3′,3″,5′,5″,6′,6″), 9.85 (s, 2, pyrimidyl-NH), 10.50 (s, 2, CON*H*). *Anal.* Calcd for $C_{28}H_{36}Cl_2N_6O_4 \cdot 2H_2O$: C, 53.59; H, 6.42; N, 13.39. Found: C, 53.46; H, 6.47; N, 13.22.

*This sample was originally synthesized by B. H. Smith, Jr.

***N,N′*-Bis[4-(4,5-dihydro-4(or 5)-methyl-1*H*-imidazol-2-yl)phenyl]-2,5-pyrazinedicarboxamide, Dihydrochloride (8).** Compound (NSC D93174) (SRI-125W) [NB-3693-55A*], 3.6 g, was dissolved in 75 mL hot water, charcoaled, filtered, cooled, and acidified with 2 *N* HCl. The product was collected, washed with 2*N* HCl and acetone, and dried at 78 °C for 16 h over phosphorus pentoxide: yield, 3.2 g; mp ~260 °C; MS (FAB): *m/e* 483 (M + 1); IR (KBr) 1692, 1613, 1570, 1515, 1326 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.39 (d, 6, CH_3), 3.57 (apparent q, 2, imidazolyl-H-5′,5″), 4.13 (apparent t, 2, imidazolyl-H-5′,5″), 4.46 (br s, 2, imidazolyl-H-4′,4″), 8.07 (2 d, 8, Ar-H), 9.43 (s, 2, pyrazinyl-H-3,6), 10.65 (br s, 2, CONH), 11.44 (s, 2, CON*H*). *Anal.* Calcd for $C_{26}H_{28}Cl_2N_8O_2 \cdot 2.25H_2O$: C, 52.39; H, 5.50; N, 18.80. Found: C, 52.39; H, 5.49; N, 18.81.

*This sample was originally synthesized by B. H. Smith, Jr.

***N,N′*-1,4-Butanediylbis[*N*-[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenyl]acetamide, Dihydrochloride (9).** Compound (NSC D93181) (SRI-133W) [NB 3887-63B*], 4.1 g, was dissolved in 13 mL 2 *N* HCl. The solution was slowly diluted alternately with acetone and water until a crystalline product formed from the mixture rather than an oil. A total volume of about 250 mL was used. The product was collected, washed with acetone, and dried 16 h at 78 °C *in vacuo* over phosphorus pentoxide: yield, 4.1 g; mp 191-195 °C, shrinks at 187 °C, MS (FAB): *m/e* 461 (M + 1), IR (KBr) 1664, 1613, 1513, 1394, 1368, 1284, 1185, and 680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.34 (br s, 4, CH_2-2,3), 1.83 (s, 6, CH_3), 3.22-3.40 (br s, H_2O), 3.65 (br s, 4, CH_2-1,4), 4.01 (s, 8, imidazolyl-H-4′,4′,4″,4″,5′,5′,5″,5″), 7.51 (apparent d, 4, H-2′,2″,6′,6″), 8.22 (apparent d, 4, H-3′,3″,5′,5″), 11.05 (br s, 2, N*H*). *Anal.* Calcd for $C_{26}H_{34}Cl_2N_6O_2 \cdot 2H_2O$: C, 54.82; H, 6.73; N, 14.76. Found: C, 54.65; H, 6.78; N, 14.72.

3,6-Diphenoxyhexahydro-1,2,4,5,3,6-tetraoxadiphosphorine (12). In an oven-dried 2-L round-bottomed 3-necked flask equipped with an addition funnel, drying tube, mechanical stirrer, and a thermometer was placed 900 mL of acetonitrile (dried over molecular sieves), 43 g (0.426 mol) of triethylamine, and 4.55 g (0.142 mol) of anhydrous hydrazine. The reaction solution was chilled to −20 °C and a solution of 30 g (0.142 mol) of phenyl dichlorophosphate in 200 mL of acetonitrile (M. S. dried) was added dropwise over 3 h with good stirring. The temperature was maintained at −20 to −15 °C during the addition and for one-half h more. The reaction was then stirred for 1 h at −10 °C. The reaction was then stirred in an ice bucket and reached 10 °C over 8 h. The reaction was stirred for 2 h at room temperature while the progress of the reaction was checked by thin-layer chromatography (TLC). The white precipitate was collected by filtration, washed with acetonitrile, and dried: 21.4 g product and triethylamine hydrochloride.

The dried mixture was suspended in water, the lumps were ground, and the insoluble material was collected, washed with water, and dried: 4.1 g (17%); mp about 240 °C cap. The crude product was recrystallized from ~350 mL hot methanol, filtered, allowed to cool slowly, chilled in the refrigerator, collected, and dried over phosphorus pentoxide, yield: 1.9 g (8%); mp 258-262 °C cap; IR (KBr) 1595, 1492, 1208, 1163, 1154, 1005, 972, 774, 767, 745, 685, 463 cm^{-1}; MS (electron-impact: direct-probe temperature, 20 °C) *m/e* 340 (M), 247 (M − OΦ); ^1H NMR (Me_2SO-d_6) δ 7.19, 7.36 (2 m, 10, phenyl), 7.49, 7.59 (2 s, 4, NH); ^{31}P NMR (Me_2SO-d_6) 17.6 ppm (referenced to external 85% H_3PO_4). *Anal.* Calcd for $C_{12}H_{14}N_4O_4P_2$: C, 42.36; H, 4.15; N, 16.47. Found: C, 42.43; H, 4.18; N, 16.46.

3,6-Diphenoxyhexahydro-1,2,4,5,3,6-tetraza diphosphorine 3,6-Disulfide[6] (14). In an oven-dried 500 mL round-bottomed 3-necked flask equipped with an addition funnel, drying tube, mechanical stirrer, and a thermometer was placed 250 mL of acetonitrile (dried over molecular sieves), 4.7 g (46.6 mmol) of triethylamine, and 0.50 g (15.5 mmol) of anhydrous hydrazine. The reaction was protected from atmospheric moisture with an argon atmosphere. The reaction solution was chilled to -20 °C and a solution of 3.3 g (0.016 mol) of phenyl dichloridothiophosphate in 20 mL of acetonitrile (molecular sieve) was added dropwise over 3 h with good stirring. The temperature was maintained at -20 to -15 °C during the addition and for one-half h more. The reaction was then stirred for 1 h at -10 °C and at room temperature overnight. After the reaction mixture was evaporated, the gummy white solid was treated with ~30 mL of ethyl acetate. The insoluble portion was removed by filtration and the filtrate evaporated to a glass, 3.0 g (56%). The glass was dissolved in ~10 mL of warm methanol, filtered, cooled, and the filtrate slowly diluted with water. As crystallization occurred more water was slowly added until a heavy precipitate had formed. The mixture was chilled and the product collected and dried: 2.2 g (41%); mp 174-177 °C cap cloudy melt, 184-186 °C clear melt.

The crude product was recrystallized from 15 mL methanol by adding 15 mL water. The product was collected, washed with water, and dried: 1.9 g (35%). The product was passed through a 50-g flash column of silica gel using 3:1 carbon tetrachloride-tetrahydrofuran. After two recrystallizations from ethyl acetate-hexane, an analytical sample was obtained, dried *in vacuo* over phosphorus pentoxide at 78 °C for 3 h: yield 1.1 g (20%); mp 193-200 °C cap; MS (EI) *m/e* 372 (M^+), 279 (372 - OPh); IR (KBr) 1590, 1488, 1196, 1160, 932, 901, 768, 703, 694, 686 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.21, 7.37 (2 m, 10, Ar-H); 7.76, 7.88 (2 d, 4, NH). *Anal.* Calcd for $C_{12}H_{14}N_4O_2P_2S_2$: C, 38.71; H, 3.79; N, 15.05. Found: C, 38.75; H, 3.89; N, 14.80.

1,5-Dimethyl-3,6-diphenoxyhexahydro-1,2,4,5,3,6-tetrazadiphosphorine 3,6-Disulfide[7,8] (17). In an oven dried apparatus consisting of a 1 L three-necked round-bottomed flask equipped with two addition funnels, a magnetic stirring bar, a reflux condenser, and a calcium sulfate drying tube was placed 12.2 g (0.121 mol) of triethylamine and 300 mL of molecular sieve (4A) dried ether. The reaction was conducted in an argon atmosphere. The triethylamine solution was heated to gentle reflux and solutions of 13.5 g (55 mmol) of phenyl 2,2'-dimethylphosphorodihydrazidothioate in 75 mL of dry ether and 12.5 g (55 mmol) of phenyldichlorothiophosphate in 75 mL of dry ether were added dropwise, simultaneously, over 3 h with good stirring. The reaction mixture was refluxed an additional 2 h before it was cooled and the precipitated triethylamine hydrochloride was removed by filtration. The filter cake was washed with ether and the filtrate (and washings) was evaporated at reduced pressure. The crude product was treated with 3:1 carbon

tetrachloride-tetrahydrofuran and passed through a flash column of 500 g of silica gel. The appropriate fractions, as indicated by TLC, were combined and evaporated.

Since TLC indicated some product was not dissolved and passed through the flash column, the residue was treated with 250 mL of ethyl acetate. The ethyl acetate solution was added to 50 g of silica gel and evaporated *in vacuo*. The silica gel was placed on top of a 200 g silica gel column and developed with 3:1 carbon tetrachloride-tetrahydrofuran. The fractions containing the product were combined, evaporated, and combined with the product fraction from the previous column by solution in toluene. The solution was filtered, cooled, and slowly diluted with hexane. Crystallization was induced by scratching. The product was collected, washed with hexane, and dried: yield 2.6 g (12%); mp 150-160 °C cap; MS (EI) *m/e* 400 (M^+), 307 (400 - OPh); IR (KBr) 1585, 1488, 1196, 1160, 1020, 938, 929, 905, 787, 768, 760, 690, 674 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.99 (apparent q, 6, CH_3 of 1,4-Me_2 II), 3.19 (apparent q, 6, CH_3 of 2,4-Me_2 I), 7.20 (m, 10, Ar), 7.40 (m, 10, Ar), 8.35 (d, 2, NH of 1,4-Me_2 II), 8.42 (d, 2, NH of 2,4-Me_2 I). *Anal.* Calcd for $C_{14}H_{18}N_4O_2P_2S_2 \cdot 0.010C_7H_8$: C, 42.63; H, 4.70; N, 13.53. Found: C, 42.56; H, 4.63; N, 13.55.

β-L-Threo-L-glycero-3-hexulofuranosonic Acid, 2-*C*-(5-Methyl-2-furanyl)-α-lactone (18). L-Ascorbic acid (24.2 g, 0.168 mol) was dissolved in 149.6 mL of distilled water that had been purged with nitrogen overnight. Freshly distilled 2-methyl-2,5-dimethoxy-2,5-dihydrofuran (25.03 g, 0.17 mol) was added dropwise with stirring over a period of approximately 1.5 h. After the addition was complete, the yellow reaction mixture was left stirring under nitrogen over the weekend. The yellow liquid was freeze-dried overnight. The brownish-yellow crude product was purified by shaking its ethyl acetate solution with neutral decolorizing carbon until a colorless solution resulted. After removal of the charcoal by filtration, the solvent was evaporated to dryness to give 9.97 g of powdered, amorphous solid, IR (KBr) 3600-3050 (s, broad, OH), 1795 (s, lactone CO), 1615 and 1550 (w, furan C=C) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.86 (br s, 1, OH-2), 6.43 (s, 1, OH-3), 6.34 (d, 1, H-3'), 6.04 (d, 1, H-4'), 5.58 (br s, 1, OH-5), 4.57 (s, 1, H-4), 4.33 (br s, 1, H-5), 4.20 (d d, 1, H-6, J = 6 Hz), 3.89 (d d, 1, 6 H, J = 3 Hz), 2.23 (s, 3, CH_3-5'); ^{13}C NMR (Me_2SO-d_6) 177.90 (C-1), 151.48 (C-5'), 148.31 (C-2'), 108.97 (C-4'), 106.84 (C03), 106.33 (C-3'), 87.47 (C-4), 77.49 (C-2), 74.48 (C-6), 73.44 (C-5), 13.16 (CH_3-5') ppm. *Anal.* Calcd for $C_{11}H_{12}O_7$: C, 51.70; H, 4.80. Found: C, 50.65; H, 5.12.

Succinic Anhydride Complex of β-L-Threo-L-glycero-3-hexulofuranosonic Acid, 2-*C*-(5-Methyl-2-furanyl)-α-lactone (19). Crude **18** (4 g, 0.016 mol) was dissolved in approximately 15 mL ethyl acetate. Recrystallized succinic anhydride (1.60 g, 0.016 mol) was added and the mixture was stirred under nitrogen and heated to reflux for 16 h. The homogeneous reaction mixture was allowed to cool to room temperature with stirring, the volume was reduced and the liquid chilled to facilitate precipitation. The mixture was allowed to return to room temperature whereupon the solid material was filtered and washed with cold ethyl acetate. The mother liquor was evaporated to dryness and the crystals were filtered and dried. The solid was recrystallized from chloroform-ethyl acetate to afford white needles (0.287 g); mp 131-134 °C; IR (KBr) 3700-3150 (broad, OH), 1789.11 (C=O), 1770.78 (anhydride); ^1H NMR (acetone-d_6) δ 6.41 (d, 1, H-3'), 6.02 (d, 1, H-4'), 4.76 (s, 1, H-4), 4.54 (t, 1, H-5, J = 3 Hz), 4.26 (d d, 1, H-6, J = 6 Hz), 4.11 (d d, 1, H-6, J = 3 Hz), 3.07 (s, 2, succinic anhydride CH_2), 2.26 (s, 3, CH_3-5'); ^{13}C NMR (Me_2SO-d_6) 172.93 (succinic anhydride), 172.99 (C-1), 151.50 (C-5'), 148.38 (C-2'), 108.99 (C-4'), 106.90 (C-3), 106.35 (C-3'), 87.51 (C-4), 77.54 (C-2),

74.52 (C-6), 73.50 (C-5), 28.68 (succinic anhydride CH_2), 13.202 (CH_3-5′). *Anal.* Calcd for $C_{26}H_{28}O_{17}$: C, 51.01; H, 4.72. Found: C, 50.61; H, 4.64.

Succinimide Complex of β-L-Threo-L-glycero-3-hexulofuranosonic Acid, 2-*C*-(5-Methyl-2-furanyl)-α-lactone (20). To a solution of crude **18** (3.00 g, 0.12 mol) in approximately 10 mL ethyl acetate was added 2.4 g (0.024 mol) succinimide and the mixture was stirred under nitrogen. After a few minutes, a white precipitate formed which redissolved upon heating. Solution was allowed to cool slowly to room temperature and the golden yellow liquid was refrigerated overnight. The crystals were filtered and washed with cold ethyl acetate and dried under a vacuum, and recrystallized from ethyl acetate-chloroform. Crystals from refrigerated mother liquor filtered, dried and recrystallized from ethyl acetate-chloroform to yield 0.745 g (11%) of long, white needles; mp 126-138 °C; IR (KBr) 3700-3025 (s, broad, OH), 1792 (s, lactone CO); ^{1}H NMR (acetone-d_6) δ 6.41 (d, 1, H-3′), 6.01 (d, 1, H-4′), 4.76 (s, 1, H-4), 4.53 (m, 1, H-5), 4.25 (d d, 1, H-6, J = 6 Hz), 4.11 (d d, 1, H-6, J = 3 Hz), 2.68 (s, 3, succinimide CH_2), 2.25 (s, 3 H, CH_3-5′)^{13}C NMR (Me_2SO-d_6) 179.21 (succinimide C=O), 172.93 (C-1), 515.52 (C-5′), 148.37 (C-2′), 109.91 (C-4′), 106.90 (C-3). 106.90 (C-3), 106.36 (C-3′), 87.50 (C-4), 77.54 (C-2), 74.54 (C-6), 73.50 (C-5), 29.42 (succinimide-CH_2), 13.19 (CH_3-5′). *Anal.* Calcd for $C_{26}H_{28}O_{17}$: C, 51.17; H, 4.93; N, 2.21. Found: C, 51.04; H, 5.02; N, 2.35.

2-Amino-5-methyl-1,3,4-selenadiazole[11] (24a). To a well stirred suspension of 5.5 g (39.9 mmol) of aminoselenosemicarbazide[12] in 40 mL of acetic acid and protected from atmospheric moisture by an argon atmosphere and a calcium sulfate drying tube was added 9.1 g (59.8 mmol) of phosphorus oxychloride over 20 min. The reaction mixture was stirred 1 h at room temperature and refluxed gently for 1 h. The reaction was then cooled and evaporated to dryness. The residue was suspended in 100 mL of water, made acidic with 10 mL of concentrated hydrochloric acid, and heated at reflux for 2 h. The reaction mixture was chilled in an ice bath and made basic with sodium hydroxide (6 *N*). The precipitate was collected, washed with water and dried. The residue was dissolved in 180 mL hot ethanol filtered, and diluted with ~250 mL of hexane. The product was collected, washed with hexane and dried: yield 3.4 g (53%); mp 227-228 °C cap dec; MS (EI) *m/e* 163 (M^+); IR (KBr) 1640, 1537, 1526, 1511, 1504, 1328, 1172 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.45 (s, 3, CH_3), 7.10 (s, 2, NH_2). *Anal.* Calcd for $C_3H_5N_3Se$: C, 22.23; H, 3.11; N, 25.93. Found: C, 22.56; H, 3.12; N, 26.00.

2-Amino-5-ethyl-1,3,4-selenadiazole[11] (24b). The 2-amino-5-ethyl-1,3,4-selenadiazole was prepared from 2.4 g (17.4 mmol) of aminoselenosemicarbazide, 20 mL of propionic acid, and 4.0 g (26.1 mmol) of phosphorus oxychloride by the procedure previously described for the 5-methyl derivative: yield 833 mg (27%); mp 201-202 °C cap, shiny platelets; MS (EI) *m/e* 177 (M^+); IR (KBr) 1632, 1517, 1501, 1326, 1010 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.21 (t, 3, CH_2CH_3), 2.80 (q, 2, CH_2CH_3), 7.13 (s, 2, NH_2). *Anal.* Calcd for $C_4H_7N_3Se$: C, 27.28; H, 4.01; N, 23.86. Found: C, 27.45; H, 4.12; N, 24.00.

2-Amino-5-phenyl-1,3,4-selenadiazole[11] (24c). The 2-amino-5-phenyl-1,3,4- selenadiazole was prepared from 3.0 g (21.7 mmol) of the aminoselenosemicarbazide, 2.65 g (21.7 mmol) of benzoic acid, and 8.3 g (54.3 mmol) of phosphorus oxychloride by the procedure previously described for the 5-methyl derivative. The thick paste was mixed with a mechanical stirrer. An analytical sample was obtained by recrystallizing the crude product from EtOH-H_2O: yield 950 mg (40%); mp 241-242 °C cap dec; MS (EI) *m/e* 225 (M^+), 183 (225 -

N=C-NH_2), 122 (225 - PhC=N), 103 (PhC=N); IR (KBr) 1630, 1507, 1473, 1255, 1040, 759, 692, 657 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.43 (m, 3, Ar-H-3',4',5'), 7.55 (s, 2, NH_2), 7.72 (apparent q, 2, Ar-H-2',6'). *Anal.* Calcd for $C_8H_7N_3Se$: C, 42.87; H, 3.15; N, 18.75. Found: C, 43.05; H, 3.28; N, 18.94.

2-Methyl-6-phenylimidazo[2,1-*b*]-1,3,4-selenadiazole[11] (25). The procedure of Lalezari and Shafiee was used with only slight modification. A mixture of 1.8 g (11.1 mmol) of 2-amino-5-methyl-1,3,4-selenadiazole, 1.7 g (11.1 mmol) of 2-chloroacetaphenone in 25 mL of 95% EtOH was refluxed gently. After 6 h reflux, TLC showed only a partial reaction. Triethylamine (1 mL, 7.2 mmol), was added and the reaction became less viscous. A second portion of Et_3N (1 mL, 7.2 mmol), was added and a brown solution was obtained. Heating was discontinued after 24 h even though some starting material remained. The reaction was evaporated to a gummy-yellow solid. The residue was dissolved in 50 mL of hot EtOH, filtered, cooled, and scratched to induce crystallization. The product was collected, washed with a little EtOH, and dried: yield 1.1 g (38%); mp 153-156 °C. An analytical sample was obtained by recrystallization from 10-15 mL hot EtOH: yield 875 mg (30%); mp 154-156 °C cap; MS (EI) *m/e* 263 (M^+), 222 (263 - CH_3C=N), 195 (263 - CH_3C=N-N=CH); IR (KBr) 1605, 1545, 1535, 1460, 1437, 1168, 740, 690, 680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.75 (s, 3, CH_3), 7.26 (t, 1, Ar-H-4'); 7.39 (t, 2, Ar-H-3',5'), 7.80 (d, 2, Ar-H-2',6'), 8.05 (s, 1, CH-5). *Anal.* Calcd for $C_{11}H_9N_3Se$: C, 50.39; H, 3.46; N, 16.03. Found: C, 50.48; H, 3.60; N, 16.02.

3-Nitroamino-1,2,4-triazole[13] (27a). Fuming nitric acid (d 1.52, 35 mL) was added slowly over 15 min to 3-amino-1,2,4-triazole (8.5 g, powder) at 0 °C with vigorous stirring. The reaction mixture was stirred further for 30 min at 10-20 °C and quenched by pouring it into ice-water. The solid was filtered and vacuum dried to afford pure product (10.1 g); mp 215-217 °C dec (lit. mp 215-217 °C); MS (EI) *m/e* 129 (M^+). UV λ_{max} (H_2O) 206 (550), 283 (1300); IR (KBr) 3490, 3450 (sh), 3260 (NH_2, $NHNO_2$, NH), 3150-2750 (C-H), 1580, 1540 (C=N), 1430, 1330, 1290, 1250, 1140, 1075, 1065, 1060, 1000, 965, 905 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 14.4-13.8 (br s, 1, NH, D_2O exchangeable), 8.5 (s, 1, CH), 3.7-3.1 (br s, 1, $NHNO_2$, D_2O exchangeable). *Anal.* Calcd for $C_2H_5N_5O_2 \cdot 0.5H_2O$): C, 17.39; H, 2.92; N, 50.73. Found: C, 17.66; H, 2.97; N, 51.17.

3-Nitroamino-5-phenyl-1,2,4-triazole (27b). Fuming nitric acid (d = 1.52, 9.7 mL) was added slowly over 15 min to 3-amino-5-phenyl-1,2,4-triazole (31) (4.45 g) at 0 °C. The reaction mixture was stirred further for 30 min at 10-20 °C and quenched by pouring it into ice-water. The solid was filtered, dried, and crystallized from water (4.85 g); mp 183-185 °C dec; MS (EI) *m/e* 205 ($M^{+\cdot}$); IR (KBr) 3420, 3100, 2975 (br s, NH, $NHNO_2$, C-H), 1617 (C=N), 1601, 1583 (aromatic), 1553, 1514, 1486, 1425, 1305, 1229 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 14.6-14.2 (br s, 1, NH), 8.05-7.9 (m, 2, *o*-Ar-H), 7.6-7.55 (m, 3, *m*-,*p*-Ar-H), 7.7-7.2 (br s, 1, $NHNO_2$); ^{13}C NMR (Me_2SO-d_6) 153.2 (C-3), 148.4 (C-5), 131.1 (C-4'), 129.1 (C-3',5'), 126.0 (C-2',6'), 125.0 (C-1'). *Anal.* Calcd for $C_8H_7N_5O_2 \cdot 0.2H_2O$: C, 46.02; H, 3.57; N, 33.55. Found: C, 45.96; H, 3.58; N, 33.62.

3-Methyl-5-nitroamino-1,2,4-triazole[17,18] (27c). A solution of 1-acetamido-3-nitroguanidine (18.7 g) and sodium carbonate (13 g) in water (180 mL) was heated for 25 min. It was then cooled, acidified with conc. HCl, and refrigerated overnight. The product was filtered, washed with cold water, and dried (22 g). A portion was recrystallized from water; mp 203-205 °C dec; MS (EI) 143 (M^+); IR (KBr) 3450, 3205, 3075 (NH), 2972, 2850 (CH), 1614 (C=N), 1572, 1496, 1445, 1380, 1370, 1338, 1300, 1248, 1100, 1090, 1025, 1010,

994 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 14.0-13.4 (NH), 3.6-3.1 (NH), 2.3 (s, 3 H, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 152.5 (C-5), 147.7 (C-3), 11.0 (CH_3). *Anal.* Calcd for $C_3H_5N_5O_2 \cdot 0.5H_2O$: C, 23.68; H, 3.98; N, 46.05. Found: C, 23.77; H, 3.85; N, 46.11.

3-Hydrazino-1,2,4-triazole hydrochloride[14] (28a). 3-Nitroamino-1,2,4-triazole (10 g) and activated zinc dust (20 g) were moistened with water and ground to a paste. The paste was suspended in water (50 mL) at 10 °C and treated with 50% aqueous acetic acid (100 mL) over 2 h, the temperature being maintained at 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess of zinc was filtered and the filtrate saturated with hydrogen sulfide (2 h). After removal of zinc sulfide the filtrate and washings were treated with 10 *N* hydrochloric acid. Evaporation of the solvent and boiled with chloroform (5-10 mL, 30 min). Desired product (5.23 g) separated upon addition of absolute ethanol (25 mL). MS (EI) *m/e* 99 (M^+); IR (KBr) 3340, 3300-2700 (NH, $NHNH_2$ and C-H), 1650 (broad, C=N), 1580, 1530, 1360, 1300, 1275, 1215, 1130, 1060, 1030, 950 cm^{-1}. (This compound was not stable to storage and was used as is for the next step.)

3-Amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (29a). A solution of 3-hydrazino-*s*-triazole hydrochloride (4.4 g) and cyanogen bromide (3.43 g) in aqueous methanol (132 mL, 85%) was refluxed for 48 h. The solvent was removed by evaporation, the solid residue was dissolved in water (12 mL), and the solution was neutralized with sodium acetate, giving a solid precipitate. The product was crystallized from water (2.4 g); mp 260 °C dec (lit.[15] 260 °C); MS (EI) *m/e* 124 (M^+); IR (KBr) 3340, 3190, 3150-2600 (broad, NH, NH_2, and C-H), 1660, 1630, 1600 (C=N), 1510, 1460, 1400, 1375, 1275, 1245, 1190, 1180, 1160, 1030, 980, 905 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.05 (s, 1, NH, D_2O exchangeable), 7.95 (s, 1, C-H), 6.5 (s, 2, NH_2, D_2O exchangeable). *Anal.* Calcd for $C_3H_4N_6$: C, 29.03; H, 3.25; N, 67.72. Found: C, 28.92; H, 3.29; N, 67.96.

3-Amino-6-phenyl-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole, hydrobromide[13-15] (29b). 3-Nitroamino-5-phenyl-1,2,4-triazole (8.6 g) and activated zinc dust (10.77 g) were moistened with water and ground to a paste. The paste was suspended in water (27 mL) at 10 °C and treated with 50% aqueous acetic acid (54 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide for 2 h. After removal of zinc sulfide, the filtrate and washings were treated with 10 *N* HCl. The hydrazino compound obtained (4.1 g) was refluxed with cyanogen bromide (1.87 g) in 85% aqueous methanol (72 mL) for 48 h. The solvent was removed by evaporation, and the solid residue was dissolved in water and neutralized with sodium acetate, giving a solid precipitate. The product was recrystallized from water and treated with one equivalent of hydrobromic acid, giving a pure product (1.45 g); mp 263-265 °C dec; MS (EI) *m/e* 200 (M^+); IR (KBr) 3450-2400 (broad, NH, NH_2, CH, HBr), 1698, 1672, 1600, 1535, 1500, 1475, 1445, 1435, 1375, 1290 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.0-9.0 (broad, NH, NH_2 and H^+), 8.2-8.0 (m, 2, *o*-Ar-H), 7.75-7.60 (m, 3, *p*-,*m*-Ar-H); ^{13}C NMR (Me_2SO-d_6) δ 160.4 (C-6), 150.7 (C-8), 141.2 (C-3), 131.7 (C-4'), 129.1 (C-3',5'), 126.6 (C-2',6') and 126.4 (C-1'). *Anal.* Calcd for $C_9H_8N_6 \cdot HBr$: C, 38.45; H, 3.23; N, 29.90. Found: 38.35; H, 3.57; N, 29.63%.

3-Amino-6-methyl-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole, Hydrobromide[13-15] (29c). 3-Methyl-5-nitroamino-1,2,4-triazole (5.37 g) and activated zinc dust (9.6 g) were moistened with water and ground to a paste. The paste

was suspended in water (24 mL) at 10 °C and treated with 50% aqueous acetic acid (48 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide (2 h). After removal of zinc sulfide, the filtrate and washings were treated with 10 *N* HCl. 3-Methyl-5-hydrazino-1,2,4-triazole hydrochloride (4.7 g) was obtained by evaporation of the solvent. This compound was treated with cyanogen bromide (3.33 g) in 85% aqueous methanol (128 mL) and was refluxed for 48 h. The solvent was removed by evaporation, and the solid residue was dissolved in water and neutralized with sodium acetate, giving a solid precipitate. The product was crystallized from water (560 mg) and treated with one equivalent of hydrobromic acid, giving a pure product, 0.75 g; mp 256-261 °C dec; MS (EI) *m/e* 138 (M^+); IR (KBr) 3270, 3228, 3187 (NH, NH_2), 3082 (C-H), 1701, 1665, 1610, 1570, 1500, 1430, 1390, 1363, 1346, 1165 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.3-12.0 (br s, 1, NH), 9.1-7.8 (br s, 2, NH_2) and 2.5 (s, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 159.2 (C-6), 148.9 (C-8), 140.8 (C-3) and 12.8 (CH_3). *Anal.* Calcd for $C_4H_6N_6 \cdot HBr$: C, 21.93; H, 3.22; N, 38.37. Found: C, 22.16; H, 3.39; N, 38.39.

Benzamidoguanidine (30). Freshly distilled benzoyl chloride (30 mL) was added dropwise to a well stirred solution of aminoguanidine hydrogen carbonate (30 g) in dry pyridine (250 mL) at 0 °C. The reaction mixture was further stirred at room temperature for 12 h, and the solvent removed under reduced pressure. The residue was treated with water (250 mL) and made strongly alkaline with 10 *N* sodium hydroxide. The solid was filtered and dried (10.46 g), mp 180-182 °C; MS (EI) *m/e* 178 (M^+).

3-Amino-5-phenyl-1,2,4-triazole (31). Benzamidoguanidine (30) (22.38 g) was heated in an oil bath at 220 °C for 5 min. The residue was crystallized from water, giving colorless silky needles (18 g); mp 183-185 °C (dec); MS (EI) *m/e* 160 (M^+); IR (KBr) 3350 (NH_2), 3250-2800 (NH, CH), 1665, 1640 (C=N), 1610, 1600, 1580 (aromatic), 1535, 1525, 1495, 1465, 1445, 1430, 1400 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.1-12.0 (s, 1, NH), 7.9 (d, 2, *o*-Ar-H) 7.5-7.3 (m, 3, *m*-,*p*-Ar-H), 6.2-5.9 (br s, 2, NH_2); ^{13}C NMR (Me_2SO-d_6) δ 153.5 (C-3), 150.1 (C-5), 130.7 (C-4'), 129.1 (C-3',5'), 126.2 (C-1'), 125.9 (C-2',6'). *Anal.* Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.07; H, 5.40; N, 35.02.

Nitroaminoguanidine[17,18] (33). Into a two liter flask equipped with a stirrer, dropping funnel, and thermometer was placed 52 g (0.5 mol) of nitroguanidine and one liter of distilled water at 60-65 °C. To the well agitated slurry was added dropwise, 32 g (0.55 mol) of 87% hydrazine monohydrate in 500 mL of water over one hour. The temperature was maintained at 55-60 °C for an additional 15 min, and then it was cooled to below 45 °C and neutralized with conc. HCl. The solution obtained from the reaction was refrigerated overnight, and the resulting solid product was filtered and dried (26.9 g); mp 170-172 °C; MS (FAB) 120 (M + 1); IR (KBr) 3432, 3400, 3322, 3220 (NH, NH_2), 1669, 1618, 1580, 1510, 1410, 1356, 1294, 1171 cm^{-1}. *Anal.* Calcd for $CH_5N_5O_2$: C, 10.08; H, 4.23; N, 58.82. Found: C, 10.17; H, 4.25; N, 58.73.

1-Acetamido-3-nitroguanidine[17,18] (34). A solution of nitroaminoguanidine (31 g), glacial acetic acid (78 mL), and acetic anhydride (26 mL) was heated for 2 h at 85-90 °C, cooled, and diluted with large excess of diethyl ether. The resulting precipitate was filtered and washed with ether. The yield of dried product was 24.7 g. A portion was recrystallized from water, mp 187-189 °C; MS (FAB) 162 (M + 1); IR (KBr) 3387, 3242 (broad), 3075, 3025 (NH), 2925 (CH), 1702 (CO), 1635 (C=N), 1587, 1525, 1425, 1390, 1373, 1300

(broad), 1197, 1040 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.95-8.1 (br s, 4, NH) and 1.9 (s, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 169.5 (C=O), 161.0 (C=NH) and 20.7 (CH_3). *Anal.* Calcd for $C_3H_7N_5O_3$: C, 22.36; H, 4.38; N, 43.47. Found: C, 22.42; H, 4.42; N, 43.11.

Triaminoguanidine Hydrochloride (35). Aminoguanidine bicarbonate (34 g) was suspended in 2 *N* HCl (63 mL), and conc. HCl was added with stirring until acidification was complete. The mixture was filtered, and the filtrate was concentrated, giving a residue which was dissolved in 125 mL boiling ethanol and heated with 32 mL of hydrazine hydrate for 4-5 h on a water bath. The reaction mixture was cooled, and the resulting precipitate was filtered and washed with methanol. It was crystallized from 2% HCl in ethanol (11.1 g); mp 228-229 °C dec (lit.[17] 231 °C dec); MS (EI) *m/e* 104 (M^+); IR (KBr) 3400-2200 ($NHNH_2$, NH_2, HCl), 2060, 1940, 1810, 1680 (C=N), 1480, 1090 cm^{-1}. *Anal.* Calcd for $CH_8N_6 \cdot HCl$: C, 8.54; H, 6.45; N, 59.79. Found: C, 8.78; H, 6.42; N, 59.73.

4-Amino-3-hydrazino-5-methyl-*s*-triazole dihydrochloride[19] (36). Triaminoguanidine hydrochloride (14.0 g) was refluxed with acetic acid (20 mL) for 2.5 h. The solution was cooled, conc. HCl (70 mL) was added, and the mixture was warmed on a water bath for 30 min. The reaction mixture was cooled and allowed to stand for several hours at 0 °C, and then the solid was filtered and crystallized from water (16.41 g); mp 218-220 °C dec; MS (EI) *m/e* 128 (M^+); IR (KBr) 3400-2300 (broad, NH_2, $NHNH_2$, HCl, CH), 1651, 1635, 1610 (C=N); ^1H NMR (Me_2SO-d_6) δ 9.5-6.0 (br s, NH_2, $NHNH_2$, H^+), 2.5 (s, CH_3); ^{13}C NMR (D_2O, dioxane as internal reference) δ 153.6 (C-5), 153.5 (C-3), 9.4 (CH_3). [Note: Compound **36** was found to decompose in dimethyl sulfoxide to 4-amino-5-methyl-1,2,4-triazole]. *Anal.* Calcd for $C_3H_8N_6 \cdot 2HCl$: C, 17.91; H, 5.01; N, 41.80. Found: C, 17.80; H, 5.02; N, 41.32.

3,7-Diamino-6-methyl-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole[15] (37). A solution of **36** (9.23 g) and cyanogen bromide (6.7 g) in aqueous methanol (235 mL, 85%) was refluxed for 48 h. The solvent was removed by evaporation, the solid residue was dissolved in water, and the solution was neutralized with sodium acetate. A precipitate was obtained which was filtered and crystallized from water (4.4 g); mp 260-265 °C dec; MS (EI) *m/e* 153 (M^+); IR (KBr) 3301, 3195, 3109 (N-NH_2, C-NH_2, C-H), 1644, 1631 (C=N), 1580, 1554, 1390, 1360 cm^{-1}; ^1H NMR (D_2O + DSS) δ 2.45 (s, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 159.849 (C-6), 148.9 (C-8), 142.1 (C-3), 10.6 (CH_3). *Anal.* Calcd for $C_4H_7N_7$: C, 31.37; H, 4.61; N, 64.03. Found: C, 31.39; H, 4.69; N, 64.08.

7-Amino-6-methyl-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole-3-thiol[15] (38). A solution of 4-amino-3-hydrazino-5-methyl-*s*-triazole dihydrochloride (6.2 g) and potassium hydroxide (5.4 g) in 70% aqueous ethanol (150 mL) was refluxed with carbon disulfide (25 mL) for 30 h. The solvent was removed and the residue was dissolved in water (25 mL). The solution was acidified (pH 3) by addition of conc. HCl. The pale yellow solid obtained was filtered and recrystallized from water, 2.0 g; mp 203-205 °C dec; MS (EI) *m/e* 170 (M^+); IR (KBr) 3425 (H_2O), 3259, 3237, 3151, 3098, 3015, 2985, 2945, 2900, 2790, 1645, 1619, 1555, 1513, 1455, 1443, 1405, 1325, 1289, 1255, 1185, 1014 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.5 (s, 1, SH), 6.3-5.5 (bs, 2, NH_2) and 2.4 (s, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 159.4 (C-6), 154.8 (C-3), 149.5 (C-8) and 10.5 (CH_3). *Anal.* Calcd for $C_4H_6N_6S \cdot H_2O$: C, 25.52; H, 4.28; N, 44.66. Found: C, 25.59; H, 4.30; N, 44.70.

3,6,7-Triamino-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole[15] (39). A solution of triaminoguanidine hydrochloride (14.06 g, 0.1 mol) and cyanogen bromide (21.2 g, 0.2 mol) in aqueous methanol (405 mL, 85%) was refluxed for 48

h. The solvent was removed by evaporation, and the resulting solid was taken up in water and neutralized with sodium acetate. The precipitate was filtered and crystallized from water (8.08 g), mp 285-288 °C dec; MS (EI) *m/e* 154 (M^+); IR (KBr) 3402, 3257, 3222, 3168, 3114 (N-NH_2, C-NH_2), 1691, 1679, 1647, 1615, 1518 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 160.0 (C-6), 147.2 (C-8), 141.0 (C-3). *Anal.* Calcd for $C_3H_6N_8 \cdot HBr$: C, 15.33; H, 3.00; N, 47.68. Found: C, 15.54; H, 3.05; N, 48.07.

4-Amino-3-hydrazino-*s*-triazole Dihydrochloride[19] (40). Triaminoguanidine hydrochloride (21.74 g) was heated at reflux with 85% formic acid (32 mL) for 30 min. The solution was cooled, conc. HCl (120 mL) was added, and the mixture was warmed for 30 min. The reaction mixture was cooled and allowed to stand overnight at 0 °C. The resulting solid was filtered and crystallized from water (29 g); mp 215-217 °C; MS (EI) *m/e* 114 (M^+); IR (KBr) 3350 (NH_2), 3300-2050 (broad, $NHNH_2$, 2 HCl, CH), 2000, 1645, 1600, 1525, 1510, 1430, 1315, 1210, 1060 cm^{-1}; ^{13}C NMR (80% H_2O, 20% D_2O, dioxane as internal reference) δ 153.3 (C-3) and 143.5 (C-5). [Note: Compound **40** was found to decompose in dimethyl sulfoxide to 4-amino-1,2,4-triazole.] *Anal.* Calcd for $C_2H_6N_6 \cdot 2HCl$: C, 12.84; H, 4.31; N, 44.94. Found: C, 12.95; H, 4.33; N, 44.76.

7-Amino-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole 3-thiol[15] (41). A solution of 4-amino-3-hydrazino-*s*-triazole dihydrochloride (5.5 g) and potassium hydroxide (5.4 g) in 70% aqueous ethanol (150 mL) was refluxed with carbon disulfide (25 mL) for 30 h. The solvent was removed and the residue was dissolved in water (25 mL). The solution was acidified (pH 3) by addition of conc. HCl. The pale yellow solid obtained was filtered and recrystallized from water, 1.7 g; mp 165-166 °C dec; MS (EI) *m/e* 156 (M^+); IR (KBr) 3240, 3220, 3155, 3135, 3112, 3010, 2940, 2911, 2860, 2810, 2750, 1636, 1607, 1493, 1430, 1387, 1330, 1275, 1240, 1215, 1155, 1075, 1030, 997 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.6 (s, 1, SH), 8. (s, 1, CH), 6.3-6.1 (br s, 2, NH_2); ^{13}C NMR (Me_2SO-d_6) δ 155.5 (C-3), 151.0 (C-6), 148.9 (C-8). *Anal* Calcd for $C_3H_4N_6S$: C, 23.07; H, 2.58; N, 53.82. Found: C, 23.11; H, 2.69; N, 53.37.

3,7-Diacetamido-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (42). 3,7-Diamino-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazolo (5.0 g) was stirred with acetic anhydride (150 mL) at room temperature for 3 days. The solid obtained was filtered, washed with diethyl ether and dried (2.45 g). Further purified by crystallizing from water; mp 220-224 °C; MS (EI) 223 (M); UV λ_{max} 238 (5800); IR (KBr) 3216, 3194 (NH), 3040, 2980 (CH), 1700, 1683 (C=O), 1615, 1564, 1531, 1505, 1440, 1380, 1263, 1245, 1180 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.7-11.55 (s, 1, NH), 10.75-10.6 (s, 1, NH), 8.8 (s, 1, CH), 2.1 (s, 6, CH_3); ^{13}C NMR (Me_2SO-d_6) 169.4 (CO), 169.3 (CO), 149.9 (C-8, $^3J_{CH}$ = 4.0 Hz), 149.2 (C-6, $^1J_{CH}$ = 221.3 Hz), 135.4 (C-3), 22.2 (CH_3), 20.1 (CH_3). *Anal.* Calcd for $C_7H_9N_7O_2$: C, 37.66; H, 4.06; N, 43.94. Found: C, 37.71; H, 4.09; N, 43.88.

3-Acetamido-7-amino-6-methyl-7*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (43). 3,7-Diamino-6-methyl-7*H*-*s*-triazolo-[5,1-*c*]-*s*-triazole (2.0 g) was stirred with acetic anhydride (100 mL) at room temperature for 3 days. The solid obtained was filtered, washed with diethyl ether and dried. Further purified by crystallizing from water (1.89 g); mp 239-241 °C dec; MS (EI) 195 (M); IR (KBr) 3320, 3280 (NH_2) 3102 (NH), 2965, 2925, 2850, 2750 (CH), 1708 (C=O), 1635, 1617 1579, 1558, 1425, 1405, 1373, 1270, 1250, 1215, 1035, 860, 775, 715, 675, 655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.55-10.4 (br s, 1, NH), 6.0 (s, 2, NH_2), 2.35 (s, 3, CCH_3), 2.05 (s, 3, $COCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 169.4 (CO), 158.0 (C-6), 152.5 (C-8), 134.3 (C-3), 22.2 ($COCH_3$), 10.4 (CCH_3). *Anal.* Calcd for $C_6H_9N_7O$: C, 36.91; H, 4.65; N, 50.24. Found: C, 36.93; H, 4.77; N, 50.08.

7-*N*-(6-Methyl-3-methylthio-7*H*-*s*-triazolo[5,1-*c*]triazolyl)dithiocarbamate (44). A solution of 4-amino-3-hydrazino-5-methyltriazole dihydrochloride (12.4 g) and potassium hydroxide (10.8 g) in 70% aqueous ethanol (300 mL) was refluxed with carbon disulfide (50 mL) for 38 h. The solvent was removed and the residue was dissolved in water (50 mL). The solution was acidified to pH 3 by addition of conc. HCl. The pale yellow solid obtained was filtered and recrystallized from water. This thiol (11.53 g) was refluxed in methanol (150 mL) in the presence of equimolar quantities of sodium hydroxide (2.98 g) and methyl iodide (4.7 mL) for 2 h. Partial evaporation of the solvent and dilution with water precipitated the desired product. Pure methylthio derivative was obtained by crystallizing twice from water, followed by silica gel column filtration (eluted with 10% methanol in chloroform), 3.0 g, mp 186-189 °C; MS (EI) 260 (M); UV λ_{max} 321 (12,600), 228 (10,100) at pH 1; 320 (13,000), 228 (10,700) at pH 7; 320 (10,800) at pH 13; IR (KBr) 3219, 3102, 3015, 2925 (NH, CS_2H, CH), 1660, 1542, 1527 (thioureido band), 1480, 1306, 1254, 1169, 1045 (CS_2H), 816 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.15-5.9 (br s, NH, SH, H_2O), 2.65 (s, 3, SCH_3), 2.4 (s, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) 188.8 (CS_2H), 159.1 (C-3, $^3J_{CH}$ = 5.5 Hz), 153.5 (C-6, $^2J_{CH}$ = 7.3 Hz), 145.9 (C-8), 15.2 (SCH_3, $^1J_{CH}$ = 143.6 Hz), 9.95 (CH_3, $^1J_{CH}$ = 130.4 Hz). *Anal.* Calcd for $C_6H_8N_6S_3 \cdot 0.2H_2O$: C, 27.30; H, 3.21; N, 31.85; S, 36.44. Found: C, 27.16; H, 3.02; N, 31.78; S, 36.32.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyltriazolotriazoles (45, 47, and 49). 3-Amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole[13,14] (23, 6.97 g) was suspended in a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (28.35 g) in anhydrous acetonitrile (915 mL). Stannic chloride (14.7 mL) was added slowly at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. It was then concentrated to a small volume and saturated sodium bicarbonate was added until the vigorous evolution of carbon dioxide had ceased. The mixture was evaporated under reduced pressure and the residual gum was extracted several times with hot chloroform. The combined extracts were dried and concentrated. Thin-layer chromatographic analysis of this crude product (silica gel, chloroform-methanol, 9:1 v/v) showed four products with Rf values of 0.45, 0.81, and 0.9 along with unchanged and decomposed sugar derivatives (Rf 0.97). The mixture was applied to a column of silica gel and eluted with chloroform followed by 1%, 2%, and 3% methanol in chloroform. The three products were separated and further purified by repeating the silica gel column chromatography. A fourth product was isolated from the chromatographic purification of the fraction containing compound **50**, when the solvent system was changed to cyclohexane-ethyl acetate, 1:1. Structures of these compounds were assigned on the basis of spectral data as follows:

3-Imino-2*H*-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (45). The above cited compound with Rf 0.45, yield 9.46 g (30 %); mp 125-127 °C; MS (FAB) *m/e* 569 (M + 1); UV λ_{max} 234 (39,400), shoulder at 280 (3200) at pH 1; 236 (33,000), shoulder at 276 (17,300) at pH 7; 225 (29,300), 276 (8600) at pH 13; IR (KBr) 3500-2500 (broad NH, NH, CH), 1727 (C=O), 1666 (C=N), 1615, 1602 (aromatic), 1585, 1475, 1450, 1315, 1267, 1200, 1175, 1116, 1093, 1070, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1-7.8 and 7.6-7.1 (m, 18, NH, NH, H-6, and benzoyl), 6.35 (d, 1, $J_{1',2'}$ = 1.7 Hz, H-1'), 6.25 (d d, 1, $J_{2',3'}$ = 5.2 Hz, H-2'), 6.19 (d d, 1, $J_{3',4'}$ = 6.8 Hz, H-3'), 4.92-4.82 (m, 1, $J_{4',5'_a}$ = 5.2 Hz, $J_{4',5'_b}$ = 3.6 Hz, H-4'), 4.82-4.77 (d, 1, H-5'b), 4.74-4.65 (d d, 1, $J_{5'_a,5'_b}$ = 12.1 Hz, H-5'a); ^{13}C NMR ($CDCl_3$) δ 166.3, 165.2, 165.1 (C=O), 160.3 (C-6, $^1J_{C\text{-}6,H}$ = 202.6 Hz), 160.1 (C-8, $J_{C\text{-}8,H}$ = 4.4 Hz), 138.3 (C-3), 133.7, 133.4, 133.0, 129.7, 129.64,

129.6, 129.2, 128.6, 128.43, 128.4, 128.39 (aromatic carbons), 88.8 (C-1', $^1J_{C\text{-}1',H}$ = 167.8 Hz), 80.4 (C-4'), 75.3 (C-2'), 71.7 (C-3'), 63.9 (C-5'). *Anal.* Calcd for $C_{29}H_{24}N_6O_7 \cdot H_2O$: C, 59.34; H, 4.47; N, 14.32. Found: C, 59.12; H, 4.42; N, 14.50.

3-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (47). The above cited compound with Rf 0.9, yield 2.34 g (7.3 %); mp 86-87 °C; MS (FAB) *m/e* 569 (M + 1); UV λ_{max} 239 (30,500), shoulder at 280 (13,300) at pH 1; 240 (30,700), shoulder at 280 (13,300) at pH 7; 229 (27,700), shoulder at 275 (2200) at pH 13; IR (KBr) 3425, 3335 (NH_2), 3175, 3065 (CH), 1727 (C=O), 1655 (C=N), 1600, 1570 (aromatic), 1452, 1317, 1269, 1175, 1160, 1121, 1096, 1070, 1025, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15-7.25 (m, 16, H-6 and benzoyl), 6.31 (d, 1, $J_{1',2'}$ = 3.86 Hz, H-1'), 6.28 (d d, 1, $J_{2',3'}$ = 5.32 Hz, H-2'), 6.15 (d d, 1, $J_{3',4'}$ = 5.31 Hz, H-3'), 4.88-4.5 (m, 3, H-4',5'); ^{13}C NMR ($CDCl_3$) δ 166.1, 165.2, 165.0 (C=O), 158.3 (C-6, $^1J_{CH}$ = 207.4 Hz), 156.0 (C-8, $^3J_{CH}$ = 9.8 Hz), 140.9 (C-3), 133.6, 133.5, 133.0, 129.8, 129.77, 129.6, 128.8, 128.7, 128.4, 128.37, 128.3 (aromatic), 88.5 (C-1'), 79.9 (C-4'), 73.7 (C-2'), 71.7 (C-3'), 63.8 (C-5'); *Anal.* Calcd for $C_{29}H_{24}N_6O_7 \cdot 0.33H_2O$: C, 60.62; H, 4.33; N, 14.63. Found: C, 60.81; H, 4.36; N, 14.27. (The CHN data was obtained from a subsequent batch of compound 47 that was identical by TLC, mp, and all other spectral data.)

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (49). The above cited compound with Rf 0.81, yield 7.5 g (23 %); mp 189-192 °C; MS (FAB) *m/e* 569 (M + 1); UV λ_{max} 233 (19,500), shoulder at 278 (1350) at pH 1; 236 (18,800), shoulder at 280 (5400) at pH 7; 226 (14,000) at pH 13; IR (KBr) 3200, 3070, 3010, 2975-2900 (NH and CH), 1734, 1725, 1716 (C=O), 1630, 1587 (broad, aromatic), 1465, 1450, 1315, 1284, 1267, 1180, 1155, 1126, 1114, 1093 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.45-12.7 (br s, 1, H-5), 8.67 (br d, 1, NH), 8.1-7.83, 7.8-7.3 (m, 16, H-6 and benzoyl), 6.39-6.32 (m, H-1' of α-isomer), 5.97-5.77 (m, 3, H-1',2',3'), 4.8-4.5 (m, 3, H-4',5'); ^{13}C NMR (Me_2SO-d_6) showed a mixture of α,β-isomers. *Anal.* Calcd for $C_{29}H_{24}N_6O_7$: C, 61.26; H, 4.26; N, 14.79. Found: C, 61.42; H, 4.56; N, 14.78.

A Second Synthesis of Protected Ribofuranosyl Triazolotriazoles 45, 47, 49. 3-Amino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (6.97 g) was suspended in a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (28.35 g) in anhydrous acetonitrile (915 mL). Stannic chloride (14.7 mL) was added slowly at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 24 h. It was then concentrated to a small volume and saturated sodium bicarbonate was added till the vigorous evolution of carbon dioxide had ceased. The mixture was evaporated under reduced pressure and the residual gum was extracted several times with hot chloroform. The combined extracts were dried and concentrated. Thin-layer chromatographic analysis of this crude product (silica gel, chloroform-methanol, 9:1 v/v) showed three spots with Rf values of 0.45, 0.81, 0.85, and 0.9 along with unchanged as well as decomposed sugar derivatives (Rf 0.97). The mixture was applied to a column of silica gel and eluted with chloroform followed by 1%, 2%, and 3% methanol in chloroform. The above three products were separated and further purified by repeating silica gel column chromatography. Structures of these compounds were assigned on the basis of spectral data as follows:

3-Imino-2*H*-2-(2',3',5'-tri-*O*-benzoyl)-β-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-*s*-triazole (45). Compound with Rf 0.45 cited above, yield 9.46 g (30%); mp 125-127 °C; MS (FAB) 569 (M + 1); UV λ_{max} 234 (39,400), shoulder at 280 (3200) at pH 1; 236 (33,000), shoulder at 276 (17,300) at pH 7; 225 (29,300), 276 (8600) at

pH 13; IR (KBr) 3500-2500 (broad park, NH, NH, C–H), 1727 (C=O), 1666 (C=N), 1615, 1602 (aromatic), 1585, 1475, 1450, 1315, 1267, 1200, 1175, 1116, 1093, 1070, 1024 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.1-7.8 and 7.6-7.1 (m, 18, NH, NH, C_6H and benzoyl protons), 6.35 (d, 1, $C_{1'}$-H, $J_{1',2'}$ = 1.7 Hz), 6.25 (d d, 1, H-2', $J_{2',3'}$ = 5.2 Hz), 6.19 (d d, 1, H-3', $J_{3',4'}$ = 6.8 Hz), 4.92-4.82 (m, 1, H-4', $J_{4',5'a}$ = 5.2 Hz, $J_{4',5'b}$ = 3.6 Hz), 4.82-4.77 (d, 1, H-5'b), 4.74-4.65 (d d, 1, H-5'a, $J_{5'a,5'b}$ = 12.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 165.2, 165.1 (C=O), 160.3 (C-6, $^1J_{C_6H}$ = 202.6 Hz), 160.1 (C-8, J_{C_8H} = 4.4 Hz), 138.3 (C-3), 133.7, 133.4, 133.0, 129.7, 129.64, 129.6, 129.2, 128.6, 128.4, 128.43, 128.39 (aromatic carbons), 88.8 (C-1', $^1J_{C_1'H}$ = 167.8 Hz), 80.4 (C-4'), 75.3 (C-2'), 71.7 (C-3'), 63.9 (C-5'). *Anal.* Calcd for $C_{29}H_{24}N_6O_7 \cdot H_2O$: C, 59.34; H, 4.47; N 14.33. Found: C, 59.12; H, 4.42; N, 14.50.

3-Imino-2*H*-2-β-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-*s*-triazole (46). The tribenzoyl ribofuranoside **45** (8.6 g) was deprotected by stirring with sodium methoxide (0.85 g) in methanol (200 mL) under dry conditions for 3 h at room temperature. The pH of the solution was brought to 7 by the careful addition of 6 *N* HCl. Reaction mixture was concentrated under reduced pressure and charged on a silica gel column. Methyl benzoate was removed by eluting with chloroform. Elution with chloroform-methanol (4:1) yielded the pure product, 2.81 g (73%); mp 160-162 °C dec; MS (FAB) 257 (M + 1); UV λ_{max} 248 (7200) at pH 1; 264 (9500) at pH 7; 277 (9100) at pH 13; IR (KBr) 3650-2600 (broad, OH, NH, CH), 1678, 1613 (C=N, C=NH), 1480, 1445, 1415, 1350, 1208, 1120, 1045 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.5-8.0 (br s, 1, NH), 7.9 (s, 1, H-6), 5.83 (d, 1, H-6), 5.83 (d, 1, H-1'), 5.6-5.4, 5.25-5.1, 5.1-4.7 (br s, OH), 4.53 (d d, 1, H-2'), 4.2 (d d, 1, H-3'), 3.92 (m, 1, H-4'), 3.64-3.42 (m, 2, H-5'); ^{13}C NMR (Me_2SO-d_6) δ 160.1 (C-6), 159.9 (C-8), 138.3 (C-3), 89.8 (C-1', $^1J_{CH}$ = 164.8 Hz), 85.3 (C-4'), 73.2 (C-2'), 70.6 (C-3'), 62.1 (C-5'). *Anal.* Calcd for $C_8H_{12}N_6O_4 \cdot 0.3CH_3OH \cdot 0.2H_2O$: C, 37.00; H, 5.09; N, 31.20. Found: C, 37.01; H, 4.99; N, 31.24.

3-Amino-1-(2',3',5'-tri-*O*-benzoyl)-β-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-*s*-triazole (47). Compound with Rf 0.9 cited above, yield 2.34 g (7.3%), mp 86-87 °C; MS (FAB) 569 (M + 1); UV λ_{max} 239 (30,500), shoulder at 280 (13,300) at pH 1; 240 (30,700), shoulder at 280 (13,300) at pH 7; 229 (27,700), shoulder at 275 (2200) at pH 13; IR (KBr) 3425, 3335 (NH_2), 3175, 3065 (CH), 1727 (C=O), 1655 (C=N), 1600, 1570 (aromatic), 1452, 1317, 1269, 1175, 1160, 1121, 1096, 1070, 1025, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15-7.25 (m, 16, H-6 and benzoyl protons), 6.31 (d, 1, H-1', $J_{1',2'}$ = 3.86 Hz), 6.28 (d d, 1, H-2', $J_{2',3'}$ = 5.32 Hz), 6.15 (d d, 1, H-3, $J_{3',4'}$ = 5.31 Hz), 4.88-4.5 (m, 3, H-4',5'); ^{13}C NMR ($CDCl_3$) δ 166.1, 165.2, 165.0 (C=O), 158.3 (C-6, $^1J_{CH}$ = 207.4 Hz), 156.0 (C-8, $^3J_{CH}$ = 9.8 Hz), 140.9 (C-3), 133.6, 133.5, 133.0, 129.8, 129.77, 129.7, 129.6, 128.8, 128.7, 128.4, 128.37, 128.3 (aromatic), 88.5 (C-1'), 79.9 (C-4'), 73.7 (C-2'), 71.7 (C-3'), 63.8 (C-5').

3-Amino-1-β-D-ribofuranosyl-*s*-triazolo[5,1-*c*]-*s*-triazole (48). The tribenzoyl derivative **47** (2.0 g) was stirred with sodium methoxide (0.2 g) in methanol (100 mL) under dry conditions for 5 h at room temperature. The pH of the solution was brought to 7 by the careful addition of 6 *N* HCl. Reaction mixture was concentrated under reduced pressure and charged on a silica gel column. Methyl benzoate was removed by eluting with chloroform. Elution with chloroform-methanol (4:1) yielded the pure product, 0.86 g (96%); mp 141-143 °C (lit.[12] mp 144-145 °C); MS (FAB) 257 (M + 1); UV λ_{max} 240 (6400) at pH 1; 240 (7000) at pH 7; 242 (6800) at pH 13; IR (KBr) 3600-2600 (broad, OH, NH_2, CH), 1657, 1626 (C=N), 1580, 1505,

1455, 1445, 1410, 1325, 1285, 1265, 1215, 1185, 1140, 1105, 1052 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.02 (s, 1, H-6). 6.85 (s, 2, NH_2), 5.48 (d, 1, H-1′), 5.43 (d, 1, OH-2′), 5.15 (d, 1, OH-3′), 4.82 (t, 1, OH-5′), 4.57 (m, 1, H-2′), 4.09 (m, 1, H-3′), 3.85 (m, 1, H-4′), 3.58-3.33 (m, 2, H-5′); ^{13}C NMR (Me_2SO-d_6) δ 157.8 (C-6, $^1J_{CH}$ = 206.7 Hz), 155.2 (C-8, $^3J_{C_8H_6}$ = 3.7 Hz, $^3J_{C_8H_{1'}}$ = 9.6 Hz), 141.2 (C-3), 90.5 (C-1′), 84.9 (C-4′), 72.0 (C-2′), 70.3 (C-3′), 62.0 (C-5′). *Anal.* Calcd for $C_8H_{12}N_6O_4$: C, 37.50; H, 4.72; N, 32.81. Found: C, 37.24; H, 4.93; N, 32.47.

3-(2′,3′,5′-Tri-*O*-benzoyl)-D-ribofuranosylamino-5*H*-*s*-triazolo[5,1-*c*]-*s*-triazole (49). Compound with Rf 0.81 cited above, yield 7.5 g (23%); mp 189-192 °C; MS (FAB) 569 (M + 1); UV λ_{max} 233 (19,500), shoulder at 278 (1350) at pH 1; 236 (18,800), shoulder at 280 (5400) at pH 7; 226 (14,000) at pH 13; IR (KBr) 3200, 3070, 3010, 2975-2900 (NH and CH), 1734, 1725, 1716 (C=O), 1630, 1587 (broad, aromatic), 1465, 1450, 1315, 1284, 1267, 1180, 1155, 1126, 1114, 1093 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.45-12.7 (br s, 1, H-5), 8.67 (b d, 1, NH), 8.1-7.83, 7.8-7.3 (m, 16, H-6 and benzoyl protons), 6.39-6.32 (m, H-1′ of α-isomer), 5.97-5.77 (m, 3, H-1′,2′,3′), 4.8-4.5 (m, 3, H-4′,5′); ^{13}C NMR (Me_2SO-d_6) of the compound showed mixture of α,β-isomers. *Anal.* Calcd for $C_{29}H_{24}N_6O_7$: C, 61.26; H, 4.26; N, 14.79. Found: C, 61.42; H, 4.56; N, 14.78.

3-Amino-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-*s*-triazolo[5,1-*c*]-*s*-triazole (47a). The above cited compound with Rf 0.85, yield 238 mg; mp 83-86 °C; MS (FAB) *m/e* 569 (M + 1); IR (KBr) 3425, 3335 (NH_2), 3175, 3065 (CH), 1727 (C=O), 1653 (C=N), 1602, 1569 (aromatic), 1452, 1317, 1268, 1176, 1165, 1110, 1069, 1025, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (m, 2, *o*-Ar-H's), 7.84 (m, *o*-Ar-H's), 7.83 (s, H-6), 7.56-7.21 (m, 9, *m*-, *p*-Ar-H's), 6.45 (d, 1, $J_{1',2'}$ = 5.5 Hz, H-1′), 5.98 (t, 1, $J_{2',3'}$ = 6.5 Hz, H-2′), 5.37 (m, 1, H-4′), 4.91 (br s, 2, NH_2), 4.81 (d d, 1, $J_{4',5'a}$ = 3.3 Hz, $J_{5'a,5'b}$ = 12.3 Hz, H-5′a), 4.65 (d d, 1, $J_{4',5'b}$ = 3.8 Hz, H-5′b); ^{13}C NMR ($CDCl_3$) δ 166.1, 165.4 and 164.8 (C=O), 158.42 (C-6, $^1J_{CH}$ = 206.7 Hz), 155.93 (C-8, $^3J_{C\text{-}8,H\text{-}6}$ = 9.9 Hz, $^3J_{C\text{-}8,H\text{-}1'}$ = 3.5 Hz), 139.85 (C-3), 133.41, 133.39, 133.29, 129.70, 129.67, 129.66, 129.38, 128.89, 128.50, 128.37, 128.26 (aromatic), 87.24 (C-1′, $^1J_{CH}$ = 168.0 Hz), 81.54 (C-4′), 71.39 (C-2′), 70.97 (C-3′), 63.85 (C-5′). *Anal.* Calcd for $C_{29}H_{24}N_6O_7 \cdot 0.2C_6H_{12}$: C, 61.96; H, 4.55; N, 14.36. Found: C, 61.73; H, 4.54; N, 14.17.

2-Nitroamino-1,3,4-thiadiazole (51). Nitration of 3-amino-1,2,4-triazole was followed. Fuming nitric acid (d 1.52, 17.5 mL) was added slowly over 15 min to 2-amino-1,3,4-thiadiazole (5 g) at 0 °C with vigorous stirring. The reaction mixture was stirred further for 30 min at 10-20 °C and quenched by pouring it into ice water. The solid was filtered and recrystallized from water to afford pure product (2.93 g); mp 168-170 °C dec; MS (EI) 146 (M); IR (KBr) 3120 (broad), 3080 (NH), 3025, 3000, 2860 (CH), 1532, 1484, 1437, 1350, 1280, 1268, 1234, 1218, 1100, 1005, 897 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 14.5-11.5 (broad, NH), 9.1 (s, 1, CH); ^{13}C NMR (Me_2SO-d_6) δ 170.5 (C-2, $^3J_{CH}$ = 2.5 Hz), 148.0 (C-5, $^1J_{CH}$ = 218.6 Hz). *Anal.* Calcd for $C_2H_2N_4SO_2$: C, 16.44; H, 1.38; N, 38.35. Found: C, 16.67; H, 1.60; N, 38.25.

5-Amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole, Hydrobromide (52). 2-Nitroamino-1,3,4-thiadiazole (12.24 g) and activated zinc dust (21.8 g) were moistened with water and ground to a paste. The paste was suspended in water (50 mL) at 10 °C and treated with 50% aqueous acetic acid (100 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C

for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide for 2 h. After removal of zinc sulfide, the filtrate and washings were treated with 10 *N* HCl. The hydrazino compound obtained [12.0 g, MS (EI) 116 (M)] was refluxed with cyanogen bromide (11.0 g) in 85% aqueous methanol (425 mL) for 48 h. The solvent was removed by evaporation, and the solid residue was dissolved in water and neutralized with sodium acetate, giving a solid precipitate. The product was recrystallized from water and treated with one equivalent of hydrobromic acid, giving a pure product (1.23 g); mp 240-250 °C dec; MS (EI) 141 (M); IR (KBr) 3400-2700 (NH_2, CH, HBr), 1685, 1588, 1500, 1485, 1325, 1275, 1200, 1020, 970, 780 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.4 (s, 1, H-2), 9.2-8.8 (br s, NH_2, H_2O, H^+); ^{13}C NMR (Me_2SO-d_6) 157.7 (C-2, $^1J_{CH}$ = 223.6 Hz), 149.7 (C-8, $^3J_{CH}$ = 3.3 Hz), 144.7 (C-5). *Anal.* Calcd for $C_3H_3N_5S \cdot HBr \cdot 0.5H_2O$: C, 15.59; H, 2.18; N, 30.30. Found: C, 15.52; H, 1.90; N, 30.01.

5-Thio-*s*-triazolo-[3,4-*b*]-1,3,4-thiadiazole-6*N*-dithiocarboxylic Acid (53). 2-Nitroamino-1,3,4-thiadiazole (22 g) and activated zinc dust (32.8 g) were moistened with water and ground to a paste. The paste was suspended in water (82 mL) at 10 °C and treated with 50% aqueous acetic acid (164 mL) over 2 h, while maintaining the temperature between 10-20 °C. The mixture was stirred at 20 °C for an additional 4 h, heated to 60 °C for 1 h, and allowed to cool. The excess zinc was removed by filtration and the filtrate saturated with hydrogen sulfide for 2 h. After removal of zinc sulfide, the filtrate and washings were treated with 10 *N* HCl to yield the hydrazino compound [15 g, MS (EI) 116 (M)]. This compound (12.7 g) was refluxed with KOH (12.4 g), carbon disulfide (50 mL) in 70% aqueous ethanol (300 mL), for 30 h. The solvent was removed and the residue was dissolved in water, acidified (pH 3) by addition of conc. HCl. The yellow solid obtained was filtered and recrystallized from water, charged on silica gel column chromatograph, eluted with chloroform-methanol (9:1). Pure product was obtained by the treatment with dilute HCl (200 mL, pH 2), filtered and dried (4.01 g); mp 121-123 °C; MS (EI) 234 (M); UV 356 (5700), 282 (17,800), 244 (10,300); IR (KBr) 3650-3150 (broad, CSSH), 3050 (C-H), 1640 (C=S), 1515, 1488, 1453, 1427, 1406, 1323, 1268, 1220, 1080, 1040, 1010 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.5 (s, 1, CH), 3.95-3.8 (br s, SH, H_2O, H^+); ^{13}C NMR (Me_2SO-d_6) δ 186.8 (CSSH), 163.1 (C-5), 156.7 (C-8, $^3J_{CH}$ = 4.3 Hz), 152.0 (C-2, $^1J_{CH}$ = 214.2 Hz) ppm. *Anal.* Calcd for $C_4H_2N_4S_4 \cdot 0.4H_2O \cdot 0.4HCl$: C, 18.77; H, 1.26; N, 21.88; S, 50.07. Found: C, 18.84; H, 1.27; N, 21.86; S, 50.00.

3,6,7-Tri-[dimethylaminomethyleneamino]-7*H*-*s*-triazolo[5,1-*c*]-triazole (55). 3,6,7-Triaminotriazolotriazole (2.5 g) was suspended in dry 1,4-dioxane (160 mL) under nitrogen atmosphere. Gold's reagent[21] (6.43 g, Aldrich) was added all at once and the reaction mixture was refluxed for 24 h. Cooled to room temperature, anhydrous sodium acetate (1.6 g) and glacial acetic acid (3.3 mL) were added and was refluxed for 3 h. Solvent was removed *in vacuo*. The residue was taken up in chloroform and washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated. Silica gel column chromatography (10% methanol in chloroform) followed by precipitation in chloroform-ether, yielded the pure product (2.1 g); mp 213-214 °C dec; MS (EI) 119 (M); UV λ_{max} 283 (32,800), 219 (19,200); IR (KBr) 2915, 2875, 2810 (CH), 1630 (C=N), 1592 (C=N), 1527, 1489, 1458, 1431, 1393, 1350, 1285, 1260, 1230, 1200, 1109, 1100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.37 and 8.35 (s, 3, olefin protons), 3.13, 3.07, 2.99, 2.94 (s, 18, methyl protons; ^{13}C NMR (Me_2SO-d_6) δ 158.4 (C-6), 157.0, 155.9, 155.6 (N=CH), 149.5 (C-8), 147.7 (C-3), 40.8, 40.5,

38.0, 34.7, 34.5 (methyl carbons). *Anal.* Calcd for $C_{12}H_{21}N_{11} \cdot 0.7H_2O$: C, 43.41; H, 6.80; N, 46.42. Found: C, 43.69; H, 6.57; N, 46.27.

6-Purinecarboxylic Acid[22] **(57a).** To 2.5 g (0.017 mol) of 6-cyanopurine was added 16.7 mL of 2 *N* sodium hydroxide, and the mixture was refluxed for 1 h. The resulting clear solution was cooled and acidified to pH 2 with concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and dried *in vacuo* to give a powdery yellow solid (1.89 g); mp 193-194 °C; IR (KBr) 3400, 2800, 1721, 1481, 1433, 1392, 1301, 1230, 1205, 1169, 928, 758 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.42 (br s, 1, H-6), 9.11 (s, 1, H-2), 8.80 (s, 1, H-8). *Anal.* Calcd for $C_6H_4N_4O_2$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.23; H, 3.33; N, 30.47.

Purine-6-thiocarboxamide[22] **(57b).** Hydrogen sulfide was passed through a solution of 1.75 g (0.012 mol) of 6-cyanopurine in approximately 40 mL ethanolic ammonia (temperature kept at 0 °C) for 4 h and was left stirring at room temperature overnight. The mixture was evaporated to dryness yielding 1.6 g of a powdery yellow solid; mp 300 °C; IR (KBr) 3353, 3260, 3145, 3125, 3114, 3082, 3064, 3059, 1600, 1398 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.74 (br s, 1, NH), 10.35 (d, 1, NH_2), 9.03 (s, 1, H-8), 8.74 (s, 1, H-4); MS (EI) *m/e* 179 (M^+). *Anal.* Calcd for $C_6H_5N_5S$: C, 40.21; H, 2.81; N, 39.08. Found: C, 40.01; H, 3.14; N, 38.95.

6-Carboxamidopurine (61).[22-24] (The 6-carboxamidopurine was prepared by a modification of the referenced procedure by Hitchings and Mackay.) Into a 100-mL round-bottomed flask equipped with a magnetic stirring bar and condenser were placed 6-cyanopurine (**56**, 4.6 g, 31.7 mmol) and EtOH (enough to allow good stirring). Then, 14.4 mL of 2.2 *N* NaOH was added, and the mixture was heated at reflux for 1 h. Since thin-layer chromatographic (TLC) monitoring of an aliquot from this mixture showed the presence of starting material, another 0.5 mL of 2.2 *N* NaOH was added, the heating was continued, and a heavy precipitate quickly formed. (In repetitions of this work, we found that in some cases, no precipitation occurred. With these cases, we suggest that 0.5 mL portions of the NaOH solution should be added at 5 min. intervals until precipitation occurs.) Since a TLC of this product showed only a trace of starting material, the EtOH was removed at reduced pressure, the residue was suspended in H_2O, chilled, and acidified to pH 6-7 with dilute HCl. The product was collected by filtration, washed well with cold H_2O, and dried *in vacuo* over phosphorus pentoxide; yield, 3.9 g (75%); IR (KBr) 1709, 1691, 1570, 1473, 1393, 607 cm^{-1}; MS (FAB) *m/e* 164 (M + 1). This material was used in the subsequent coupling reaction without further purification.

6-Carboxamido-9-β-D-ribofuranosylpurine, 2',3',5'-Tribenzoate (62).[24] Into a 100-mL round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, and a drying tube was placed 6-carboxamidopurine (**61**, 500 mg, 3.07 mmol), hexamethyl disilazane (HMDS, 30 mL), and $(NH_4)_2SO_4$ (10 mg). The mixture was heated at gentle reflux in an argon atmosphere for 18 h before excess HMDS was removed *in vacuo*. The residue was dissolved in dry 1,2-dichloroethane (30 mL), and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.6 g, 3.07 mmol) and anhydrous $SnCl_4$ (1.1 g, 4.3 mmol) were added. The reaction mixture was protected from moisture, covered with an argon atmosphere, and stirred at room temperature for 24 h. The mixture was poured into a cold mixture of 5% aqueous $NaHCO_3$ and $CHCl_3$ (1:1) and stirred for 2 h. The resulting emulsion was further separated by removing any separated water and $CHCl_3$ portions and treating the remaining emulsion with more $CHCl_3$ until the emulsion was broken. The $CHCl_3$ layer was washed with brine, dried with $MgSO_4$, filtered, and evaporated. The crude product was chromatographed with

a 200 g silica gel flash column (using 99:1 $CHCl_3$-MeOH as eluent), and the appropriate fractions were combined and evaporated; yield, 1.1 g; MS (FAB) *m/e* 608 (M + 1), 445 (sugar), 164 (B + 2 H). The TLC showed a single spot when developed in 98:2 $CHCl_3$-MeOH.

6-Carboxamido-9-β-D-ribofuranosylpurine (63).[22-24] Into a 1-L round-bottomed flask was suspended 2',3',5'-tribenzoyl-6-carboxamido-9-β-D-ribofuranosylpurine (**62**, 11 g, 18.1 mmol) in 600 mL absolute EtOH with good stirring. A solution of sodium methoxide in EtOH was added slowly over 45 min to adjust the mixture to pH 8-9 (monitored by pH paper). After 3 h, a TLC aliquot monitoring indicated complete deblocking had occurred, and the reaction was quenched by the addition of 1 mL of glacial acetic acid. The reaction mixture was evaporated, and the residue was suspended in ether, collected by filtration, washed with ether, and dried, giving a crude yield of 5.2 g. This crude product was purified by silica gel flash chromatography (eluted with 2:1 $CHCl_3$-MeOH). Since the product still contained an appreciable amount of sodium acetate, it was dissolved in 75 mL of water, treated with ~0.5 mL of mixed-bed resin (AG 501X8D) for 5 min, filtered, and the filtrate was freeze-dried: yield 2.0 g; mp 110-115 °C cap; UV λ_{max} 280 nm (7,960) at pH 1; 282 (7,870) at pH 7; 287 (10,750) at pH 13; IR (KBr) 1690, 1585, 1500, 1415, 1335, 1210, 1125, 1085, 1060, 645 cm^{-1}; MS (FAB) *m/e* 296 (M + 1); ^1H NMR (Me_2SO-d_6) δ 3.59, 3.71 (2 m, 2, H-5'), 3.99 (q, 1, H-4'), 4.20 (t, 1, H-3'), 4.61 (t, 1, H-2'), 5.20, 5.36, 5.65 (3 br s, 3, OH-5',3',2'), 6.08 (d, 1, H-1'), 8.05, 8.35 (2 br s, 2, $CONH_2$), 8.99 (s, 1, H-2), 9.03 (s, 1, H-8). *Anal.* Calcd For $C_{11}H_{13}N_5O_5 \cdot 0.7H_2O \cdot 0.25NaOAc$: C, 42.06; H, 4.73; N, 21.33. Found: C, 42.10; H, 4.60; N, 21.33.

Methyl 2-Chloro-4-cyanomethylimidazole-5-carboxylate (65). To a 11.1 g (0.056 mol) of methyl 4-carboxamidomethyl-2-imidazolone-5-carboxylate (**70**) was added 250 mL of phosphorus oxychloride. This mixture was refluxed for 3 h, cooled, and then evaporated under reduced pressure until the reaction mixture was a viscous blackish-brown gum. The reaction mixture was cooled in a dry-ice acetone bath while a mixture of ice and water was slowly added to the flask. The pH of the reaction mixture was then slowly adjusted to 5 with 28% aqueous ammonia, and the dark liquid was extracted with ether (1 L). Drying over sodium sulfate followed by rotovapping gave a viscous, light-yellow solid which was recrystallized from benzene (5.5 g, 49.4%, mp 136.7 °C); IR (KBr) 1657 cm^{-1} (C=O), 2270 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 10.8 (br s, 1, NH), 3.99 (s, 2 H, CH_2CN); ^{13}C NMR ($CDCl_3$) ppm 17.63, 52.53, 115.88, 121.38, 134.48, 137.57, 59.43. *Anal.* Calcd for $C_7H_6ClN_3O_2$: C, 42.11; H, 3.00; N, 21.05. Found: C, 42.16; H, 3.06; N, 21.00.

4-Cyanomethyl-2-chloroimidazole-5-carboxamide[25,26] **(66).** Methyl 4-cyanomethyl-2-chloroimidazole-5-carboxylate (7.0 g, 0.035 mol) was slowly added to liquid ammonia in a cooled (-78 °C) glass-lined stainless steel bomb. The bomb was sealed, allowed to warm slowly to room temperature, and then heated at 110 °C for 21 days. The bomb was then cooled to room temperature, and the ammonia was slowly removed by evaporation at atmospheric pressure followed by vacuum. The resulting brown solid was then Soxhlet-extracted with ether, giving 3.3 g of an insoluble light brown solid (found to be starting material) and 7.1 g of a light yellow solid (from the ether extract), which was the desired product; mp 233-235 °C; MS (EI) 199 (M^+), 201 (M + 2); ^1H NMR (Me_2SO-d_6) δ 13.56 (br s, 1, NH), 7.42 (br s, 2, NH_2), 4.28 (s, 3, CH_2CN); IR (KBr) 3393, 3207, 2267, 1669, 1600, 1500, 1425, 1408, 1379, 1250, 625 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + HCl) δ 162.2

(C=O), 129.9 (C-2), 129.1 (C-4), 128.5 (C-5), 117.1 (CN), 14.7 (CH_2). *Anal.* Calcd for $C_6H_5ClN_4O$: C, 39.03; H, 2.73; N, 30.37. Found: C, 39.12; H, 2.92; N, 30.18.

Methyl 4(5)-Cyanomethyl-2-methylthioimidazole-5(4)-carboxylate[25,26] **(72).** Methyl 4(5)-carboximidomethyl-2-methylthioimidazole-5(4)-carboxylate (6.4 g, 0.028 mol) was added to 125 mL freshly distilled phosphorus oxychloride. The mixture was refluxed for 3 h before it was cooled to room temperature and then evaporated to dryness, under vacuum. After most of the $POCl_3$ had been removed, the reaction flask was cooled in a dry ice/acetone bath at -78 °C. Water/ice (300 mL) was slowly added with swirling, and then the reaction mixture was allowed to warm to room temperature. The pH was adjusted to 7-8 with slow addition of NH_4OH, and then the mixture was extracted with ether (~1 L), dried and evaporated. A dark blue solid was obtained (6.3 g) which was chromatographed (in 10:1 $CHCl_3$-MeOH, silica gel) to give 1.53 g of the desired product as a light yellow solid, mp 117-118 °C. An additional 2.1 g of this material was later obtained from a second chromatographic effort with a 1:1 ethyl acetate-pet. ether solvent system. MS (EI) *m/e* 211 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 4.22 (s, 2, CH_2CN), 3.82 (s, CH_3O-3), 2.60 (s, 3, SCH_3); IR (KBr) 3255, 2266, 1712, 1593, 1488, 1439, 1431, 1357, 1308, 1251, 1098 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + HCl) δ 159.3 (C=O), 146.1 (C-2), 135.1 (C-5), 121.6 (C-4), 116.8 (C≡N), 51.8 (OCH_3), 15.9 (CH_2), 14.5 (SCH_3). *Anal.* Calcd for $C_3H_9N_3O_2S$: C, 45.50; H, 4.29; N, 19.89. Found: C, 45.50; H, 4.36; N, 19.66.

4-Cyanomethyl-2-methylthioimidazole-5(4)-carboxamide[25,26] **(73).** Methyl 4-cyanomethyl-2-methylthioimidazole-5(4)-carboxylate (3.4 g, 0.16 mol) was slowly added to a cooled (-78 °C) glass-lined stainless steel bomb, filled with 50 mL liquid ammonia. The bomb was capped, sealed, and allowed to warm slowly to room temperature before it was heated to 110 °C. After 21 days, the bomb was cooled to room temperature, the ammonia allowed to slowly evaporate, and the residual dark brown viscous product was kept under vacuum for ~2 h. Column chromatography with silica gel and a 10:1 $CHCl_3$-MeOH solvent system gave a brown solid which was recrystallized from ethyl acetate to give the desired product as a lighter brown solid (1.59 g); mp 146-147 °C; MS (EI) 196 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 17.76 (br s, 1, NH), 7.30 (br s, 2, NH_2), 4.22 (s, 2, CH_2CN), 2.60 (s, 3, SCH_3); IR (KBr) 3200, 1654, 1603, 1492, 1396, 2260 (CN) cm^{-1}. *Anal.* Calcd for $C_7H_8N_4OS$: C, 42.85; H, 4.11; N, 28.55. Found: C, 42.74; H, 4.33; N, 28.29.

Ethyl 5-Methylpyrazole-3-carboxylate[27] **(76a).** (Following the molar proportions of the reference, but using hydrazine hydrate instead of hydrazine sulfate and NaOH.) Ethyl 2,4-dioxovalerate (20 g, 0.127 mol) was added to 100 mL water. The solution was cooled in an ice-water bath while hydrazine monohydrate (6.54 g, 0.108 mol) was slowly added with stirring. After the hydrazine addition was complete, stirring was continued and the solution was allowed to come to room temperature. After about 45 min, a light yellow solid began precipitating. Stirring at room temperature was continued for another 3.25 h before the solid was filtered (14.9 g). The solid was added to 40 mL ether, heated, and stirred. Insoluble solid was filtered. The ether solution was concentrated to about 250 mL before pet. ether was added until the solution became cloudy. Cooling overnight yielded the desired product, a white solid. Further concentration of the mother liquor solution followed by pet. ether addition yielded more of this solid (final yield 9.4 g, mp 63-64 °C); MS (EI) *m/e* 154 (M^+); ^{1}H NMR (d_6-acetone) δ 6.53 (s, 1, vinyl-H), 4.28 (q, J = 7.5 Hz, 2, OCH_2CH_3), 2.30 (s, 3, CH_3), 1.30 (t, J = 7.75 Hz, 3, OCH_2CH_3); IR (KBr) 3224, 1722, 1420, 1227, 1175, 1097, 1029, 995, 781

cm^{-1}; ^{13}C NMR (Me_2SO-d_6, mixture of tautomers) δ 162.3 (C=O), 143.3 (C-5), 139.7 (C-3), 106.4 (C-4), 60.0 (OCH_2CH_3), 14.2 (OCH_2CH_3), 10.2 (C-1'). *Anal.* Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.53; N, 18.17. Found: C, 54.31; H, 6.88; N, 17.84.

Ethyl 5-(p-Fluorophenyl)pyrazole-3-carboxylate (76b). Ethyl 4-(*p*-fluorophenyl)-2,4-dioxobutyrate (13 g, 0.055 mol) was added to 50 mL water and hydrazine monohydrate (2.7 g, 0.054 mol) was slowly added with stirring. After 30 min at room temperature, the solution was heated to 50-60 °C for 3 h, and then kept at room temperature overnight. The solid was then filtered, dried, and added to 600 mL MeOH. The insoluble solid was removed, and the methanol solution was concentrated to 20% original volume. The resulting light yellow solid (4.2 g) was isolated by filtration and was found to be the desired product. Another 6.1 g of the desired product was obtained by further concentration etc., of the methanolic solution: yield 16.3 g; mp 145-146 °C; MS (EI) *m/e* 234 (M^+); ^1H NMR (d_6-acetone) δ 7.93-8.05 (m, 5, Ar-H's and pyrazole-H), 4.33 (q, J = 7 Hz, 2, OCH_2CH_3), 2.82 (br s, 1, NH), 1.36 (t, J = 7 Hz, 3, OCH_2CH_3); IR (KBr) 3135, 1726, 1509, 1276, 1246, 1190, 1166, 995, 841, 779 cm^{-1}; ^{13}C NMR (Me_2SO + CF_3COOD) 163.7 (C=O or C-4'), 160.4, 160.5 (C=O or C-4'), 146.5 (C-5), 139.6 (C-3), 127.4, 127.5 (C-2'), 127.3 (C-1'), 115.6, 115.9 (C-3'), 105.2 (C-4), 60.5 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.51; H, 5.05; N, 12.00.

Ethyl 5-(p-Bromophenyl)pyrazole-3-carboxylate (76c). Ethyl 5-(*p*-bromophenyl)-2,4-dioxybutyrate (10.2 g, 0.034 mol) was mixed with 75 mL water. Hydrazine hydrate (1.65 g, 0.033 mol) was added slowly with stirring. The mixture was heated at 40-50 °C for 4 h and stirred at room temperature overnight. The resulting solid was vacuum filtered and added to ~400 mL MeOH. All undissolved solids were removed by filtration, and the filtrate was reduced to ~20% of the original volume. A small portion was isolated and dried, giving a solid with a broad melting point. This solid was recombined with the MeOH mother liquor and the whole was evaporated to dryness and chromatographed (silica gel, 9.5:1, $CHCl_3$-MeOH), giving 6.3 g of a light orange solid. Some of the orange solid (2.5 g) was then recrystallized from hot methanol giving 2.0 g of a light yellow solid; mp 128-129 °C; MS (EI) *m/e* 294 (M^+); ^1H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.1, 13.98 (s, 1, -NH), 7.81, 7.64 (s, 4, Ar-H), 7.34, 7.26 (m, 3, pyrazole-H), 4.32 (m, 2, OCH_2CH_3), 1.34 (t, J = 9 Hz, 3, OCH_2CH_3); IR (KBr) 3294, 1696, 1444, 1303, 1277, 1028, 1012, 956, 829, 774 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.3 (C=O), 146.4 (C-3), 139.2 (C-5), 131.8 (C-2'), 129.9 (C-1'), 127.3 (C-3'), 121.3 (C-4'), 105.5 (C-4), 60.5 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_2O_2Br$: C, 48.83; H, 3.76; N, 9.49. Found: C, 48.86; H, 3.93; N, 9.37.

Ethyl 5-(p-Chlorophenyl)pyrazole-3-carboxylate (76d). Ethyl 5-(*p*-chlorophenyl)-2,4-dioxobutyrate (13.9 g, 0.055 mol) was mixed with water (75 mL). Hydrazine monohydrate (2.7 g, 0.054 mol) was then slowly added with stirring. After overnight stirring at room temperature, the resulting yellowish solid was vacuum filtered. The solid material was added to hot ether and the whole was heated to ~40 °C. The solution was cooled, the ether-insoluble material was filtered, and the ether solution was then evaporated to dryness giving 4.2 g of a orange-colored solid. Since an NMR of the crude product showed that starting material was still present, the solids were recombined and added to water (78 mL) and hydrazine hydrate (~2.0 g). The reaction mixture was then heated at 40-50 °C for 4 h, cooled, and filtered giving a light orange solid. The

solid was added to hot MeOH (600 mL). MeOH-insoluble was filtered off and the MeOH was concentrated to ~20% volume giving 8.5 g of a yellowish solid. Because this material had an unacceptably broad melting point (138-146 °C), it was filtered through silica gel with $CHCl_3$ giving light yellowish-brown flakes (6.9 g), mp 148-150 °C. A smaller fraction (2.5 g) was then chromatographed (silica gel, $CHCl_3$-MeOH, 9.5:1) giving 1.6 g of an off-white solid which melted in two stages (128-130 °C partially and 146-148 °C). Re-melting the melted material occurred only at the higher 146-148 °C range. MS (EI) *m/e* 250, 252 (M, M + 2); ^{1}H NMR (Me_2SO-d_6) δ 14.06 (s, 1, NH), 7.89 (m, 2, Ar-H), 7.51 (m, 2, Ar-H), 7.30 (s, 1, pyrazole-H), 4.34 (q, 2, OCH_2CH_3), 1.34 (t, 3, OCH_2CH_3); IR (KBr) 3294, 1697, 1444, 1303, 1285, 1278, 1093, 1016, 956, 832 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.3 (C=O), 146.4 (C-3), 139.3 (C-5), 132.8 (C-4'), 129.6 (C-1'), 128.8 (C-3'), 127.0 (C-2'), 105.5 (C-4), 60.5 (OCH_2), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_2O_2Cl$): C, 57.49; H, 4.42; N, 11.17. Found: C, 57.45; H, 4.71; N, 11.35.

Ethyl 5-Phenylpyrazole-3-carboxylate (76e). Ethyl 5-phenyl-2,4-dioxobutyrate (10.7 g, 0.049 mol) was mixed with 100 mL water. Hydrazine hydrate (2.45 g, 0.049 mol) was slowly added with stirring, and the mixture was stirred overnight at room temperature. The resulting yellow powdery precipitate was filtered, dried, dissolved in ether, extracted with water, dried, and evaporated to dryness giving 9.7 g crude product. TLC in silica gel (9.5:1, $CHCl_3$-MeOH) showed one main component. Recrystallization of 2.5 g crude product gave 2.0 g of a white solid; mp 129-130 °C; MS (EI) *m/e* 216 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 13.99 (s, 1, NH), 7.87 (m, 2, Ar-H), 7.48 (m, 2, Ar-H), 7.39 (m, 1, Ar-H), 7.26 (s, 1, H-4), 4.32 (q, J = 6.6 Hz, 2, OCH_2CH_3), 1.34 (t, J = 6.6 Hz, 3, OCH_2CH_3); IR (KBr) 1725, 1419, 1277, 1240, 1192, 1138, 1023, 1000, 760 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + 1 drop TFA) δ 160.9 (C=O), 146.9 (C-5), 140.2 (C-3), 130.5 (C-1'), 129.0 (C-3'), 128.3 (C-4'), 125.4 (C-2'), 105.2 (C-4), 60.5 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.57; H, 5.77; N, 13.14.

Ethyl 5-(*p*-Tolyl)pyrazole-3-carboxylate (76f). Ethyl 5-(*p*-tolyl)-2,4-dioxobutyrate (13.9 g, 0.059 mol) was mixed with ~100 mL water. Hydrazine hydrate (3.0 g, 0.059 mol) was slowly added with stirring, and then the mixture was stirred overnight at room temperature. The resulting light yellow powdery precipitate was filtered and dried, giving 10.4 g of crude product. TLC in silica gel (ether:petroleum ether, 2:2) showed only a slight amount of impurities present. The solid (2.2 g) was chromatographed with silica gel (ether:petroleum ether, 2:3) giving 2.1 g of the desired product as a white solid, mp 144-145 °C; MS (EI) *m/e* 230 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 13.91 (s, 1, NH), 7.76 (m, 2, Ar-H), 7.28 (m, 2, Ar-H), 7.20 (s, 1, H-4), 4.32 (q, J = 8.4 Hz, 2, OCH_2CH_3), 2.36 (s, 3, $ArCH_3$), 1.44 (t, J = 8.4 Hz, 3, OCH_2CH_3); IR (KBr) 3140, 1724, 1487, 1413, 1272, 1242, 1131, 994, 986, 817, 783 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + 1 drop TFA) δ 160.9 (C=O), 146.5 (C-5), 140.5 (C-3), 137.7 (C-4'), 129.5 (C-3'), 127.4 (C-1'), 125.3 (C-2'), 104.7 (C-4), 60.4 (OCH_2), 20.8 ($ArCH_3$), 14.2 (CH_2CH_3). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.50; H, 6.14; N, 12.38.

Ethyl 5-(*p*-Nitrophenyl)pyrazole-3-carboxylate (76g). Ethyl 5-(*p*-nitrophenyl)-2,4-dioxobutyrate (10.6 g, 0.04 mol) was mixed with 200 mL H_2O. Hydrazine hydrate (2 g, 0.04 mol) was slowly added with stirring, and the mixture was stirred overnight at room temperature. The resulting yellow powdery solid was filtered and dried giving 7.2 g crude product. Chromatography (silica gel, ether-pet. ether, 1:2) of 4 g yielded 2.6 g of pure

product; mp 210-212 °C; MS (EI) *m/e* 261 (M+); ^{1}H NMR (Me_2SO-d_6) δ 14.35 (s, 1, NH), 8.31 (d, *J* = 8.4 Hz, 2, Ar-H), 8.16 (d, *J* = 8.4 Hz, 2, Ar-H), 7.52 (s, 1, H-4), 4.34 (q, *J* = 7 Hz, 2, OCH_2CH_3), 1.35 (t, *J* = 7 Hz, 3, OCH_2CH_3); IR (KBr) 3180, 1735, 1722, 1607, 1523, 1514, 1338, 1286, 1258, 1203, 1154, 854, 755 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.8 (C=O), 158.7 (C-4'), 146.8 (C-5), 138.3 (C-3), 137.7 (C-1'), 126.2 (C-2'), 124.1 (C-3'), 107.0 (C-4), 60.9 (OCH_2), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 54.99; H, 4.36; N, 16.36.

Ethyl 5-(*p*-Methoxyphenyl)pyrazole-3-carboxylate (76h). Ethyl 4-(*p*-methoxyphenyl)-2,4-dioxobutyrate (10.0 g, 0.04 mol) was mixed with 75 mL water. Hydrazine hydrate (2 g, 0.04 mol) was slowly added, and the mixture was stirred overnight at room temperature. The resulting yellow solid was filtered and washed with water. Four grams of the crude product was chromatographed (silica gel, ether-pet. ether, 2:3) giving 3.1 g pure product as an off white solid; mp 142-143 °C; MS (EI) 246 (M$^+$); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 13.84 (s, 1, NH), 7.77 (m, 2, Ar-H), 7.14 (s, 1, pyrazole-H), 7.02 (m, 2, Ar-H), 4.30 (m, 2, OCH_2CH_3), 3.80 (s, 3, OCH_3), 1.32 (t, *J* = ~7.8 Hz, 3, OCH_2CH_3); IR (KBr) 3284, 3196, 1705, 1452, 1443, 1269, 1247, 1175, 1026, 956, 826 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 161.4 (C=C), 150.0 (C-4'), 146.8 (C-5), 140.9 (C-3), 127.2 (C-2'), 123.3 (C-1'), 114.7 (C-3'), 104.6 (C-4), 60.7 (CH_2), 55.3 (OCH_3), 14.4 (CH_2CH_3). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.40; H, 5.91; N, 11.46.

Ethyl 5-(2',4'-Dimethoxyphenyl)pyrazole-3-carboxylate (76i). Ethyl 4-(2',4'-dimethoxyphenyl)-2,4-dioxobutyrate (16.3 g, 0.058 mol) was added to 300 mL H_2O. Hydrazine hydrate (2.9 g, 0.058 mol) was added slowly with stirring, and the reaction mixture was stirred overnight at room temperature. The resulting yellow solid was filtered and dried giving 15.8 g crude product. Three grams of the crude product was chromatographed (silica gel, ether-pet. ether, 2:3) giving 2.3 g of a yellow granular solid; mp 102-103 °C; MS (EI) 276 (M$^+$); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 13.90, 13.41 (s, 1, NH), 7.85, 7.65 (m, 1, Ar-H), 7.13, 7.02 (m, s, 1, Ar-H), 6.68, 6.62 (m, 1, Ar-H), 4.29 (m, 2, OCH_2CH_3), 3.90 (s, 3, OCH_2CH_3), 3.82 (s, 3, $-OCH_3$), 1.31 (t, 3, OCH_2CH_3); IR (KBr) 3346, 3138, 1712, 1615, 1587, 1302, 1258, 1250, 1209, 1146, 1029, 997 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CH_3COOD) δ 161.7 (C=C), 160.9 (C-4'), 157.2 (C-2'), 141.8 (C-5), 141.4 (C-3), 128.7 (C-5'), 110.9 (C-1'), 106.5 (C-4), 105.6 (C-5'), 98.8 (C-3'), 60.2 ($OCH2CH_3$), 55.6 (OCH_3), 55.3 (OCH_3), 14.3 (OCH_2CH_3). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83; N, 10.14. Found: C, 60.77; H, 5.97; N, 10.05.

Ethyl 5-(2',4'-Dichlorophenyl)pyrazole-3-carboxylate (76j). Ethyl 4-(2',4'-dichlorophenyl)-2,4-dioxobutyrate (28.9 g, 0.035 mol) was added to ~100 mL H_2O. Hydrazine hydrate (1.73 g, 0.035 mol) was slowly added with swirling, and the reaction mixture was stirred overnight at room temperature. The resulting yellow solid (22.5 g) was filtered and dried. Although thin layer chromatography showed this crude product was essentially pure, 4 g of the crude was chromatographed (silica gel, ether-pet. ether, 2:3) giving 3.0 g of a light yellow solid, mp 127-128 °C; MS (EI) 284 (M$^+$); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.35, 13.96 (s, 1, NH), 7.83, 7.73, 7.54 (m, 3, Ar-H), 7.37, 7.10 (s, 1, pyrazole-H), 4.34 (m, 2, OCH_2CH_3), 1.33 (t, 3, OCH_2CH_3), IR (KBr) 1728, 1474, 1263, 1240, 1205, 1139, 1026, 1000, 802, 776 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.2 (C=O), 144.2 (C-5), 138.2 (C-3), 133.8 (C-4'), 132.2 (C-2'), 131.7 (C-6'), 129.9 (C-

3'), 129.0 (C-1'), 127.7 (C-5'), 109.0 (C-4), 60.8 (OCH_2), 14.3 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}Cl_2N_2O_2$: C, 5055; H, 3.54; N, 9.82. Found: 50.47; H, 3.69; N, 9.71.

Ethyl 5-(2',4'-Difluorophenyl)pyrazole-3-carboxylate (76k). Ethyl 4-(2',4'-difluorophenyl)-2,4-dioxobutyrate (13.0 g, 0.051 mol) was mixed with water (15 mL). Hydrazine hydrate (2.54 g, 0.051 mol) was slowly added with stirring, and then the mixture was stirred overnight at room temperature. The resulting light-yellow powdery precipitate was filtered and dried, giving about 12 g of the crude product. The solid was chromatographed with silica gel (ether-pet. ether, 2:3) yielding 9.8 g of the desired product as a white solid; mp 44-45 °C; MS (EI) *m/e* 252 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.14 (s, 1, NH), 7.98, 7.40, 7.25 (m, 3, Ar-H), 7.09, d, J = ~3.2 Hz, 1, pyrazole H), 4.34 (q, 2, OCH_2CH_3), 1.33 (t, 3, OCH_2CH_3); IR (KBr) 3226, 3132, 3007, 1723, 1489, 1276, 1256, 1141, 1108, 996, 980, 842, 780 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 162.1 (d d, $^1J_{C_4',F_4}$ = 248.2 Hz, $^3J_{C_4',F_2}$ = 1.23 Hz, C-4'), 160.3 (C=O), 159.2 (d d, $^1J_{C_2',F_2}$ = 251.2 Hz, $^3J_{C_2',F_4}$ = 12.2 Hz, C-2'), 141.3 (C-5), 138.8 (C-3), 129.5 (d d, $^3J_{C_6',F_2}$ = 4.8 Hz, C-6'), 115.6 (d d, $^2J_{C_1',F_2}$ = 12.7 Hz, $^4J_{C_1',F_4}$ = 3.3 Hz, C-1'), 112.2 (d d, $^2J_{C_5',F_4}$ = 21.5 Hz, $^4J_{C_5',F_2}$ = 3.3 Hz, C-5'), 107.7 (d, $^4J_{C_4,F_2'}$, C-4), 104.8 (t, $^2J_{C_3',F_2}$ = $^2J_{C_3',F_4}$ = 26.0 Hz, C-3'), 60.7 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}F_2N_2O_2$: C, 57.15; H, 4.00; N, 11.11. Found: C, 56.92; H, 4.16; N, 10.98.

Ethyl 5-(2'-Pyridyl)pyrazole-3-carboxylate (76l). Ethyl 4-(2-pyridyl)-2,4-dioxybutyrate (13.1 g, 0.059 mol) was mixed with 200 mL H_2O. Hydrazine hydrate (2.96 g, 0.059 mol) was slowly added with swirling, and the mixture was stirred overnight at room temperature. The resulting light brown solid was filtered, dried, filtered through silica gel with $CHCl_3$-MeOH (9.5:1) as solvent. Evaporation gave 9.0 g of a thick brown resin which solidified upon cooling. A 2.3 g portion of this solid was further washed with cold ether and filtered giving 1.6 g of the desired product as an off-white granular solid; mp 103-104 °C; MS (EI) *m/e* 217 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.19 (s, 1, NH), 8.64 (m, 1, H-6'), 7.98 (m, 1, H-3'), 7.90 (m, 1, H-4'), 7.37 (br s, 2, H-5' and H-4), 4.32 (apparent q, 2, OCH_2CH_3), 1.33 (t, 3, OCH_2CH_3); IR (KBr) 3151, 3102, 2981, 1743, 1408, 1232, 1195, 1156, 1141, 1068, 1007, 766 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 160.5 (C=O), 147.8 (C-6'), 147.8 (C-2'), 145.6 (C-5), 140.0 (C-3), 139.5 (C-4'), 123.9 (C-5'), 121.0 (C-6'), 145.6 (C-5), 140.0 (C-3), 139.5 (C-4'), 123.9 (C-5'), 121.0 (C-3'), 107.1 (C-4), 60.8 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.67; H, 5.24; N, 19.28.

Ethyl 5-(3'-Pyridyl)pyrazole-3-carboxylate (76m). Ethyl 4-(3'-pyridyl)-2,5-dioxybutyrate (12.3 g, 0.056 mol) was mixed with 150 mL H_2O. Hydrazine hydrate (2.8 g, 0.056 mol) was slowly added with swirling, and the mixture was stirred overnight at room temperature. Four grams of the resulting light-yellow solid was recrystallized from EtOH giving 1.5 g yellow needles (and a second crop, 1.4 g of a yellow solid); mp 162-163 °C, MS (EI) *m/e* 217 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.22, 14.11 (s, 1, H-2), 9.10, 9.06 (2 s, 1, H-2'), 8.55 (m, 1, H-6'), 7.50 (m, 1, H-5'), 7.46, 7.35 (2 s, 1, H-4), 4.35 (m, 2, OCH_2CH_3), 1.34 (m, 3, OCH_2CH_3, IR (KBr) 3107, 2988, 1725, 1332, 1284, 1254, 1187, 1034, 959, 814 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.5 (C=O), 144.7 (C-5), 143.2 (C-2'), 140.8 (C-6'), 138.9 (C-4'), 137.6 (C-3), 130.3 (C-3'), 126.6 (C-5'), 107.1 (C-4), 61.1 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.70; H, 5.27; N, 19.48.

Ethyl 5-(4'-Pyridyl)pyrazole-3-carboxylate (76n). Ethyl 4-(4'-pyridyl)-2,4-dioxybutyrate (11.9 g, 0.054 mol) was mixed with 150 mL H_2O. Hydrazine hydrate (2.8 g, 0.056 mol) was slowly added with swirling, and the mixture was stirred overnight at room temperature. Two grams of the resulting light-yellow solid were chromatographed through silica gel with EtOAc-pet. ether (3:1) giving 1.4 g of a white granular solid; mp 211-213 °C; MS (EI) 217 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.34 (br s, 1, H-2), 8.14 (d, J = 6 Hz, 2, H-2'), 7.86 (m, 2, H-3'), 7.52 (s, 1, H-4), 4.35 (q, 2, OCH_2CH_3), 1.34 (t, 3, CH_3); IR (KBr) 1727, 1610, 1448, 1283, 1249, 1207, 1154, 1005, 957, 840 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.0 (C=O), 147.5 (C-4'), 145.6 (C-5), 142.7 (C-2'), 137.5 (C-3), 122.1 (C-3'), 109.5 (C-4), 61.3 (OCH_2), 14.2 (CH_3). *Anal.* Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.64; H, 5.43; N, 19.27.

Ethyl 4-Bromo-5-methylpyrazole-3-carboxylate (77a). 5-Methyl pyrazole-3- carboxylic acid, ethyl ester (1.54 g, 0.01 mol) was dissolved in 60 mL of glacial acetic acid. The solution was cooled in an ice water bath before bromine (1.6 g, 0.01 mol) was slowly added with stirring. The solution was stirred at 0 °C for 1 h. A white solid formed which partially dissolved while the reaction mixture was allowed to warm to room temperature. The solution was poured over 200 mL ice water. Sodium bicarbonate was slowly added to the solution until all of the acetic acid had been neutralized. The mixture was then extracted with 300 mL ether. The ether was dried and evaporated to a light yellow solid. Since the odor of HOAc persisted, even after 24 h under vacuum, the solid material was again added to a $NaHCO_3$ solution and extracted with ether. Drying and concentration gave a 1.4 g of the desired product as a light yellow solid; mp 80-81 °C; MS (EI) *m/e* 232, 234 (M, M + 2); ^{1}H NMR (Me_2SO-d_6) δ 11.2 (br s, 1, NH), 4.36 (q, J = 7 Hz, 2, *OCH2CH3*), 2.30 (s, 3, CH_3), 1.35 (t, J = 7 Hz, 3, OCH_2CH_3); IR (KBr) 3180, 3080, 2972, 2952, 2857, 1731, 1451, 1267, 1175, 1086 cm^{-1}. ^{13}C NMR (Me_2SO + CF_3COOD) δ 160.1 (C=O), 141.8 (C-5), 137.3 (C-3), 95.0 (C-4), 60.3 (OCH_2CH_3), 14.1 (OCH_2CH_3), 10.1 (C-1'). *Anal.* Calcd for $C_7H_9N_2O_2Br$: C, 36.07; H, 3.89; N, 12.04. Found: C, 36.15; H, 4.14; N, 12.08.

Ethyl 5-Methyl-4-chloropyrazole-3-carboxylate (77b). Ethyl 5-methylpyrazole-3-carboxylate (3.4 g, 0.022 mol) was dissolved in glacial acetic acid (25 mL) at room temperature. Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the glacial acetic solution. After 1 h, a white solid precipitated. Stirring was continued until the solid had gone back into solution, and the whole was stirred for a total of about 4 h. The reaction mixture was poured over ~200 mL of ice and water and neutralized with aqueous bicarbonate solution. The resulting off-white solid was filtered, dried, and recrystallized from ether. Chromatography with silica gel and $CHCl_3$ gave 0.8 g of pure compound as well as some slightly impure product (~1.1 g); mp 95-96 °C; MS (EI) *m/e* 188 (M^+); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) 13.85, 13.58 (s, 1, NH), 4.29 (q, J = 7.2 Hz, 12, OCH_2CH_3), 2.23 (s, 3, CH_3), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3). IR (KBr) 3092, 2981, 2961, 2932, 2866, 1733, 1458, 1266, 1176, 1107 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 160.0 (C=O), 140.1 (C-5), 135.7 (C-3), 109.6 (C-4), 60.4 (OCH_2), 14.1 (OCH_2CH_3), 9.2 (C-11).

Ethyl 5-(*p*-Fluorophenyl)-4-bromopyrazole-3-carboxylate (77c). Ethyl 5-(*p*-fluorophenyl)pyrazole carboxylate (2.34 g, 0.1 mol) was added to 60 mL glacial acetic acid. Bromine (1.6 g, 0.1 mol) was then added, and the reaction mixture was stirred for 4 h. The acetic acid was removed under vacuum before water was added. Aqueous sodium bicarbonate was added until the solution was neutral. Ether extraction, drying, and partial

solvent evaporation yielded two crops of solids (the first white and the second a light orange). Neither of these were pure by MS, and therefore they were combined with the mother liquor and the whole chromatographed (silica gel, $CHCl_3$-MeOH 9.5:1) giving 1.5 g of a white solid; mp 176-178 °C; MS (EI) *m/e* 312 (M^+); ^1H NMR (Me_2SO-d_6) δ 14.35 (s, 1, NH), 7.80 (m, 2, Ar-H), 7.36 (m, 2, Ar-H), 4.34 (q, J = 7 Hz, 2, OCH_2CH_3), 1.34 (t, J = 7 Hz, 3, OCH_2CH_3); IR (KBr) 2989, 1735, 1505, 1413, 1235, 1191 1164, 1048, 973 cm^{-1}; ^{13}C NMR data; (Me_2SO-d_6 + CF_3COOD) δ 164.1, 160.8 (C-4'), 159.5 (C=O), 144.7 (C-3), 136.8 (C-5), 130.1, 130.0 (C-2'), 126.0 (C-1'), 115.8, 115.5 (C-3'), 94.2 (C-4), 60.9 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2BrF$: C, 46.03; H, 3.22; N, 8.97. Found: C, 46.39; H, 3.27; N, 9.03.

Ethyl 5-(*p*-Fluorophenyl)-4-chloropyrazole-3-carboxylate (77d). Ethyl-5-(*p*-fluorophenyl)pyrazole carboxylate (2.34 g, 0.1 mol) was dissolved in 60 mL glacial acetic acid. Chlorine gas (scrubbed with conc. H_2SO_4) was bubbled through the reaction mixture for a total of 18 h before the reaction mixture was poured over ice-water. The resulting yellow solid (~2.9 g) was recrystallized from hot ether, giving a light yellow solid which was further washed with room temperature ether. A white solid was obtained (1.6 g); mp 176-178 °C; MS (EI) *m/e* 268 (M^+) ^1H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.45 and 14.20 (s, 1, NH), 7.84, 7.38 (m, 4, Ar-H), 4.36 (br s, 2, OCH_2CH_3), 1.34 (m, 3, OCH_2CH_3); IR (KBr) 2991, 1736, 1505, 1416, 1236, 1192, 1165, 1058, 974, 842 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 164.0, 160.8 (C-4'), 159.3 (C=O), 142.9 (C=3), 135.1 (C-5), 129.6, 129.5 (C-2'), 125.6 (C-1'), 116.0, 115.7 (C-3'), 109.1 (C-4), 60.9 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2ClF$: C, 53.73; H, 3.76; N, 10.44. Found: C, 53.60; H, 3.83; N, 10.30.

Ethyl 5-(*p*-Bromophenyl)-4-bromopyrazole-3-carboxylate (77e). Ethyl 5-(*p*-bromophenyl)pyrazole-3-carboxylate (2.0 g, 0.0068 mol) was dissolved in 25 mL glacial acetic acid. Bromine (1.62 g, 0.01 mol) was added and the mixture was stirred for 20 h. The reaction was worked up by pouring over 40 mL ice and water. The resulting white solid was washed with aqueous sodium bicarbonate and recrystallized from EtOH, giving a total of 1.7 g of product; mp 187-189 °C; MS (EI) *m/e* 372 (M^+); ^1H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.56, 14.28 (s, 1, NH), 7.79, 7.21 (m, 4, Ar-H), 4.35 (m, 2, OCH_2CH_3), 1.33 (m, 3, OCH_2CH_3); IR (KBr) 3125, 2975, 1730, 1480, 1464, 1240, 1193, 1046, 1008, 968, 962, 841 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) 159.3 (C=O), 144.7 (C-3), 136.5 (C-5), 131.6 (C-2'), 129.6 (C-3'), 128.8 (C-1'), 122.3 (C-4'), 92.4 (C-4), 60.9 (OCH_2CH_3), 14.1 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2Br_2$: C, 38.53; H, 2.69; N, 7.49. Found: C, 38.90; H, 2.85; N, 7.44.

Ethyl 5-(*p*-Chlorophenyl)-4-bromopyrazole-3-carboxylate (77f). Ethyl 5-(*p*-chlorophenyl)pyrazole carboxylate (1.9 g, 0.0076 mol) was dissolved in 25 mL glacial acetic acid. Bromine (1.3 g, 0.008 mol) was then added and the reaction mixture was stirred for 2 days. The mixture was then added to 400 mL ice and water and was neutralized with $NaHCO_3$ (added slowly). Ether extraction, drying, and solvent evaporation followed by recrystallization from ether gave a white solid (1.6 g); mp 195-197 °C; MS (EI) 268 (M^+); ^1H NMR (Me_2SO-d_6) δ 14.42 (s, 1, NH), 7.30 (d, J = 8 Hz, 2, Ar-H), 7.60 (d, J = 8 Hz, 2, Ar-H), 4.35 (q, J = 7 Hz, 2, OCH_2CH_3), 1.35 (t, 3, OCH_2CH_3); IR (KBr) 2985, 2922, 1735, 1492, 1237, 1192, 1095, 1048, 973, 837 cm^{-1}. ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 159.4 (C=O), 144.5 (C-3'), 136 (C-5'), 133.8 (C-4'), 129.4 (C-2'),

128.7 (C-3'), 128.5 (C-1'), 94.5 (C-4), 60.9 (OCH_2), 14.1 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2BrCl$: C, 43.73; H, 3.06; N, 8.50. Found: C, 43.88; H, 3.15; N, 8.60.

Ethyl 5-(*p*-Chlorophenyl)-4-chloropyrazole-3-carboxylate (77g). Ethyl 5-(*p*-chlorophenyl)pyrazole-3-carboxylate (2.1 g, 0.084 mol) was dissolved in glacial acetic acid (≈25 mL). Chlorine (scrubbed through conc. H_2SO_4) was slowly bubbled through the HOAc solution with stirring for three days. The reaction mixture was poured over 400 mL ice-water, stirred, and neutralized with the slow addition of $NaHCO_3$. Ether extraction gave a crude product which was chromatographed (silica gel, ether-petroleum ether, 2:3) to give 1.5 g of a white solid; mp 194-195 °C; MS (EI) *m/e* 284 (M^+); ^1H NMR (Me_2SO-d_6, tautomeric mixture) δ 14.52, 14.38 (s, 1, NH), 7.39, 7.30 (m, 2, Ar-H), 7.66, 7.58 (m, 2, Ar-H), 4.38 (m, 2, OCH_2CH_3), 1.36 (m, 3, OCH_2CH_3); IR (KBr) 3175, 2987, 1736, 1486, 1413, 1239, 1193, 1096, 1058, 973, 964, 836 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.1 (C=O), 142.9 (C-5), 134.9 (C-3), 133.7 (C-4'), 128.9 (C-2',3'), 128.2 (C-1'), 109.5 (C-4), 60.9 (OCH_2CH_3), 14.2 (CH_2CH_3). *Anal.* Calcd for $C_{12}H_{10}N_2O_2Cl_2$: C, 50.55; H, 3.54; N, 9.82. Found: C, 50.17; N, 3.64; N, 9.79.

Ethyl 5-Phenyl-4-bromopyrazole-3-carboxylate (77h). Ethyl 5-phenylpyrazole-3-carboxylate (2.0 g, 0.0093 mol) was dissolved in glacial acetic acid (50 mL). Bromine (1.48 g, 0.0093 mol) was added, and the reaction mixture was stirred for 40 h at room temperature. It was then poured over 158 mL of ice and water. The resulting white gummy solid was filtered, washed with 500 mL aqueous $NaHCO_3$, and again filtered to dryness. The crude white solid was then chromatographed (silica gel, ether-petroleum ether, 2:3) and recrystallized from ether giving 1.2 g white solid; mp 129-131 °C; MS (EI) *m/e* 295 (M^+); ^1H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.48, 14.25 (s, 1, NH), 7.76 (m, 2, Ar-H), 7.20 (m, 3, Ar-H), 4.34 (m, 2, OCH_2CH_3), 1.35 (t, J = 7 Hz, 3, OCH_2CH_3); IR (KBr) 2973, 2929, 1736, 1457, 1236, 1193, 1051, 972, 764, 688 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + 1 drop TFA) δ 159.8 (C=O), 145.0 (C-5), 137.4 (C-3), 129.4 (C-1'), 128.9 (C-4'), 128.7 (C-3'), 127.8 (C-2'), 94.1 (C-4), 60.8 (OCH_2), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_{11}N_2O_2Br$: C, 48.93; H, 3.76; N, 9.49. Found: C, 48.68; H, 3.97; N, 9.73.

Ethyl 5-Phenyl-4-chloropyrazole-3-carboxylate (77i). Ethyl 5-phenylpyrazole-3-carboxylate (1.4 g, 0.0064 mol) was dissolved in glacial acetic acid (50 mL). Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the solution, and the reaction mixture was stirred for 2 h at room temperature. It was then poured over ~400 mL ice-water, the solution was neutralized with $NaHCO_3$, and the resulting light yellow flaky solid was filtered and dried. The solid was then dissolved in ether and insoluble material was removed by filtration. The ether solution was evaporated to dryness and the resulting gummy solid was chromatographed (silica gel, ether-pet. ether, 2:3) giving 0.8 g of a fluffy white solid; mp 115-116 °C; MS (EI) *m/e* 250 (M^+); ^1H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.44, 14.20 (s, 1, NH), 7.80, 7.50 (m, 5, Ar-H), 4.35 (m, 2, OCH_2CH_3), 1.33 (m, 3, OCH_2CH_3); IR (KBr) 3250, 2985, 1723, 1709, 1276, 1181, 1162, 1055, 843, 771, 691, 685 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + 1 drop TFA) δ 159.8 (C=O), 143.6 (C-5), 135.9 (C-3), 129.2 (C-1'), 129.1 (C-4'), 129.0 (C-3'), 127.5 (C-2'), 61.0 (C-4), 39.5 (OCH_2), 14.2 (CH_2CH_3). *Anal.* Calcd for $C_{12}H_{18}N_2O_2Cl$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.45; H, 4.64; N, 11.44.

Ethyl 5-(*p*-Nitrophenyl)-4-bromopyrazole-3-carboxylate (77k). Ethyl 5-(*p*-nitrophenyl)pyrazole-3-carboxylate (2.1 g, 0.008 mol) was dissolved in glacial acetic acid (25 mL). Bromine (1.27 g, 0.007 mol) was added

to the solution, and the mixture was stirred overnight at room temperature. An aliquot of the reaction mixture was then poured over ice and water and the resulting solid was filtered and dried. An additional 0.001 mol of bromine was added and the mixture was stirred over a second night. The reaction mixture was poured over ice and water (~400 mL), and the resulting slurry was neutralized with sodium bicarbonate. The slurry was filtered giving a light brown solid which was added to another ~300 mL H_2O and refiltered giving a white solid (1.9 g); mp 173-174 °C; MS (EI) *m/e* 339 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 14.70 (s, 1, NH), 8.36 (d, J = ~9 Hz, 2, Ar-H), 8.10 (d, J = ~9 Hz, 2, Ar-H), 4.36 (q, J = ~6 Hz, 2, OCH_2CH_3), 1.46 (t, J = ~8.5 Hz, 3, OCH_2CH_3); IR (KBr) 33.6, 3110, 1734, 1689, 1603, 1517, 1347, 1236, 1215, 1044, 958, 855 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.4 (C=O), 147.9 (C-4'), 145.6 (C-5), 137.4 (C-1'), 136.1 (C-3), 129.0 (C-2'), 124.2 (C-3'), 96.1 (C-4'), 61.7 (CH_2), 14.3 (CH_3). *Anal.* Calcd for $C_{12}H_{10}N_3O_4Br$: C, 42.37; H, 2.96; N, 12.35. Found: C, 41.95; H, 3.06; N, 12.66.

Ethyl 4-(*p*-Nitrophenyl)-4-chloropyrazole-3-carboxylate (77l). Ethyl 5-(*p*-nitrophenyl)pyrazole-3-carboxylate (2.3 g, 0.0088 mol) was dissolved in glacial acetic acid. Chlorine gas, scrubbed through H_2SO_4, was bubbled through the median mixture overnight. The mixture was then poured over ice, giving a light yellow solid. Sodium bicarbonate was slowly added until no more solid appeared to be precipitating from the solution. The solid was filtered, dried, chromatographed, (silica gel, ether-pet. ether, 2:3), and recrystallized, giving 1.7 g of a pure white solid (as well as a second crystal fraction consisting of 0.2 g of a slightly impure product), mp 177-178 °C); MS (EI) 295 (M^+); ^{1}H NMR (Me_2SO-d_6 + 1 drop CH_3COOD) δ 14.36 (s, 1, NH), 8.36 (m, 2, Ar-H), 8.15 (m, 2, Ar-H), 4.40 (q, J = 7.5 Hz, 2, OCH_2CH_3), 1.36 (m, 3, OCH_2CH_3); IR (KBr) 3355, 1751, 1698, 1517, 1389, 1348, 1296, 1262, 1225, 830 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + 1 drop CF_3COOD) δ 158.7 (C=O), 147.4 (C-4'), 143.2 (C-5), 136.3 (C-1'), 134.2 (C-2'), 128.2 (C-2'), 124.1 (C-3'), 110.9 (C-4), 61.3 (CH_2), 14.2 (CH_3). *Anal.* Calcd for $C_{12}H_{10}ClN_3O_4$: C, 48.75; H, 3.51; N, 14.21. Found: C, 48.90; H, 3.54; N, 14.09.

Ethyl 5-(*p*-Methoxyphenyl)-4-bromopyrazole-3-carboxylate (77m). Ethyl 5-(*p*-methoxyphenyl)pyrazole-3-carboxylate (2.0 g, 0.0087 mol) was dissolved in 50 mL glacial acetic acid. Bromine (1.39 g, 0.0087 mol) was added and the whole stirred for 2 h. The reaction mixture was poured over ice water and neutralized with sodium bicarbonate. The resulting white solid was filtered and recrystallized from ethanol, giving fine white needles (1.5 g); mp 148-149 °C; MS (EI) 324 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 14.16 (br s, 1, NH), 7.70 (m, 2, Ar-H), 7.09 (m, 2, Ar-H), 4.34 (q, J = ~7.2 Hz, 2, OCH_2CH_3), 3.82 (s, 3, OCH_3), 1.33 (t, J = ~7.2 Hz, 3, OCH_2CH_3); IR (KBr) 3109, 3067, 2971, 1720, 1611, 1511, 1420, 1277, 1257, 1197, 1180, 1045, 843, 828 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 160.0 (C=O), 159.8 (C-4'), 144.2 (C-5), 137.7 (C-3), 129.1 (C-2'), 121.2 (C-1'), 114.1 (C-3'), 93.3 (C-4), 60.6 (OCH_2CH_3), 55.5 (OCH_3) 14.1 (CH_2CH_3). *Anal.* Calcd for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N, 8.45. Found: C, 47.76; H, 4.05; N, 8.63.

Ethyl 5-(2',4'-Dichlorophenyl)-4-bromopyrazole-3-carboxylate (77n). Ethyl 5-(2',4'-dichlorophenyl)-4-bromopyrazole-3-carboxylate (2.0 g, 0.007 mol) was dissolved in glacial acetic acid (25 mL). Bromine (1.12 g, 0.007 mol) was added to the solution, and the mixture was stirred overnight at room temperature. After work up (by pouring into ice water acid, and neutralizing with bicarbonate solution) the reaction mixture was found to still contain starting material. The solid was dissolved in glacial acetic acid again, more bromine (~1

g) was added, and the mixture was stirred at room temperature for two days. The reaction mixture was poured over ice water, and the mixture neutralized with sodium bicarbonate giving a gummy yellow solid which was isolated, dried, and filtered through ~40 g silica gel with ether giving a white powder (1.6 g); mp 119-120 °C; MS (EI) 362 (M^+); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.62, 14.35 (s, 1, NH), 7.84, 7.56 (m, 3, Ar-H), 4.38 (s, 2, OCH_2CH_3, 1.36 (m, 3, OCH_2CH_3); IR (KBr) 3303, 1711, 1474, 1467, 1250, 1101, 1041, 966, 829, 806 cm^{-1}; ^{13}C NMR ($MeSO$-d_6) δ 159.3 (C=O), 144.3 (C-5), 135.8 (C-3), 135.3 (C-4′), 134.5 (C-2′), 133.7 (C-6′), 129.4 (C-3′) 128.0 (C-1′), 127.6 (C-5′), 97.4 (C-4), 61.0 (OCH_2), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_9BrCl_2N_2O_2$: C, 39.59; H, 2.49; N, 7.70. Found: C, 39.57; H, 2.56; N, 7.69.

Ethyl 5-(2′,4′-Dichlorophenyl)-4-chloropyrazole-3-carboxylate (77o). Ethyl 5-(2′,4′-dichlorophenyl)pyrazole-3-carboxylate (2.1 g, 0.008 mol) was dissolved in glacial acetic acid. Chlorine gas (scrubbed with conc. sulfuric acid) was bubbled through the solution for 4 h. The reaction mixture was poured over ice water, and the resulting solution was neutralized with bicarbonate and extracted with ether. Drying and evaporation resulted in 2.4 g of a viscous, pale yellow oil which was chromatographed (silica gel, ether:pet ether, 2:3) to give 2.0 g of a colorless viscous oil. The oil was redissolved in ether, petroleum ether was added, and after sitting overnight, a white solid precipitated from the solution. The precipitate was isolated as a white granular solid (1.4 g); mp 127.8 °C; ^{1}H NMR (Me_2SO-$d6$, mixture of tautomers) δ 14.62, 14.36 (s, 1, NH), 7.82-7.59 (br s, 3, Ar-H), 4.40 (m, 2, OCH_2CH_3), 1.37 (t, 3, OCH_2CH_3); IR (KBr) 3301, 1713, 1471, 1252, 1101, 1077, 1046, 968, 831, 805 cm^{-1}; ^{13}C NMR (Me_2SO-d_6 + CF_3COOD) δ 159.1 (C=O), 142.5 (C-5), 135.4 (C-4′), 134.4 (C-2′), 134.1 (C-3), 133.6 (C-6′), 129.4 (C-3′), 127.6 (C-5′), 127.3 (C-1′), 111.8 (C-4), 61.0 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_9Cl_3N_2O_2$: C, 45.10; J, 2.84; N, 8.77. Found: C, 45.07; H, 3.03; N, 8.79.

Ethyl 5-(2′,4′-Difluorophenyl)-4-bromopyrazole-3-carboxylate (77p). Ethyl 5-(2-difluorophenyl)pyrazole-3-carboxylate (2.4 g, 0.0095 mol) was dissolved in 30 mL glacial acetic acid. Bromine (1.71 g, 0.01 mol) was added and the mixture was stirred for 6 h. The reaction mixture was poured over ice water (~400 mL) and neutralized with sodium carbonate. The resulting gummy yellow solid was filtered and dried. Since mass spectrometric and TLC analysis of this product showed the presence of starting material, the solid was redissolved in glacial acetic acid, and about 1 g of bromine was added. Overnight stirring was followed by the mixture again being poured over ice water (~400 mL) and neutralized with sodium carbonate. The resulting white solid was isolated and chromatographed (silica gel, 2:3 ether-petroleum ether), giving 1.3 g of a white granular solid; mp 87.8 °C; MS (EI) *m/e* 295 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.62, 14.38 (s, 1, NH), 7.62, 7.48, 7.28 (m, 3, C-3′,5′,6′-H), 4.35 (m, 2, OCH_2CH_3), 1.34 (t, 3, OCH_2CH_3); IR (KBr) 3245, 1732, 1444, 1266, 1147, 1123, 1051, 980, 955, 849 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 163.4 (q, $^1J_{C_4',F_4}$ = 249.2 Hz, $^3J_{C_4',F_2}$ = 11.8 Hz, C-4′), 159.6 (C=O), 160.0 (q, $^1J_{C_2',F_2}$ = 251.2 Hz, $^3J_{C_2,F4}$ = 12.3 Hz, C-2′), 141.5 (C-5), 136.4 (C-3), 133.3 (d d, $^3J_{C_6',F4}$ = 10.1 Hz, $^3J_{C_5',F2}$ = 4.1 Hz, C-6′), 114.4 (d d, $^2J_{C_4',F_2}$ = 15.2 Hz, $^4J_{C_4',F_4}$ = 3.7 Hz, C-1′), 112.1 (d d, $^2J_{C_5',F_4}$ = 21.7 Hz, $^4J_{C_5',F_4}$ = 3.7 Hz, C-5′), 97.1 (C-4), 61.1 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_9BrF_2N_2O_2$: C, 43.53; H, 2.75; N, 8.46. Found: C, 43.50; H, 2.78; N, 8.45.

Ethyl 5-(2',4'-Difluorophenyl)-4-chloropyrazole-3-carboxylate (77q). Ethyl 5-(2',4'-difluorophenyl)pyrazole-3-carboxylate (2.1 g, 0.0083 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the solution and the reaction mixture was stirred for 6 h at room temperature. It was then poured over ~400 mL ice water, and the solution was neutralized with $NaHCO_3$. The resulting gummy yellow solid was filtered, dried, and chromatographed (silica gel, 2:3 ether-petroleum ether), giving 1.3 g of a granular white solid. Further drying in vacuum resulted in a yield of 1.2 g of the granular white powder; mp 102-103 °C; MS (EI) *m/e* 286 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.60, 14.24 (s, 1, NH), 7.45 (m, 3, H-3',5',6'), 4.36 (m, 2, OCH_2CH_3), 1.32 (m, 3, OCH_2CH_3), 1.32 (m, 3, OCH_2CH_3); IR (KBr) 3251, 1729, 1444, 1270, 1245, 1148, 1058, 950, 957, 850 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 163.3 (d d, ^1J = 249.6 Hz, ^3J = 11.6 Hz, C-4'), 159.9(d d, ^1J = 252.3 Hz, ^3J = 12.7 Hz, C-2'), 159.3 (C=O), 139.5 (C-5), 134.6 (C-3), 132.9 (m, $^3J_{C_6',F_4}$ = 9.9 Hz, $^3J_{C_6',F_2}$ = 4.2 Hz, C-6'), 115.6 (d d, $^2J_{C_1',F_2}$ = 15.4 Hz, $^4J_{C_1',F_4}$ = 3.3 Hz, C-1'), 112.2 (d d, $^2J_{C_5',F_4}$ = 21.6 Hz, $^4J_{C_5',F_2}$ = 3.6 Hz, C-5'), 111.5 (C-4), 104.8 (t, $^2J_{C_3',F_2}$ = $^2J_{C_3',F_4}$ = 26.0 Hz, C-3'), 61.1 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{12}H_9ClF_2N_2O_2$: C, 50.28; H, 3.16; N, 9.77. Found: C, 49.97; H, 3.29; N, 9.51.

Ethyl 5-(2'-Pyridyl)-4-bromopyrazole-3-carboxylate (77r). Ethyl 5-(2'-pyridyl)pyrazole-3-carboxylate (2.1 g, 0.0097 mol) was dissolved in glacial acetic acid (30 mL). Bromine (1.55 g, 0.0097 mol) was added, and the reaction mixture was stirred overnight at room temperature. It was then poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and filtered through silica gel with ethyl acetate. Solvent evaporation gave 2.5 g of a fluffy light-brown solid; mp 107-108 °C; MS (EI) *m/e* 295 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.51 (s, 1, NH), 8.73 (m, 1, H-6'), 8.11 (br s, 1, H-3'), 7.99 (br s, 1, H-4'), 7.49 (m, 1, H-5'), 4.33 (q, 3, OCH_2CH_3), 1.34 (t, 3, OCH_2CH_3); IR (KBr) 3175, 2928, 1732, 1600, 1468, 1446, 1265, 1246, 1192, 1047, 786 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.6 (C=O), 148.2 (C-6'), 146.4 (C-2'), 142.2 (C-5), 139.6 (C-4'), 139.1 (C-3), 124.7 (C-5'), 122.7 (C-3'), 95.1 (C-4), 61.0 (OCH_2CH_3). *Anal.* Calcd for $C_{11}H_{10}BrN_3O_2$: C, 44.62; H, 3.40; N, 14.19. Found: C, 44.75; H, 3.63; N, 14.23.

Ethyl 5-(2'-Pyridyl)-4-chloropyrazole-3-carboxylate (77s). Ethyl 5-(2'-pyridyl)pyrazole-3-carboxylate (1.7 g, 0.0078 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the reaction mixture with stirring for 1.5 h at room temperature. The reaction mixture was poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried and chromatographed (silica gel, ether) giving 1.8 g of the desired product as a light-brown solid; mp 127-128 °C. MS (EI) *m/e* 251 (M); ^{1}H NMR (Me_2SO-d_6) δ 13.5 (br s, 1, NH), 8.73 (d, 1, H-6'), 8.05 (m, 2, H-2',3'), 7.49 (m, 1, H-5'), 4.34 (q, 2, OCH_2CH_3), 1.34 (t, 3, OCH_2CH_3); IR (KBr) 3185, 1731, 1480, 1251, 1198, 1158, 1068, 1052, 1002, 787, 680 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 159.5 (C=O), 148.3 (C-6'), 146.0 (C-2'), 140.4 (C-5), 139.8 (C-4'), 136.6 (C-3), 124.7 (C-5'), 122.3 (C-2'), 110.5 (C-4), 61.1 (OCH_2CH_3), 14.2 (OCH_2CH_3). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.16; H, 4.17; N, 16.83.

Ethyl 5-(3'-Pyridyl)-4-bromopyrazole-3-carboxylate (77t). Ethyl 5-(3'-pyridyl)pyrazole-3-carboxylate (2.1 g, 0.0097 mol) was dissolved in glacial acetic acid (30 mL). Bromine (1.55 g, 0.0097 mmol) was added, and the reaction mixture was stirred for 3 h at room temperature. It was then poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and filtered through silica gel with

ether. solvent evaporation gave 1.5 g of a fluffy white solid (further elution gave an additional 0.7 g of a slightly impure light-brown solid); mp 162-163 °C; MS (EI) *m/e* 295 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.66, 14.46 (br s, 1, H-2), 89.88 (s, 1, H-2'), 8.68 (m, 1, H-6'), 8.18 (2 s, 1, H-4'), 7.68 (m, 1, H-5'), 4.38 (apparent q, 2, OCH_2CH_3), 1.36 (t, 3, OCH_2CH_3); IR (KBr) 2792, 2730, 2678, 1339, 1561, 1414, 1229, 959, 812, 705 cm^{-1} ^{13}C NMR (Me_2SO-d_6) δ 158.4 (C=O), 144.6 (C-2'), 143.1 (C-6', C-5), 140.8 (C-4'), 135.1 (C-3), 128.9 (C-3'), 126.2 (C-5'), 95.9 (C-4), 61.3 (OCH_2CH_3), 14.1 (OCH_2CH_3). *Anal.* Calcd for $C_{11}H_{10}BrN_3O_2$: C, 44.62; H, 3.40; N, 14.19. Found: C, 44.71; H, 3.68; N, 14.03.

Ethyl 5-(3'-Pyridyl)-4-chloropyrazole-3-carboxylate (77u). Ethyl 5-(3'-pyridyl)pyrazole-3-carboxylate (1.8 g, 0.0083 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the reaction mixture with stirring for 2 h at room temperature. The reaction mixture was poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and chromatographed (silica gel, ether) giving 1.2 g of the desired product as a light-brown granular solid; mp 180-181 °C; MS (EI) *m/e* 251 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.35 (br s, 1, NH), 9.2 (m, 1, H-2'), 6.7 (d, 1, H-6'), 8.19 (2 t, 1, H-4'), 7.57 (2 d, 1, H-5'), 4.36 (q, 2, OCH_2CH_3), 1.35 (t, 3, OCH_2CH_3); IR (KBr) 1726, 1717, 1385, 1230, 1219, 1205, 1196, 961, 811, 700 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 158.3 (C=O), 144.7 (C-2'), 142.8 (C-6'), 141.3 (C-5), 140.0 (C-4'), 133.4 (C-3), 128.2 (C-3'), 126.2 (C-5'), 110.8 (C-4), 81.3 (OCH_2CH_3), 14.1 (OCH_2CH_3). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.36; H, 4.08; N, 16.79.

Ethyl 5-(4'-Pyridyl)-4-bromopyrazole-3-carboxylate (77v). Ethyl 5-(4'-pyridyl)pyrazole-3-carboxylate (2.0 g, 0.0092 mol) was dissolved in glacial acetic acid (30 mL). Bromine (1.47 g, 0.0092 mol) was added, and the reaction mixture was stirred for 3 h at room temperature. It was then poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting solid was filtered, dried, and filtered through silica gel with ether. Solvent evaporation gave 1.8 g of a fluffy white solid; mp 192-194 °C; MS (EI) *m/e* 295 (M); ^{1}H NMR (Me_2SO-d_6) δ 14.70 (s, 1, H-2), 8.72 (br d, J = 4 Hz, 2, H-2'), 7.83 (br d, J = 6 Hz, 2, H-3'), 4.37 (q, 2, OCH_2), 1.36 (t, 3, OCH_2CH_3); IR (KBr) 1720, 1607, 1410, 1380, 1220, 1206, 1008, 958, 834, 776 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 158.1 (C=O), 144.6 (C-2'), 144.3 (C-4'), 143.2 (C-5), 135.1 (C-3), 123.1 (C-3'), 97.1 (C-4), 61.5 (OCH_2), 14.1 (CH_3). *Anal.* Calcd for $C_{11}H_{10}BrN_3O_2 \cdot 0.1H_2O$: C, 44.07; H, 3.50; N, 14.02. Found: C, 43.71; H, 3.62; N, 13.70.

Ethyl 5-(4'-Pyridyl)-4-chloropyrazole-3-carboxylate (77w). Ethyl 5-(4'-pyridyl)pyrazole-3-carboxylate (2.0 g, 0.0092 mol) was dissolved in glacial acetic acid (30 mL). Chlorine (scrubbed with conc. H_2SO_4) was bubbled through the reaction mixture with stirring for 4 h at room temperature. The reaction mixture was poured over ice water (~400 mL) and neutralized with $NaHCO_3$. The resulting dark-yellow solid was filtered through silica gel with ether, and recrystallized from ether giving two crystal fractions (0.9 and 0.8 g). The first fraction was found to be sufficiently pure compound 77w as a yellow granular solid; mp 180-182 °C; MS (EI) *m/e* 251 (M); ^{1}H NMR (Me_2SO-d_6, mixture of tautomers) δ 14.74-14.56 (br s, 1, H-2), 8.72 (br s, 2, H-2'), 7.86 (br s, 2, H-3'), 4.36 (m, 2, OCH_2CH_3), 1.34 (t, 3, OCH_2CH_3); IR (KBr) 1716, 1609, 1407, 1384, 1237, 1218, 1209, 1009, 954, 833 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.8 (C=O), 145.5 (C-4'), 143.4 (C-2'),

141.4 (C-5), 133.4 (C-3), 123.0 (C-3'), 112.8 (C-4), 61.6 (OCH_2CH_3), 14.1 (OCH_2CH_3). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.26; H, 4.08; N, 16.99.

5-(2',4'-Dimethoxyphenyl)pyrazole-3-carboxamide (78a). Ethyl 5-(2',4'-dimethoxyphenyl)pyrazole-3-carboxylate (2.0 g, 0.0072 mol) was dissolved in conc. NH_4OH (50 mL) and stirred at room temperature for 80 h. The reaction mixture was then poured into ~100 mL water and acidified to pH 5-6 with diluted H_2SO_4. The resulting solid was filtered, dried, and chromatographed (silica gel, 1:9 MeOH-$CHCl_3$) giving 1.8 g of an off-white granular solid; mp 174-175 °C; MS (EI) *m/e* 247 (M); ^{1}H NMR (Me_2SO-d_6, mixture of rotomers) δ 13.38, 13.12 (s, 1, NH), 7.92, 7.80, 7.42, 7.20 (m, 2, NH_2), 7.12 (d, 1, H-6'), 6.92 (s, 1, H-4), 6.67 (s, 1, H-3'), 6.65 (d, 1, H-5'), 3.89 (s, 3, OCH_3), 3.81 (s, 3, OCH_3); IR (KBr) 3229, 1680, 1639, 1612, 1602, 1594, 1498, 1310, 1297, 1210 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 163.5 (C=O), 160.9 (C-4'), 157.3 (C-2'), 145.0 (C-3), 142.1 (C-5), 128.8 (C-6'), 111.4 (C-1'), 105.7 (C-5'), 104.7 (C-4), 98.9 (C-3'), 55.7 (OCH_3), 55.4 (OCH_3). *Anal.* Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.56; H, 5.62; N, 16.96.

5-(2',4'-Dichlorophenyl)pyrazole-3-carboxamide (78b). Ethyl 5-(2',4'-dichlorophenyl)pyrazole-3-carboxylate (2.1 g, 0.0074 mol) was dissolved in 50 mL conc. NH_4OH and the solution was stirred at room temperature for two days. Since starting material still was detectable by mass spectrometric analysis, dioxane (20 mL) was added and the solution was heated to 40-50 °C for two more days. The reaction mixture was cooled and poured into ~100 mL water. The solution was acidified to pH 5-6 with diluted H_2SO_4. The resulting off-white solid was filtered and dried, yielding 1.5 g of the desired product; mp 294-295 °C; MS (EI) *m/e* 255, 257 (M, M + 2); ^{1}H NMR (Me_2SO-d_6) δ 13.69 (s, 1, NH), 7.90 (s, 1, H-4), 7.80 (d, J = 8.2 Hz, 1, H-6'), 7.74 (d, J = 2 Hz, 1, H-3'), 7.53 (d d, J = 2.2 Hz, J = 8.5 Hz, H-5'), 7.46 (s, 1, NH_2), 7.29 (s, 1, NH_2); IR (KBr) 3390, 3280, 3218, 3179, 1705, 1689, 1606, 1481, 1408, 815 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 161.1 (C=O), 144.2 (C-5), 141.2 (C-3), 133.1 (C-4'), 131.7 (C-2'), 131.4 (C-6'), 129.5 (C-1'), 127.5 (C-5'), 106.2 (C-4). *Anal.* Calcd for $C_{10}H_7N_3Cl_2O$: C, 46.90; H, 2.76; N, 16.42. Found: C, 47.04; H, 2.90; N, 16.04.

Methyl 2-[(2-ethoxy-2-oxoethyl)hydrazono]propanoate [AVS-2909] (79). Sodium acetate (6.36 g, 77.6 mmol) and methyl pyruvate (7.93 g, 77.6 mmol) were dissolved in a mixed solvent system consisting of MeOH (97 mL) and water (32 mL). Ethyl hydrazinoacetate monohydrochloride (12 g, 77.6 mmol) was added as a solid and the reaction mixture was stirred at room temperature for 48 h. The solvents were then evaporated to dryness and the residue was dissolved in chloroform and washed with water. The pH 5 water layer was then adjusted to pH 7 with 1 *N* NaOH. The aqueous layer was then extracted twice with chloroform. The chloroform layers were combined, dried with $MgSO_4$, filtered, and evaporated. After drying *in vacuo* over P_2O_5, the resulting yellow oil crystallized giving a pale-yellow solid in from 80-100% yield. Crystallization from ether-pet. ether (30-60 °C) (5:1) provided **79** as a white crystalline solid; mp 65 °C; MS (EI) *m/e* 202 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 1.22 (t, 3, $COOCH_2CH3$), 1.87 (s, 4, CH_3C=N), 3.64 (s, 3, $COOCH_3$), 4.05 (d, 2, $NHCH_2CO_2$), 4.11 (q, 2, $COOCH_2CH_3$), 7.67 (t, 1, NH). *Anal.* Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.30; H, 6.97; N, 13.90.

3(5)-Carbomethoxy-4-hydroxy-5(3)-methylpyrazole (80).[29] Sodium (3.1 g, 135 mmol) was added to cold (5 °C) MeOH (200 mL). After the sodium had reacted, crude methyl pyruvate hydrazone (**79**) (7.4 g, 51.4 mmol) was added in one aliquot, and the solution was heated at reflux for 4 h. The solution was chilled in

an ice bath and then, concentrated HCl (11.2 mL) was added slowly over 10 min. (If necessary, more HCl or $NaHCO_3$ is added to adjust the pH to near neutral by pH paper.) Most of the MeOH was then evaporated, and the residue was dissolved in water. After readjusting the pH to near 7, the product was extracted with ethyl acetate (7 x 40 mL). The ethyl acetate layers were combined, dried with sodium sulfate, filtered, and evaporated to dryness. The crude product (7.22 g, 90 % yield) was used in the next step without further purification. An analytical sample was obtained by column chromatography on 400 mesh silica gel with chloroform-methanol (9:1) as the eluant; mp 154-155 °C; MS (EI) *m/e* 156 (M^+); ^1H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 3.77 (s, 3, $COOCH_3$), 8.35, 12.75 (br s, 2, OH and NH). *Anal.* Calcd for $C_6H_8O_3N_2$: C, 46.15; H, 5.16; N, 17.94. Found: C, 45.82; H, 5.36; N, 17.89.

Methyl 1-Acetyl-4-acetyloxy-3-methyl-1*H*-pyrazole-5-carboxylate [AVS-2956] (81). Crude **80** (5.78 g, 37 mmol) was dissolved in acetic anhydride (50 mL) and pyridine (27 mL), and the mixture was then heated at 90 °C for 3 h. After cooling, the solvents were removed by vacuum, and the residue was dissolved in diethyl ether and washed with water (2 x 30 mL). The ether layer was dried with sodium sulfate, filtered, and evaporated to give an orange-tinted residue. Trituration with cold ether, filtering, and drying gave 7.55 g of **81** (two crops, 85 %) as fine white needles; mp 75-77 °C; MS (EI) *m/e* 240 (M^+); ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3, $COCH_3$), 2.4 (s, 3, $COCH_3$), 2.68 (s, 3, CH_3), 3.84 (s, 3, $COOCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 10.64 (CH_3-3), 20.03, 22.39 ($OCOCH_3$ and $NCOCH_3$), 52.10 ($COOCH_3$), 134.38, 134.56, 136.61 (C-3, C-4, C-5), 160.25 ($COOCH_3$), 168.33, 171.38 (NCO, OCO). *Anal.* Calcd for $C_{10}H_{12}N_2O_5$: C, 50.02; H, 5.00; N, 11.67. Found: C, 49.73; H, 5.15; N, 11.66.

Methyl 1-Acetyl-4-acetyloxy-3-bromomethyl-1*H*-pyrazole-5-carboxylate [AVS 2996] (82). Compound **81** (3.0 g, 12.5 mmol), benzoyl peroxide (250 mg, 1.03 mmol), *N* bromosuccinimide (4.90 g, 27.5 mmol) and potassium carbonate (1.0 g, 7.23 mmol) were added to CCl_4 (120 mL) and refluxed for 2 h. After chilling the mixture to 5-10 °C, the solution was filtered and evaporated *in vacuo*. Trituration of the residue with isopropanol crystallized the product which was filtered and dried to give 3.28 g (82%) of **82** as a white solid; mp 94-96 °C; MS (FAB) *m/e* 319 (M + 1); ^1H NMR (Me_2SO-d_6) δ 2.38 (s, 3, $OCOCH_3$), 2.73 (s, 3, $NCOCH_3$), 3.87 (s, 3, $COOCH_3$), 4.86 (s, 2, CH_2Br); *Anal.* Calcd for $C_{10}H_{11}BrN_2O_5$: C, 37.64; H, 3.47; N, 8.78. Found: C, 37.73; H, 3.63, N, 8.64.

3(5)-[(1,3-Dibenzyloxy-2-propoxy)methyl]-4-hydroxy-1*H*-pyrazole-5(3)-carboxamide (84) via Methyl 3(5)-[(1,3-dibenzyloxy-2-propoxy)methyl]-4-hydroxy-1*H*-pyrazole-5(3)-carboxylate (83). Di-*O*-benzylglycerol (17.07 g, 62.66 mmol) in dry THF (20 mL) was added dropwise over 0.5 h at room temperature to a stirred suspension of 60% NaH (2.51 g, 62.64 mmol) in dry THF (60 mL). Approximately 1 h after the addition was complete, bromomethylpyrazole **82** (4.5 g, 14.1 mmol) in dry THF (20 mL) was added in one aliquot at room temperature under nitrogen. After stirring 15 min at room temperature, the temperature was raised to 60 °C for 0.5 h. The reaction was immediately cooled in an ice bath, and acetic acid (3.76 g, 62.66 mmol) was added dropwise, resulting in the reaction mixture acquiring a deep red color. The solvents were evaporated, and the residue was partitioned between water and ethyl acetate. The resulting emulsion was treated with a small amount of acetic acid and extracted with ethyl acetate (4 x 100 mL). The ethyl acetate extracts were combined and evaporated to dryness to give a semisolid residue that was chromatographed on silica gel (70-

230 mesh) eluting first with chloroform to remove excess di-*O*-benzylglycerol and then with ethyl acetate to elute product **83** as part of a complex mixture. The combined product-containing fractions were evaporated to dryness giving 4.5 g of a residue which was added to cold saturated methanolic ammonia (~25 mL) and transferred to a steel bomb. The mixture was heated at 95 °C for 5 h, cooled, and evaporated to dryness. After being dissolved in a small amount of chloroform and filtering, the filtrate was chromatographed on silica gel (230-400 mesh) with a $CHCl_3$-MeOH gradient (98-95%). An additional 1.4 g of di-*O*-benzylglycerol and a small amount of unreacted **83** were obtained by eluting with $CHCl_3$-MeOH (98:2). Switching the gradient to 95:5 resulted in the elution of product **84** as a clear oil which solidified on standing, 740 mg (35 % per step over two steps); MS (FAB) *m/e* 412 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 3.52 (m, 4, CH_2CHCH_2), 3.80 (br s, 1, $CHOCH_2$), 4.47 (s, 4, CH_2Ph), 4.56 (s, 2, $CHOCH_2$), 7.31 (m, 10, Ar-H), 7.33-7.7 (m, 2, $CONH_2$), 8.69, 9.38 (br s, 1, OH-4), 12.89, 12.96 (br, s, 1, NH, mixture of tautomers).

3(5)-[(1,3-dihydroxy-2-propoxy)methyl]-4-hydroxy-1*H*-pyrazole-5(3)-carboxamide (85). Compound **84** (520 mg, 1.26 mmol) and palladium hydroxide on carbon (100 mg) were added to 1:1 EtOH-cyclohexene and heated at reflux for 16 h. Because the reaction was incomplete, additional catalyst (20 mg) was added and reflux was continued for 8 h. The reaction mixture was cooled, filtered through Celite, and the filtrate was evaporated to dryness. Acetone was added and evaporated away several times to produce a white solid which was filtered and dried to give 239 mg of the desired product (82% in two crops); mp 134-136 °C; MS (FAB) *m/e* 232 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 3.42 (m, 5, CH_2CHCH_2), 4.56 (s, 2, CH_2OCH), 6.86 (br s, 1, $CONH_2$), 7.44 (br s, 2, OH-4, $CONH_2$), 12.84 (br s, 1, NH). *Anal.* Calcd for $C_8H_{13}N_3O_5$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.10, H, 5.83; N, 18.29.

***N,N*-Dimethyl-1-adamantanecarboxamide (86a).** 1-Adamantanecarboxylic acid chloride (2.0 g, 0.01 mol) was added to a solution containing approximately 20 mL benzene and 20 mL dimethylamine. The solution was heated in a hot water bath, with stirring, for 2 min. The solution was extracted with H_2O (10 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and H_2O (10 mL), respectively. The benzene was evaporated to dryness to yield 1.5 g of white crystals; mp 164-167 °C; MS (EI) *m/e* 207 (M^+); IR (KBr) 2971, 2944, 2902, 2848, 1614, 1492, 1451, 1379, 1343, 1161 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.96 (s, 6, NCH_3), 1.96 (s, 3, H-3), 1.92 (s, 6, H-2), 1.66 (s, 6, H-4); ^{13}C NMR (Me_2SO-d_6) δ 175.2 (CO), 40.8 (C-1), 38.3 (C-4), 38.0 (NCH_3), 36.1 (C-2), 27.9 (C-3). *Anal.* Calcd for $C_{13}H_{21}NO \cdot 0.2H_2O$: C, 74.03; H, 10.23; N, 6.64. Found: C, 74.18; H, 10.01; N, 6.24.

***N,N*-Butyl-1-adamantanecarboxamide (86b).** 1-Adamantanecarboxylic acid chloride (1.0 g, 0.005 mol) was added to a solution containing approximately 10 mL benzene and 10 mL *n*-butylamine. The solution was heated in a hot water bath, with swirling, for 2 min. The solution was then extracted with H_2O (5 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (5 mL), respectively. The benzene was evaporated to dryness to yield 0.54 g of white crystals; mp 85-87 °C; MS (EI) *m/e* 235 (M^+); IR (CBr) 3314, 2927, 2916, 2901, 2891, 2871, 2849, 1632, 1557, 1283 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 0.86 (t, 3, CH_3), 1.24 (m, 2, CH_2CH_3) 1.36 (m, 2, $CH_2CH_2CH_2$), 1.64 (s, 6, H-4), 1.72 (d, 6, H-2), 1.96 (s, 3, H-3), 3.02 (m, 1, $NHCH_2$). 7.28 (s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 39.67 (C-1), 38.71 (C-4), 38.04 ($NHCH_2$), 36.13 (C-2), 31.28 ($CH_2CH_2CH_2$),

27.64 (C-3), 19.43 (CH_2CH_3), 13.66 (CH_3). *Anal.* Calcd for $C_{15}H_{25}NO$: C, 76.54; H, 10.70; N, 5.95. Found: C, 76.59; H, 10.73; N, 5.94.

1-Adamantanecarboxanilide (86c). 1-Adamantanecarboxylic acid chloride (1.5 g, 0.008 mol) was added to a solution that contained approximately 10 mL benzene and 5 mL aniline. The solution was heated in a hot water bath for two min with swirling. The solution was then extracted with H_2O (5 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (5 mL), respectively. The benzene was evaporated to dryness to yield 1.3 g of white crystals. To insure the removal of any acid present, the solid was dissolved in ether, and reextracted with a saturated sodium bicarbonate solution. The ether extract was evaporated to dryness to yield 1.25 g white crystals; mp 190-192 °C; MS (EI) *m/e* 255 (M^+); IR (KBr) 3285. 2915, 2899, 2848, 1652, 1645, 1597, 1538, 1439, 1310, 757 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.70 (s, 6, H-4), 1.91 (d, 6, H-2), 2.02 (s, 3, H-3), 7.02 (t, 1, Ar-H-4), 7.28 (t, 1, Ar-H-3,5), 7.66 (d, 1, Ar-H-2,6), 9.09 (s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 175.74 (C=O), 139.23 (NHC), 128.21 (Ar-C-3,5), 122.93 (Ar-C-4), 120.08 (Ar-C-2,6), 40.81 (C-1), 38.22 (C,4,9), 35.95 (C-2,8,10), 27.62 (C-3,5,7). *Anal.* Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.84; H, 8.32; N, 5.44.

***N*-(2-Thiazolo)-1-adamantylcarboxamide (86d).** To 1-adamantanecarboxylic acid chloride (1 g, 0.005 mol) was added 2-aminothiazole (2 g, 0.02 mol) in approximately 30 mL benzene. The solution was warmed in a hot water bath for 2 min. The benzene solution was then extracted successively with H_2O (5-10 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (5-10 mL). The benzene was evaporated yielding a white solid which was recrystallized from hot ethanol (0.62 g); mp 198-200 °C; MS (FAB) *m/e* 263 (M + 1); IR (KBr) 3246, 2915, 2906, 2850, 1650, 1542, 1313, 1278, 1268, and 1154 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.69 (s, 1, O=C-NH), 7.48 (d, 1, J = 3.8 Hz, thiazole H-4), 7.19 (d, 1, J = 3.8 Hz, thiazole H-5), 2.06 (s, 3, H-3), 1.95 (s, 6, H-2), 1.70 (s, 6, H-4); ^{13}C NMR (Me_2SO-d_6) δ 176.78 (O=C-NH), 158.5 (thiazole C-2), 137.3 (thiazole C-4), 113.1 (thiazole C-5), 40.4 (C-1), 37.5 (C-2), 35.7 (C-4), 27.5 (C-3). *Anal.* Calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91; N, 10.68. Found: C, 63.97; H, 7.11, N, 10.98.

***N*-Methyl-1-adamantaneacetamide (87a).** Thionyl chloride (0.44 mL, 0.006 mol) was added to 1 g (0.005 mol) of 1-adamantaneacetic acid and the mixture was heated gently, with stirring, for several hours. After bringing the mixture to room temperature, the aniline (5 mL, 0.05 mol) in approximately 20 mL ether was added. The solution was again heated gently over a hot water bath, cooled to room temperature, and let stir over the weekend. The mixture was extracted with H_2O (10 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (10 mL). The ether layer was then evaporated to dryness to yield 1.0 g of white crystals, mp 113-116 °C; MS (EI) *m/e* 207 (M^+); IR (KBr) 3272, 2926, 2901, 2847, 1653, 1636. 1562, 1451, 1409, 1339 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.57 (br s, 1, NH), 2.54 (d, 3, J = 6 Hz, CH_3), 1.91 (br s, 3, H-3), 1.81 (s, 2, CH_2C=O), 1.59 (m, 12, H-2,4); ^{13}C NMR (Me_2SO-d_6) δ 170.1 (C=O), 50.0 (CH_2C=O), 42.1 (C-2), 36.5 (C-4), 32.1 (C-1), 28.0 (C-3), 25.3 (CH_3). *Anal.* Calcd for $C_{13}H_{21}NO \cdot 0.5H_2O$: C, 72.18; H, 10.25; N, 6.48. Found: C, 72.15; H, 9.95; N, 6.40.

***N*-Methyl-1-noradamantanecarboxamide (88).** Thionyl chloride (0.51 mL, 0.007 mol) was added to 3-adamantanecarboxylic acid (1.0 g) with stirring. The mixture was heated gently for approximately 2-3 h. The mixture was let cool to room temperature, then about 0.5 mL methylamine in 10 mL ether was added

slowly with stirring. The mixture was left stirring overnight at room temperature. Additional ether was added and the mixture was extracted with H_2O (10 mL), 5% HCl (10 mL), 5% NaOH (10 mL), and again with H_2O (10 mL). The ether layer was then evaporated to dryness to yield 0.73 g of white crystals; mp 160-163 °C; MS (EI) *m/e* 179 (M^+); IR (KBr) 3335, 2929, 2867, 2849, 1631, 1630, 1540, 1461, 1406, 1311, 1293 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.42 (s, 1, NH), 2.59 (d, 2, J = 6 Hz, CH_3), 2.50 (t, 1, J = 3 Hz, H-7), 2.22 (s, 2, H-3,5), 1.87 (d d, 3, J = 12 Hz, H-4), 1.68 (d d, 4, J = 6 Hz, H-6,9), 1.52 (d d, 4, J = 6 Hz, H-2,8); ^{13}C NMR (Me_2SO-d_6) δ 54.2 (C-1), 46.7 (C-6,9), 43.1 (C-2,8), 42.4 (C-7), 36.9 (CH_3), 34.2 (C-4), 25.9 (C-3,5). *Anal.* Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.82. Found: C, 73.65; H, 9.61; N, 7.73.

1-Adamantyl, 3-*t*-Butylthiourea [AVS-2885] (91). 1-Adamantamine (10 g, 66 mmol) was dissolved in 150 mL hexane. Insoluble material was filtered out and then *t*-butylisothiocyanate (8.4 mL, 66 mmol) was added. After stirring for 3 h, solvent was removed yielding 10.7 g in two batches of white solid. Submitted batch mp 137-139 °C; ^1H NMR ($CDCl_3$) δ 5.8 (br s, 1, NH), 5.6 (br s, 1, NH), 2.15 (s, 9, CH, CH_2), 1.7 (s, 4, CH_2), 1.45 (s, 9, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 179.5 (s, 1, C=S), 54.2, 53.2 (2 s, 2, C-NH), 42.2 (s, 3, C-4), 36.2 (s, 3, C-2), 29.5 (s, 3, C-3), 29.4 (s, 3, $C(CH_3)_3$); IR (KBr) 3274, 2907, 1537, 1391, 1356, 1324, 1310, 1299, 1201 cm^{-1}. *Anal.* Calcd for $C_{15}H_{26}N_2S$: C, 67.64; H, 9.84; N, 10.52. Found: C, 67.36; H, 9.99; N, 10.25.

1-Adamantylthiosemicarbazide (92). 1-Adamantylisothiocyanate (11.3 g, 0.059 mol) and hydrazine (1.89 mL, 0.059 mol) were combined in THF and the reaction mixture heated at reflux for approximately 2 h. The white solid that precipitated out was filtered, washed with ether, and dried, yield 15.69 g; mp 199-200 °C; MS (EI) *m/e* 225 (M^+); IR (KBr) 3287, 3197, 2913, 2893, 2855, 2848, 1530, 1361, 1236, and 805 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.6 (s, 1, S=C-*NH*-NH_2 or *NH_2*-C=S), 7.41 (s, 1, S=C-*NH*-NH_2 or *NH*-C=S), 4.50 (s, 2, S=C-NH-*NH_2*), 2.26 (d, 6, H-2), 2.01 (s, 3, H-3), 1.52 (s, 6, H-4); ^{13}C NMR (Me_2SO-d_6) δ 179.0 (NH-*C*=S), 51.9 (C-1), 41.3 (C-4), 35.9 (C-2), 29.0 (C-3). *Anal.* Calcd for $C_{11}H_{19}N_3S$: C, 58.63; H, 8.50; N, 18.65. Found: C, 58.95; H, 8.90; N, 18.76.

2-[1-(1-Adamantyl)ethylidene]hydrazinecarboximidamide Hydrochloride (93a). To a mixture of 1-adamantylmethyl ketone (1.78 g, 10 mmol) and aminoguanidine bicarbonate (1.36 g, 10 mmol) in 10 mL of methanol was added 1 mL concentrated HCl. After heating at reflux for 1.25 h, the reaction mixture was reduced by approximately two-thirds and then refrigerated overnight, resulting in the formation of a white solid. The solid was filtered, washed with ether, and dried; mp 210-212 °C; MS (EI) *m/e* 234 (M^+); IR (KBr) 3396, 3388, 3379, 3370, 3358, 2924, 2904, 1672, 1661, cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.86 (s, 1, NH), 7.53 (br s, 4, NH_2, H^+), 1.99 (s, 3, H-3), 1.85 (s, 3, N=C-*CH_3*), 1.73 (d, 6, H-2), 1.67 (m, 6, H-4); ^{13}C NMR (Me_2SO-d_6) δ 162.7 (HN-*C*-NH_2), 156.1 (N=*C*-CH_3), 39.9 (C-1), 38.7 (C-2), 36.1 (C-4), 27.6 (C-3), 12.4 (N=C-*CH_3*). *Anal.* Calcd for $C_{13}H_{23}N_4Cl \cdot 0.75H_2O$: C, 54.92; H, 8.68; N, 19.71. Found: C, 54.83; H, 8.57; N, 19.90.

2-[1-(1-Adamantyl)ethylidene]hydrazinecarbothioamide (93b). To a mixture of 1-adamantylmethyl ketone (0.89 g, 5 mmol) and thiosemicarbazide (0.45 g, 5 mmol) in 6 mL methanol was added 0.25 mL concentrated HCl, and the reaction mixture heated at reflux for 1 h. The mixture was allowed to cool at room temperature and stand overnight. The white solid that separated was filtered off, washed with ethanol, and dried, yielding 0.92 g of crystals; mp 206-207 °C; MS (EI) *m/e* 251 (M^+); IR (KBr) 3411, 2917, 2899, 2845, 1591, 1492, 1449, 1426, 1082, 527 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.82 (s, 1, *NH*OC=S), 8.09 (s, 1, S=C-*NH_2*), 7.30 (s, 1,

S=C*NH*), 1.98 (s, 3, H-3), 1.84 (s, 3, N=C-CH_3), 1.71 (d, 6, H-2), 1.67 (s, 6, H-4); ^{13}C NMR (Me_2SO-d_6) δ 178.7 (NHO*C*-NH_2), 159.3 (NH=*C*-CH_3), 39.9 (C-1), 38.7 (C-2), 36.1 (C-4), 27.6 (C-3), 12.4 (NH=C-*C*H_3). *Anal.* Calcd for $C_{13}H_{21}N_3S$: C, 62.21; H, 8.42; N, 16.72. Found: C, 62.12; H, 8.68; N, 17.01.

3-Bromo-*N*-1-(2′,3′-dihydroxypropyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one[34] (100). In a 250 mL round-bottomed flask equipped with a magnetic stirrer and a calcium sulfate tube was placed a mixture of 3-bromopyrazolo[3,4-*d*]pyrimidine (5 g, 25 mmol), glycidol (1.73 g, 23 mmol), a trace of anhydrous potassium carbonate, and DMF (100 mL). The mixture was stirred at 60 °C for 24 h. After cooling to room temperature the undissolved material was filtered by suction and the solution was evaporated by reduced pressure. The resulting orange syrup was recrystallized from ethanol and applied to a cation exchange column with 50% MeOH and 50% H_2O as the eluting solvents. The eluant was concentrated, recrystallized from ethanol, and dried to yield 600 mg (9%); mp 230-232 °C; MS (EI) *m/e* 289 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 3.48 (m, 2, H-4′,5′), 3.98 (m, 1, H-3′), 4.46 (m, 2, H-1′,2′), 4.75 (s, 1, OH), 4.95 (d, 1, OH), 8.2 (d, 1, *J* = 29.77, H-7), 12.49 (s, 1, NH); IR 3292, 3287, 2884, 1690, 1609, 1541, 1392, 1074, 1032, 786 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 50.8 (C-1′), 69.8 (C-2′), 63.6 (C-3′), 104.3 (C-4), 120.2 (C-3), 148.7 (C-7), 153.1 (C-5), 156.3 (C-8). *Anal.* Calcd for $C_8H_{10}N_4O_3Br$: C, 33.20; H, 3.13; N, 19.38. Found: C, 33.08; H, 3.45; N, 18.90.

1-(2,3-Dihydroxypropyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (101). To a solution of 3-bromo-1-(2,3-dihydroxypropyl)pyrazolo[3,4-*d*]pyrimidin-4,5-one (3.5 g, 12 mmol) in 50% aqueous ethanol (300 mL) was added Pd/C (5%) 600 mg, and the mixture was hydrogenated at 48 psi at room temperature for 24 h. The reaction mixture was filtered through Celite pad and the filtrate was evaporated to dryness. Crystallization of the residual solid from 50% aqueous methanol gave white crystals, yield 0.9 g (35.7%); mp 232-234 °C; MS (FAB) *m/e* 210 (M); ^{1}H NMR (Me_2SO-d_6) δ 3.40 (m, 2, H-3′), 4.00 (m, 1, H-2′), 4.26 (m, 2, H-1′), 4.81 (br s, 2, OH), 8.05 (s, 1, H-3), 12.1 (s, 1, H-5); IR (KBr) 3270, 3262, 3250, 3085, 1700, 1651, 1595, 1580, 1535, 782 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.3 (C-4), 152.2 (C-7a), 147.5 (C-6), 134.0 (C-3), 105.6 (C-3a), 70.1 (C-2′), 63.7 (C-3′), 50.4 (C-1′). *Anal.* Calcd for $C_8H_8N_4O_3$: C, 45.71; H, 4.79; N, 26.66. Found: C, 45.72; H, 5.11; N, 26.29.

3-Bromo-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (102). 3-Bromoallopurinol **99** (11 g, 51 mmol) and β-D-ribofuranose 1-acetate 2,3,5-tribenzoate (30 g, 50 mmol) were added to dry nitromethane (125 mL) and brought to reflux temperature. $BF_3 \cdot Et_2O$ (9.9 g, 8.8 mL, 69.7 mmol) was added. The suspension became clear within 5 min and refluxing continued for 2.5 h. The solvent was evaporated to yield a dark brown foam which was dissolved in ethyl acetate (800 mL) and washed with saturated $NaHCO_3$ (2 x 300 mL) and then water (2 x 300 mL) and dried over $NaSO_4$. The solvent was removed to yield a brown foam. The foam was applied to a silica gel column using ethylacetate and cyclohexane (2:1) as the eluting solvents. The unreacted sugar eluted first and was followed by the N-1 isomer (Rf 0.37). The N-1 isomer was recrystallized from ethyl acetate and methanol (4:1) yield 4.7 g, 15%; mp 213-215 °C; MS (FAB) *m/e* 658 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 4.63 (m, $J_{5'a,5'b}$ = 12.5 Hz, 2, H-5′), 4.91 (m, $J_{4',5'b}$ = 3.3 Hz, $J_{4',5'a}$ = 3.8 Hz, 1, H-4′), 6.15 (t, $J_{3',4'}$ = 6.50 Hz, 1, H-3′), 6.25 (q, $J_{2',3'}$ = 5.35 Hz, 1, H-2′), 6.68 (d, $J_{1',2'}$ = 3.09 Hz, 1, H-1′), 7.45-8.07 (Ar-H's), 8.2 (s, 1, H-7), 12.59 (s, 1, H-5).

3-Bromo-1-β-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (102a). 3-Bromo-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (4.7 g, 7 mmol) was combined with methanolic ammonia (329 mL saturated at 0 °C) and placed in a steel bomb. The solution heated at 90-100 °C for 4 h overnight. The solution was evaporated to a clear brown residual oil and washed with benzene to remove benzamide. Crystals were formed from water and ethyl-acetate (4:1), yield 1.5 g (60.7%); mp 228-230 °C; MS (FAB) *m/e* 346 (M + 1); IR (KBr) 3399, 3392, 3377, 3373, 3370, 1697, 1599, 1533, 1093, 1044 cm^{-1}; 1H NMR (Me_2SO-d_6) δ 3.44 (m, $J_{4',5'_a}$ = 60 Hz, 1, H-5′, 3.55 (m, $J_{4',5'_b}$ = 4.7 Hz, 1, H-5′, 3.90 (q, 1, H-4′), 4.15 (q, $J_{3',4'}$ = 4.3 Hz, 1, H-4′), 4.52 (q, $J_{2',3'}$ = 4.9 Hz, 1, H-2′), 4.75 (t, $J_{5',5'\text{-OH}}$ = 5.6 Hz, 1, OH-5′), 5.28 (d, $J_{3',3'\text{-OH}}$ = 5.4 Hz, 1, OH-3′), 5.54 (d, $J_{2',2\text{-OH}}$ = 5.8 Hz, 1, OH-2′), 6.02 (d, $J_{1',2}$ = 4.7 Hz, 1, H-1), 8.16 (s, 1, H-6), 12.56 (s, 1, H-5); ^{13}C NMR (Me_2SO-d_6) δ 149.7 (C-6), 156.1 (C-4), 105.0 (C-4a), 122.2 (C-3), 153.7 (C-7a), 88.2 (C-1), 85.3 (C-2′), 73.1 (C-3′), 70.5 (C-4′), 62.0 (C-5′). *Anal.* Calcd for $C_{10}H_{11}N_4O_5Br$: C,34.59; H, 3.19; N, 16.13. Found: C, 34.67, H, 3.43; N, 16.45.

4-Amino-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (105). The 10% Pd/C catalyst (200 mg) was added to a solution of 4-amino-3-bromoribofuranosylpyrazolopyrimidine **104** (2.3 g, 6.4 mmol) and 50% aqueous ethanol (150 mL), and the mixture was hydrogenated at 40 psi at room temperature for 48 h. The reaction mixture was the filtered through a Celite pad, and the filtrate was evaporated to give a residual solid (0.7 g, 37.6%); mp 205-210 °C; MS (EI) *m/e* 267 (M^+); IR (KBr) 3424, 3258, 3221, 3165, 3157, 3151, 1658, 1603, 1573, 1041; ^1H NMR (Me_2SO-d_6) δ 3.44 (m, 1, H-5′), 3.56 (m, 1, H-5′), 3.92 (m, 1, H-4′), 4.22 (m, 1, H-3′) 4.62 (m, 1, H-2′), 4.88 (t, 1, OH), 5.12 (d, 1, OH), 5.36 (d, 1, OH), 6.08 (d, 1, H-1′), 7.76 (br s, 2, NH_2), 8.2 (d, 1, Ar-H); ^{13}C NMR (Me_2SO-d_6) δ 133.2 (C-3), 100.4 (C-4), 157.9 (C-5), 153.8 (C-7), 155.9 (C-9), 88.5 (C-1′), 73.1 (C-2′), 70.8 (C-3′), 85.0 (C-4′), 62.3 (C-5). *Anal.* Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.53. Found: C, 42.10; H, 5.42; N, 24.42.

A second batch of 4-amino-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**105**) was prepared by the reduction of **104** (2.2 g, 6.3 mmol) with $Pd/BaSO_4$ (200 mg) in ethanol to give 0.7 g (41.6%). MS (EI) *m/e* 267 (M^+); *Anal.* Calcd for $C_{10}H_{13}N_5O_4 \cdot 2H_2O$: C, 39.60; H, 5.65; N, 23.05. Found: C, 39.20; H, 5.40; N, 23.03. All other analytical data was essentially the same.

4(5)-Bromo-1(3*H*)-imidazole (111)[37]. Sodium sulfite 33 g (0.26 mol) in approximately 200 mL water and 2,4,5-tribromoimidazole (8 g, 0.026 mol) were refluxed for 3.5 h, cooled, and refrigerated overnight. Completeness of reaction checked with TLC (silica gel in ethyl acetate, developed in iodine). The reaction mixture was extracted with ether (5 x 250 mL), dried over sodium sulfate, filtered, and evaporated to dryness, yielding 3 g of a pale yellow solid; mp 118-119 °C; MS (EI) 302 (M^+); ^1H NMR (Me_2SO-d_6) δ 12.44 (br s, 1, H-1), 7.64 (s, 1, H-2), 7.25 (d, 1, J = 1.2 Hz, H-5); IR (KBr) 2817, 2811, 2590, 1297, 1189, 1069, 961, 821, 755, 619 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 135.7 (C-2, $^3J_{CH}$ = 8.3 Hz, $^1J_{CH}$ = 210.6 Hz), 115.6 (C-5, $^3J_{CH}$ = 3.0 Hz, $^1J_{CH}$ = 196.3 Hz), 113.2 (C-4 = C-Br), $^3J_{CH}$ = 9.4 Hz, $^1J_{CH}$ = 13.8 Hz). *Anal.* Calcd for $C_3H_3N_2Br \cdot 0.1H_2O$: C, 24.22; H, 2.17; N, 18.83. Found: C, 24.06; H, 1.97; N, 18.64.

4-Amino-1-pentanol (113). The preparation of *endo*-norbornylamine was followed.[38,39] A solution of 3-acetyl-1-propanol (51 mL), ammonium acetate (385 g) and sodium cyanoborohydride (22 g) in absolute

methanol (1.5 L) was stirred 48 h at 25 °C. Concentrated HCl was added until pH <2 and methanol was removed *in vacuo*. The residue was taken up in a minimum amount of water and extracted with ether (3 x 150 mL). The aqueous solution was brought to pH >10 with solid KOH, and extracted with chloroform (5 x 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give fairly pure product (47 g). The product was further purified by distillation (30 g); bp 124 °C/26 mm [lit.[27] bp 117-119 °C/25 mm]; IR (neat + a drop chloroform) 3342, 3277, 3219 (NH_2, OH), 2955, 2930, 2865 (CH), 1595, 1450, 1375, 1061 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.3-3.4 (t, 2, CH_2OH), 3.0-2.6 (m, 4, CH, OH, NH_2), 1.5-1.35, 1.35-1.2 (2 m, 4, CH_2CH_2), 1.0-0.9 (d, 3, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 60.9 (C-1), 46.1 (C-4), 36.1 (C-3), 29.4 (C-2) and 23.7 (C-5).

4-(4'-Hydroxy-1'-methylbutylamino)-7-chloroquinoline (114).[38,39] A mixture of 4,7-dichloroquinoline (22.3 g) and 4-amino-1-pentanol (23.2 g) was cautiously heated to 145 ± 2 °C with stirring in a 1L round bottom flask under dry conditions. The constant temperature and stirring was maintained for 4 h. The mixture was then cooled to below 100 °C, ice-water (200 mL) was added, and the reaction was stirred overnight. The solid obtained was filtered, washed with water and dried, 32.5 g; MS (EI) *m/e* 264 (M^+). This compound was used in the next step without further purification.

4-(4'-Hydroxy-1'-methylbutylamino)-7-chloroquinoline (114). A mixture of 4,7-dichloroquinoline (10.3 g, 0.05 mol) and 4-amino-1-pentanol (10.7 g, 0.1 mol) was cautiously heated to 145 °C under dry conditions while stirring in a 500 mL round bottom flask. The temperature and stirring were maintained for 4 h. The mixture was cooled to below 100 °C before ice water (100 mL) was added. After overnight stirring, the resulting white solid was filtered, washed with water, and dried to give 10.4 g of a white solid. MS (EI) *m/e* 264 (M^+). The product was then used without further purification.

4-(4'-Ethylamino-1'-methylbutylamino)-7-chloroquinoline (115a).[38,39] To 70 mL of 48% hydrobromic acid was cautiously added with cooling and stirring, 15 mL of concentrated sulfuric acid. carbinol 114 (32 g) was dissolved in the acid mixture and the resulting solution heated to boiling as rapidly as possible in an Erlenmeyer flask. The mixture was simmered gently until the formation of turbidity denoted the separation of a second phase (usually about 5-10 min. of heating was required). Heating was discontinued at once (longer heating appeared to destroy the product), the mixture was allowed to cool to 50 °C, and 100 mL of water was added. The dense, viscous lower layer was taken up in chloroform, and the aqueous layer was extracted with chloroform several times. The chloroform extracts were combined, dried ($MgSO_4$), and transferred to the flask to be used for the final step. Solvent was removed under reduced pressure with gentle warming, and the resulting viscous liquid was evenly distributed over the walls. The flask was then cooled in an ice-bath, and 200 mL of anhydrous ethylamine was added. The flask was sealed with a stopper wired on tightly, and the mixture was cooled and shaken until all of the salt dissolved. The solution was then stirred for 42 h at room temperature. Excess ethylamine was removed by distillation and the residue was taken up in 300 mL of water containing 100 g of potassium carbonate. The aqueous layer was extracted several times with chloroform, and the organic layers were pooled and concentrated. The residual liquid was taken up in an equal volume of alcohol, and water was added to incipient turbidity. Then, 6 *N* HCl was added until pH was between 8-8.2. The solution was further diluted with 600 mL of water and extracted

thoroughly with ether to remove the byproduct. The aqueous solution, upon treatment with 30 g of potassium hydroxide yielded crude product, which was removed by extraction with chloroform. The solvent was removed and distilled to give the pure product, 8.23 g; bp 175-180 °C (0.03 mm) [lit.[7] bp 173-175 °C 0.05 mm]. The distillate slowly solidified to a pale yellow solid, mp 100-102 °C; MS (EI) *m/e* 291 (M^+); IR (KBr) 3274 (broad, NH, NH), 2964 (CH), 2930, 2820, 1612, 1575, 1540 (aromatic), 1490, 1454, 1424, 1381, 1366, 1331, 1280, 1255, 1205, 1150, 1130, 1080 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.45-8.35 (d, 2, H-2,5), 7.85-7.80 (d, 1, H-8), 7.5-7.4 (d d, 1, H-6), 7.05-6.90 (d, 1, H-1), 6.50-6.45 (d, 1, H-3), 3.8-3.6 (m, 1, CH), 2.6-2.4 (m, 5, CH_2NHCH_2), 1.8-1.4 (m, 4, CH_2CH_2), 1.3-1.2 (d, 3, $CHCH_3$), 1.05-0.95 (t, 3, CH_2CH_3); ^{13}C NMR (Me_2SO-d_6) δ 151.6 (C-2), 149.3 (C-4 or C-8a), 149.1 (C-4 or C-8a), 133.1 (C-7), 127.3 (C-6 or C-8), 124.1 (C-5), 123.5 (C-6 or C-8), 117.3 (C-4a), 98.5 (C-3), 49.0 (C-4'), 47.5 (C-1'), 43.4 (CH_2CH_3), 33.3 (C-2' or C-3'), 26.2 (C-2' or C-3') 19.6 ($CHCH_3$), 15.0 (CH_2CH_3). *Anal.* Calcd for $C_{16}H_{22}N_3Cl$: C, 65.85; H, 7.60; N, 14.40. Found: C, 65.62; H, 7.69; N, 14.33.

1-Amino-6-iminopurine (117). A stirred suspension of adenine (1.35 g, 10.0 mmol) in ethanol (250 mL) was treated with *O*-mesitylenesulfonylhydroxylamine (6.0 g, 28.0 mmol). After 1 h all of the suspended solid had dissolved, and stirring was continued for 0.5 h, and a white solid separated. The mixture was chilled in a dry-ice/isopropanol bath, and the solid was collected, washed with cold methanol, and dried *in vacuo*: yield, 193 g (55%) [a second crop was obtained from the filtrate, and was crystallized to give another isomer (by MS and TLC)]. The product (1.93 g) was crystallized from methanol to give 1.25 g (which still contained a trace of an impurity by TLC). This mesitylenesulfonate salt of 1-aminoadenine was dissolved in a solution of acetonitrile and 1 *N* ammonium hydroxide (4:2), and evaporated with 6 g of silica gel (230-400 mesh, Aldrich) and then was chromatographed on a flash column (silica gel), and eluted with acetonitrile and 1 *N* ammonium hydroxide (4:1). Fractions containing the product were combined, evaporated, and dried *in vacuo* to give the free base of 1-amino-6-iminopurine (500 mg, 93% recovery); mp 205-207 °C dec; IR (KBr) (strong 1680-1625), 1545, 1470, 1425, 1375, 1335, 1185, 1175, 1120, 975, 645, 555. UV λ_{max} 207 (21,320), 257 (10,500) at pH 1; 208 (19,400), 260 (9,700) at pH 7; 269 (12,700) at pH 13. ^1H NMR (D_2O) δ 8.04 (s, 1, H-3), 8.32 (s, 1, H-8). *Anal.* Calcd for $C_5H_6N_6 \cdot 0.86H_2O$): C, 36.25; H, 4.70; N, 50.74. Found: C, 36.56; H, 4.42; N, 50.57.

1-Aminoadenosinium Mesitylene Sulfonate [AVS-4610] (118). Freshly prepared *O*-mesitylenesulfonylhydroxylamine (6 g) was added to a solution of adenosine (2.67 g) in methanol (200 mL). The solution was stirred at room temperature for 30 min and then immersed in a dry ice-isopropanol bath. The precipitate (2.7 g) was collected and dried, mp 193-194 °C; MS (FAB) *m/e* 283 (M + 1); UV λ_{max} 258 (12,740) at pH 1, 258 (12,790) at pH 7, 258 (13,460) at pH 13; IR (KBr) 3282, 3149, 3650-2800 (broad, NH_2, NH, OH, SO_3H), 2930, 1692 (SC_3H)1635, 1605 (aromatic), 1560, 1510, 1420, 1230, 1210, 1175, 1120, 1085, 1065, 1015, 905, 860 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.15-10.05 and 9.25-9.15 (br s, 2, C=NH and MesOH), 6.65-6.50 (br s, 2, NH_2), 5.95 (d, 1, J = 5 Hz, H-1'), 4.52 (t, 1, H-2'), 4.18 (t, 1, H-3'), 4.0 (q, 1, H-4'), 3.64 (2 q, 2, H-5'), 2.5 (s, 6, *O*-mesitylene-H's), 2.15 (s, 3, *p*-mesitylene-H's); ^{13}C NMR (Me_2SO-d_6) δ 151.4 (C-6), 148.9 (C-2, $^1J_{CH}$ = 218.8 Hz), 145.7 (C-4, $^3J_{C_4,H_8}$ = 13.15 Hz, $^3J_{C_4,H_2}$ = 5.1 Hz), 142.5 (C-8, $^1J_{C_8,H_8}$ = 217.8 Hz, $^3J_{C_1,H_1}$ = 4.05 Hz), 142.2 ($C\text{-}SO_3H$), 136.3 (Ar-C 4), 135.7 (Ar-C-2), 129.7 (Ar-C-3),

118.5 (C-5), 87.7 (C-1', $^1J_{C_1',H_1'}$ = 167.2 Hz), 85.8 (C-4'), 74.3 (C-2'), 70.0 (C-3'), 60.9 (C-5'), 22.6 (*o*-CH_3), 20.2 (*p*-CH_3); *Anal.* Calcd for $C_{19}H_{26}N_6SO_7$: C, 46.84; H, 5.49; N, 17.27. Found: C, 46.93; H, 5.53; N, 17.46.

1-Aminoadenosine, Hydrochloride (118, X = Cl). Freshly prepared *o*-mesitylenesulfonylhydroxylamine (6 g, 0.028 mol) was added to a solution of adenosine (2.67 g, 0.01 mol) in methanol (200 mL). The solution was stirred at 25 °C for 1 h, and was then chilled in a dry-ice/isopropyl alcohol bath. The solid was collected and dried *in vacuo*: yield 2.7 g (56%); mp 178-182 °C dec. This product (1.8 g, 0.0037 mol) was passed through a Dowex 1-X2 (Cl^- form) to get the chloride salt (1.15 g). The crude product was dissolved in a small amount of water, stirred with activated carbon and filtered. The clear solution was diluted with ethanol until cloudy and then ether was added to aid crystallization. The mixture was stirred, and then chilled. The product was collected, washed with ether, and dried *in vacuo*: yield 777 mg (24%); mp 200-203 °C; MS (FAB) 283 (M + 1); IR (KBr) 3400-3050 (broad, NH, NH_2, OH's, HCl), 1780, 1500, 1425, 1410, 1165, 1030, 1000, 820, 730, 710, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.68 (2 m, 2, CH_2-5'), 3.99 (apparent q, 1, H-4'), 4.17 (apparent q, 1, H-3') 4.52 (q, 1, H-2'), 5.16 (t, 1, OH-5'), 5.35 (d, 1, OH-3'), 5.68 (d, 1, H-1'), 6.74 (s, 2, NH_2-1), 8.68 (s, 1, H-8), 8.78 (s, 1, H-2), 9.39, 10.11 (2 br s, 2, H-$\overset{\oplus}{N}H_2$-6; ^{13}C NMR (Me_2SO-d_6) δ 60.83 (C-5'), 70.03 (C-3'), 74.35 (C-2'), 85.83 (C-4'), 87.66 ($^1J_{C_1',H_1'}$ = 166.3 Hz, C-1'), 118.48 ($^3J_{C_5,H_8}$ = 11.9 Hz, C-5), 142.60 ($J_{C_8,H_1'}$ = 3.9 Hz, J_{C_8} = 218.0 Hz, C-8), 147.82 ($^3J_{C_4,H_8}$ = 131.1 Hz, $^3J_{C_4,H_2}$ = 5.3 Hz, $J_{C_4,H_1'}$ = 2.6 Hz, C-4), 148.82 ($^1J_{C_2,H_2}$ = 218.7 Hz, C-2), 151.39 ($^3J_{C_6,H_2}$ = 5.5 Hz, C-6). *Anal.* Calcd for $C_{10}H_{15}ClN_6O_4 \cdot 0.5H_2O$: C, 36.64; H, 4.92; N, 25.65. Found: C, 36.83, 36.79; H, 5.27, 5.21; N, 25.68, 25.54.

1-Amino-7-deazainosine (122). A solution of 7-deazainosine (**121**) (534 mg, 2.0 mmol) in 1*N* sodium hydroxide (6 mL) was treated with a solution of hydroxylamine-*O*-sulfonic acid (340 mg, 3.00 mmol) in water (4 mL). The reaction solution was left in the refrigerator overnight. The solid that had formed was collected, and dried *in vacuo*: yield, 383 mg. This product was crystallized from water, and dried *in vacuo*: yield, 323 mg (57%); mp 220-222 °C dec; IR (KBr) 3430, 3310, 1665, 1495, 1420, 1226, 1085, 1055, 1030, 740 cm^{-1}. UV λ_{max} 205 nm (20,730), 213 (20,710), 261 (6,610) at pH 1; 213 (20,630), 261 (6,580) at pH 7; 216 (17,750), 262 (6,500) at pH 13; ^1H NMR (Me_2SO-d_6) δ 3.55 (2 m, 2, $J_{4',5'_a}$ = 4.0 Hz, $J_{4',5'_b}$ = 11.9 Hz, CH_2-5'), 3.88 (q, 1, H-4'), 4.07 (q, 1, $J_{3',4'}$ = 4.2 Hz, H-3'), 4.31 (q, 1, $J_{2',3'}$ = 5.6 Hz, H-2'), 5.0 (t, 1, $J_{5',5'\text{-OH}}$ = 5.4 Hz, OH-5'), 5.13 (d, 1, $J_{3',3'\text{-OH}}$ = 4.9 Hz, OH-3'), 5.33 (d, 1, $J_{2',2'\text{-OH}}$ = 6.04 Hz, OH-2'), 5.75 (s, 2, NH_2-1), 6.00 (s, 1, $J_{1',2'}$ = 6.1 Hz, H-1'), 6.57 (d, 1, J_{C_7,H_8} = 3.6 Hz, H-7), 7.41 (d, 1, H-8), 8.23 (s, 1 H-2). *Anal.* Calcd for $C_{11}H_{14}N_4O$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.53; H, 5.17; N, 19.89

1-Aminoguanosine (124). Guanosine hydrate (5.7 g, 20 mmol) was dissolved in 1*N* sodium hydroxide (60 mL), and then was treated with a solution of hydroxylamine-*O*-sulfonic acid (3.4 g, 30 mmol) in water (30 mL). The solution was stirred at room temperature overnight. The solid that formed was chilled, collected, washed with water, acetone, and dried under nitrogen: yield, 3.5 g (59%). This product was crystallized from dilute ammonium hydroxide followed by one crystallization from water. The product was dried *in vacuo* (P_2O_5): yield, 2.5 g (39%); mp 240 °C; IR (KBr) 3480, 3465, 3350, 3120, 1670, 1625, 1590, 1575, 1505, 1415, 1100, 1055, 1035, 1020. UV λ_{max} 257 nm (11,093), 277 (8,029) at pH 1; 208 (15,086), 257 (11,093) at pH

7; 254 (12,931), 274 (sh) at pH 13; ^{1}H NMR (Me_2SO-d_6) δ 3.56 (2 m, 2, CH_2-5′), 3.77 (q, 1, H-4′), 4.09 (t, 1, H-3′), 4.92 (t, 1, H-2′), 5.70 (d, 1, H-1′), 7.10 (s, 2, NH_2-1), 7.95 (s, 1, H-8). *Anal.* Calcd for $C_{10}H_{14}N_6O_5$: C, 40.27; H, 4.73; N, 28.18. Found: C, 40.50; H, 4.77; N, 28.42.

Ethyl 2,2,4-Trimethyldihydroquinoline-6-carboxylate (127). A mixture of ethyl 4-aminobenzoate (50 g, 0.302 mol) and iodine (3 g, 0.012 mol) in acetone (200 mL) and toluene (1000 mL) was refluxed for 24 h with stirring. The refluxing apparatus was then equipped with a distillation receiver to collect the acetone-water distillate. The reaction mixture was then cooled and the distillation was replaced with dry acetone. Distillation was then resumed and this process was repeated until the reaction had gone to completion. The solution was then cooled to room temperature, and the mixture was evaporated to yield a brown residue which was dissolved in ethyl acetate (200 mL), washed with 10% NaOH (2 x 100 mL), water (2 x 100 mL), and dried over $MgSO_4$. The ethyl acetate was evaporated to yield a dark solid which was washed with $CHCl_3$ and pet. ether. Crystallization from $CHCl_3$ and pet. ether (1:2) yielded pale-green crystals. MS (FAB) 245 (M + 1); IR (KBr) 3346, 1684, 1660, 1598, 1368, 1289, 1270, 1258, 1219, 111 cm^{-1}; UV λ_{max} 255 nm at pH 1; 233 nm at pH 7 and 13. ^{1}H NMR (Me_2SO-d_6) δ 1.25 (t, 9, CH_2CH_3, CH_3), 4.20 (q, 2, OCH_2CH_3), 5.34 (s, 1, H-3), 6.42 (d, 1, Ar-H), 6.77 (s, 1, NH), 7.5 (d, 2, Ar-H); ^{13}C NMR (Me_2SO-d_6) δ 51.8 (C-2), 31.6 (C-2′ + C-2″), 128.3 (C-3), 115.5 (C-4), 181.0 (C-4′), 126.6 (C-4a), 124.5 (C-5), 118.5 (C-6) 130.5 (C-7), 111.2 (C-8), 148.2 (C-8a), 165.9 (C-6′), 59.5 (C-6″), 14.4 (C-6‴). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 6.07. Found: C, 72.95; H, 8.12; N, 6.07.

Ethyl 1-*N*-Formyl-2,2,4-trimethyldihydroquinoline-6-carboxylate (128). Formic acetic anhydride[20] (18.05 g) was added dropwise to ethyl 2,2,4-trimethyldihydroquinoline-6-carboxylate (127) in a round-bottomed flask equipped with a calcium sulfate drying tube. The reaction stirred at room temperature for 24 h and the solution formed was evaporated to yield a residual green oil. The product was taken up into chloroform (100 mL) and washed with $NaHCO_3$ (100 mL), water (100 mL) and dried over $NaSO_4$. The solvent was filtered through 50 g of silica gel and then concentrated by evaporation. Crystallization with chloroform-pet. ether (1:2) gave a 26% yield of the compound; mp 68-69 °C; MS (FAB) 273 (M + 1); IR (KBr) 1718, 1704, 1666, 1602, 1340, 1290, 1261, 1421, 1109, 767 cm^{-1}; UV λ_{max} 252 nm at pH 1 and 7; 247 nm at pH 13; ^{13}C NMR (Me_2SO-d_6) δ 1.40 (t, 3, OCH_2CH_3), 1.54 (s, 6, $C(CH_3)_2$), 2.10 (s, 3, CH_3), 5.6 (s, 1, H-3), 6.42 (d, 1, Ar-H), 7.92 (s, 2, Ar-H), 8.60 (s, 1, HC=O); ^{13}C NMR (Me_2SO-d_6) δ 56.5 (C-2), 27.4 (C-2′ + C-2″), 134.4 (C-3), 126.2 (C-4), 175.5 (C-4′), 126.9 (C-4a), 128.5 (C-5), 127.7 (C-6), 124.0 (C-7), 121.8 (C-8), 138.5 (C-8a), 165.3 (C-6), 60.6 (C-6″), 14.2 (C-6‴), 161.2 (C-1′). *Anal.* Calcd for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.01; N, 5.12. Found: C, 69.83; H, 7.22; N, 4.83.

2,2,4-Trimethyl-1,2-dihydroquinoline-6-carboxylic Acid (129). A 250-mL round-bottomed flask fitted with a reflux condenser was used to mix ethyl 2,2,4-trimethyl-1,2-dihydroquinoline carboxylate (5 g, 20 mmol) in a 1 *N* NaOH (100 mL) aqueous solution. Ethanol (40 mL) was added dropwise to help the compound to into solution. The reaction mixture was heated at reflux (105 °C) for 18 h. After cooling to room temperature the reaction mixture was diluted with an equal volume of water (150 mL) and poured with stirring into 50 mL of HCl. The mixture was filtered and the filtrate was evaporated down to yield 3 g of crude product. Recrystallization from ethanol gave beige crystals (2 g); mp 226-228 °C; MS (EI) *m/e* 217;

^{1}H NMR (Me_2SO-d_6) δ 1.24 (s, 6, $C(CH_3)_2$), 1.9 (s, 3, CH_3), 5.32 (s, 1, H-vinyl), 6.42 (d, 1, Ar-H-8), 6.68 (s, 1, NH), 7.5 (m, 2, Ar-H-7,5), 11.96 (br s, 1, OH); IR (KBr) 2967, 1653, 1597, 1437, 1339, 1293, 1276, 1256, 1229, 1162 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 18.1 (1-Me), 31.5 (3-Me), 51.6 (C-2), 128.1 (C-3), 118.3 (C-4), 126.6 (C-4a), 124.7 (C-5), 116.2 (C-6), 113.1 (C-7), 111.0 (C-8), 147.1 (C-8a). *Anal.* Calcd for $C_{13}H_{15}NO_2 \cdot 0.5H_2O$: C, 69.00; H, 7.12; N, 6.19. Found: C, 69.14; H, 7.11; N, 6.15.

1-Formyl-2,2,4-trimethyl-3-[(3-chlorophenyl)carbonyloxy]-1,2,3,4-tetrahydro-4-hydroxyquinoline-6-carboxylic Acid Ethyl Ester (130). In a 200-mL round-bottomed flask *m*-chloroperoxybenzoic acid (3.58 g, 20.8 mmol) was added to a solution of 1-*N*-formyl-2,2,4-trimethyl-1,2-dihydroquinoline carboxylate and CH_2Cl_2 (100 mL). The reaction mixture was allowed to reflux (50 °C) with stirring for 18 h. After allowing the reaction mixture to cool to room temperature, the mixture was poured over cooled water (300 mL) and stirred for 30 min. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (2 x 100 mL), H_2O (1 x 100 mL), and dried over Na_2SO_4. Solvent was removed *in vacuo*. The residue was taken up in chloroform-pet. ether (1:3) and precipitation followed yielding pure product (1 g); mp 180-182 °C; MS (EI) *m/e* 445 (M); ^{1}H NMR (Me_2SO-d_6) δ 1.32 (t, 3, OCH_2CH_3), 1.49 (s, 3, CH_3), 1.55 (s, 3, CH_3), 1.78 (br s, 3, CH_3), 4.34 (q 2, OCH_2CH_3), 5.26 (s, 1, H-3). 5.85 (s, 1, OH), 7.5-7.7 (m, 5, Ar-H-3'), 7.92 (m, d d, 1, $J_{7,8}$ = 60.9 Hz, $J_{1,5}$ = 2.4 Hz, H-7), 8.19 (d, 1, Ar-H-5), 8.74 (s, 1, NCO-H); IR (KBr) 1724, 1694, 1685, 1674, 1667, 1609, 1336, 1292, 1266, 744 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 59.3 (C-2), 83.9-81.3 (C-3), 69.7 (C-4), 139.9 (C-4a), 128.4 (C-5), 126.1 (C-6), 120.6 (C-8), 139.4 (C-8a), 161.9 (C=O), 165.2 (C=O), 27.7-26.3, 23.5, 14.2 (CH_3), 60.6 (CH_2), 163.9 (C=O), 128.3, 130.6, 131.3, 133.1, 133.2 (aromatic). *Anal.* Calcd for $C_{23}H_{24}ClNO_6 \cdot 0.3H_2O$: C, 61.21; H, 5.49; N, 3.10. Found: C, 61.38; H, 5.50; N, 3.07.

Ethyl 2,2,4-Trimethyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (132). To a solution of ethyl 2,2,4-trimethyl-1,2-dihydroquinoline-6-carboxylate (2 g) in 50% aqueous ethanol (250 mL) was added Pd/C (5%, 425 mg). The mixture was hydrogenated at 25 psi for 72 h at room temperature. The reaction mixture was filtered through a Celite pad which was then further washed with hot ethanol. The filtrates were combined and evaporated to dryness. The resulting crude crystalline solid was recrystallized from aqueous ethanol (50%) to give off-white crystals. The compound was dried *in vacuo* over P_2O_5 (yield 1.6 g, 80%); mp 108-109 °C; MS (EI) 247 (M); IR (KBr) 3366, 3351, 1689, 1600, 1517, 1364, 1291, 1261, 1250, 1202 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.11 (s, 1, H-3), 1.21 (m, 12, CH_3), 1.72 (d d, 1, H-3), 2.81 (m, 1, H-4), 4.20 (q, 2, OCH_2CH_3), 6.44 (d, 1, H-8), 6.51 (s, 1, NH), 7.48 (d, 1, H-7), 7.65 (s, 1, H-5); ^{13}C NMR (Me_2SO-d_6) δ 165.9 (CO), 148.6 (C-8a), 128.4 (C-7), 127.9 (C-5), 122.6 (C-4a), 115.1 (C-6), 112.3 (C-8), 59.2 (OCH_2CH_3), 48.7 (C-1), 43.3 (C-3), 30.4 (CH_3), 28.1 (CH_3), 26.7 (C-4), 19.7 (CH_3), 14.4 (OCH_2CH_3). *Anal.* Calcd for $C_{15}H_{21}N_1O_2 \cdot 0.1H_2O$: C, 72.30; H, 8.59; N, 5.63. Found: C, 72.37; H, 8.83; N, 5.70.

5-Bromo-3-nitro-1,2,4-triazole (135). A solution of 3-nitro-1,2,4-triazole (5.7) g 0.05 mol), sodium hydroxide (2.0 g, 0.05 mol) and bromine (3.0 mL) in water (25 mL) was heated at 80 °C until the bromination appeared to be complete as shown by TLC (ethyl acetate developer). Because MS revealed the presence of some starting material, an additional 0.5 mL of bromine was added to the reaction solution, and the solution was stirred at 80 °C for 1 h, then stirred at room temperature for two days. A small aliquot was worked up and was found to still contain starting material, so another 1 mL addition of bromine was made and the

solution was again stirred at room temperature for two days. Work-up of another small aliquot still showed starting material, and therefore, a final addition of 1 mL bromine along with 1 mL 50% NaOH was made. The final reaction solution was acidified to pH 2 with 1 *N* HCl and extracted (4 x 50 mL) with ethyl acetate. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness yielding 5.0 g of an orange solid. Recrystallization from EtOAc-benzene gave 7 g of an off-white solid; mp 146-149 °C; MS (EI); *m/e* 192 (M); ^{1}H NMR (Me_2SO-d_6) δ 13.68 (br s, 1, H_2O + H^+ + NH); ^{13}C NMR (Me_2SO-d_6) δ 162.5 (CNO_2), 131.0 (CBr). *Anal.* Calcd for $C_2HN_3O_2Br$: C, 13.02; H, 0.64; N, 28.64 Found: C, 13.05; H, 0.68; N, 28.12.

6-Ethylthiopurine Riboside (137a). In a 250-mL round-bottomed flask stoppered with a calcium sulfate drying tube was mixed 11 g (38.7 mmol) of 6-mercaptopurine riboside, 5.9 g (42.6 mmol) of freshly dried K_2CO_3 and 150 mL of dry *N,N*-dimethylacetamide. To this well stirred mixture was added 4.2 g (38.7 mmol) of ethylbromide. The addition was dropwise over 3-5 min. The reaction was run under a nitrogen atmosphere. After 1-1/2 h of stirring at room temperature, thin-layer chromatography (TLC) indicated much product but some starting 6-MPR. The reaction mixture was heated at 55-60 °C for 1 h, filtered hot through a Celite pad, the flask and residue were washed with several portions of acetone, and the combined filtrate and washings was evaporated *in vacuo* to a syrup <50 °C. The syrup was treated twice with 150 mL portions of EtOH and evaporated. The syrup was then pumped at maximum vacuum for several hours. The residue was dissolved in 150 mL of hot acetone, filtered, concentrated to ~100 mL, cooled and scratched to induce crystallization. The white product was collected, washed with a little acetone ad dried at 65 °C for 18 h over phosphorus pentoxide; yield, 6.3 g (51%); mp 100-107 °C cap; UV λ_{max} 294 nm (17,600) 225 nm (10,300) at pH 1; 292 (19,300) 225 (10,800) at pH 7; 293 (19,400) 225 (10,700 at pH 13; MS (FAB) *m/e* 313 (M + 1); IR (KBr) 1567, 1435, 1420, 1335, 1211, 1170, 1127, 1119, 1084, 1058, 944 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.37 (t, 3, SCH_2CH_3), 3.36 (q, 2, SCH_2CH_3), 3.57 3.70 (2 m, 2, H-5′), 3.98 (apparent q, 1, H-4′), 4.18 (apparent q, 1, H-3′), 4.61 (q, 1, H-2′), 5.13 (t, 1, OH-2′), 5.24 (d, 1, OH-3′), 5.53 (d, 1, OH-5′), 6.00 (d, 1, H-1′), 8.71 (s, 1, H-8), 8.74 (s, 1, OH-2′). *Anal.* Calcd for $C_{12}H_{16}N_4O_4S$: C, 46.14, H, 5.16, N, 17.94. Found: C, 46.02; H, 5.18; N, 17.84.

6-Ethylthiopurine Riboside [AVS-2700] (137a). In a 250-mL round-bottomed flask stoppered with a calcium sulfate drying tube was mixed 6-mercaptopurine riboside (11 g, 38.7 mmol), freshly dried potassium carbonate (5.9 g, 42.6 mmol), and dry *N,N*-dimethylacetamide. To this well-stirred mixture was added ethylbromide (4.2 g, 38.7 mmol), dropwise over 3-5 min under nitrogen atmosphere. After 1.5 h at room temperature, thin-layer chromatography indicated mostly product along with some starting 6-MPR. The reaction mixture was heated at 55-60 °C for 1 h and filtered hot through a Celite pad. The flask and residue were washed with several portions of acetone, and the combined filtrate and washings were evaporated *in vacuo* to a syrup at <50 °C. The syrup was treated twice with 150 mL portions of EtOH and evaporated. The syrup was then pumped at maximum vacuum for several hours. The residue was dissolved in 150 mL of hot acetone, filtered, concentrated to ~100 mL, cooled, and scratched to induce crystallization. The white product was collected, washed with a little acetone, and dried at 65 °C for 18 h over phosphorus pentoxide; yield, 6.0 g (50%); mp 100-107 °C cap; UV λ_{max} 294 nm (17,600) 225 nm (10,300) at pH 1; 292 (19,300), 225 (10,800)

at pH 7; 292 (19,400), 225 (10,700) at pH 13; MS (FAB) *m/e* 313 (M + 1); IR (KBr) 1567, 1435, 1420, 1335, 1211, 1170, 1127, 1119, 1084, 1058, 944 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.37 (t, 3, SCH_2CH_3), 3.36 (q, 2, SCH_2CH_3), 3.57, 3.70 (2 m, 2, CH_2-5′), 3.98 (apparent q, 1, H-4′), 4.18 (apparent q, 1, H-3′), 4.61 (q, 1, H-2′), 5.13 (t, 1, OH-2′), 5.24 (d, 1, OH-3′), 5.53 (d, 1, OH-5′), 6.00 (d, 1, H-1′), 8.71 (s, 1, H-8), 8.74 (s, 1, H-2). *Anal.* Calcd for $C_{12}H_{16}N_4O_4S$: C, 46.14; H, 5.16; N, 17.94. Found: C, 45.90; H, 5.31; N, 17.80.

6-Allylthiopurine riboside (137b). Into a 100-ml round-bottomed flask stoppered with a calcium drying tube was mixed 6-mercaptopurine riboside (1.9 g, 6.69 mmol), freshly dried potassium carbonate (1.02, 7.36 mmol), and *N,N*-dimethylacetamide (60 ml). Allyl bromide (0.81 g 6.85 mmol) was added dropwise to this well-stirred mixture, and the reaction mixture was stirred for 2 h at room temperature. When TLC showed the reaction to be complete, it was evaporated *in vacuo* at less than 40 °C, and then ethanol (75 ml) was added and evaporated twice. The resulting gummy material was dissolved in chloroform:methanol and passed through a silica gel flash column with 19:1 chloroform-methanol as eluant. Appropriate fractions (TLC) were combined and evaporated. This material was again column chromatographed on 150 g silica gel with 9:1 $CHCl_3$-MeOH as solvent. The proper fractions were combined and evaporated to give a glassy hygroscopic solid (750 mg, 36%); UV λ_{max} 293 nm (18,900) at pH 1; 292 (20,300) at pH 7; 292 (20,400) at pH 13; MS (FAB) *m/e* 325 (M + 1); IR (KBr) 1568, 1334, 1207, 1120, 1080, 1051 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.58, 3.70 (2 m, 2, CH_2-5′), 3.98 (apparent q, 1, H-4′), 4.07 (d, 2, $SCH_2CH{=}CH_2$), 4.19 (apparent q, 1, H-3′). 4.60 (apparent q, 1, H-2′), 5.10 (m, 1, OH-5′), 5.14 (m, 2, $CH{=}CH_2$), 5.21 (d, 1, OH-3′); 5.36 (m, 2, $CH{=}CH_2$), 5.52 (d, 1, OH-2′), 6.00 (d, 1, H-1′), 6.00 (m, 1, $SCH_2CH{=}CH_2$), 8.72, 8.75 (2 s, 2, H-2,8). *Anal.* Calcd for $C_{13}H_{16}N_4O_4S \cdot 0.15EtOH \cdot 0.05CHCl_3$: C, 47.19, H, 5.07; N, 16.61. Found: C, 47.10; H, 5.50; N, 16.52.

6-Ethylsulfonyl-9-β-D-ribofuranosylpurine (139). A stirred solution of 6-etbylthiopurine riboside (1.57 g, 5.03 mmol) in 200 mL of acetone was treated with *m*-chloroperoxybenzoic acid (2.71 g, 15.72 mmol). The reaction was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was stirred with ether (50 mL). The ether was decanted from the solid, and the ether washing was repeated several times. This crude solid product was purified on a silica gel column by eluting with chloroform:methanol (7:1, v/v). The combined product fractions were evaporated to give a glassy hygroscopic solid that was dissolved in water and lyophilized to give a hygroscopic solid that was dried *in vacuo*: yield 770 mg (45%), mp ~65 °C; UV λ_{max} 279 nm (ε 8,800) at pH 1, 279 (8,800) at pH 7; 254 (12,160), 309 (1,524) at pH 13; MS (FAB) *m/e* 345 (M + 1); IR (KBr) 1590, 1563, 1495, 1395, 1355, 1205, 1130, 1080, 1045, 725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.40 (t, 3, SCH_2CH_3), 3.62 (2 m, 2, CH_2-5′), 3.76 (q, 2, SCH_2CH_3), 4.01 (app. q, 1, H-4′), 4.22 (q, 1, H-3′), 4.62 (q, 1, H-2′), 5.10 (t, 1, OH-5′), 5.26 (d, 1, OH-3′), 5.60 (d, 1, OH-2′), 6.11 (d, 1, H-1′), 9.14 (s, 1, H-8). *Anal.* Calcd for $C_{12}H_{16}N_4O_6S \cdot 0.15EtOH \cdot 0.2H_2O$: C, 41.63; H, 4.91; N, 15.79. Found: C, 41.77; H, 5.27; N, 15.80.

1-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (147). A suspension of 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazole-7-carbonitrile (145, 13 g, 0.023 m) in about 500 ml of methanolic ammonia (saturated at 0 °C) was allowed to stand with occasional stirring at room temperature in a bomb for 3 days. The ammonia was then allowed to escape and the solution was evaporated to a yellow

gum. The residue was extracted with hot benzene (4 x 500 mL) to remove benzamide. The residue was recrystallized from ethanol and the product was collected and dried at room temperature over phosphorus pentoxide, yield, 3.7 g; UV λ_{max} 243 nm (16,100) at pH 1; 243 (15,800) at pH 7; 244 (15,700) at pH 13; MS (FAB) *m/e* 265 (M + 1); IR (KBr) 1614, 1499, 1305, 1210, 1186, 1135, 1120, 1105, 1060, 1047, 1020, 870, 855, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60 (m, 2, CH_2-5′), 3.94 (apparent q, 1, H-4′), 4.06 (apparent q, 1, H-3′), 4.35 (q, 1, H-2′), 5.03 (t, 1, OH-5′), 5.31 (d, 1, OH-3′), 5.59 (d, 1, OH-2′), 5.65 (d, 1, H-1′), 7.68 (d, 1, H-2), 7.98 (d, 1, H-3), 8.15 (d, 1, H-6). *Anal.* Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 50.24; H, 4.88; N, 20.90.

2-β-D-Ribofuranosyl-5′-phosphate-1,3-thiazole-4-carboxamide (149). Water (1.7 g, 94.5 mmol) was added carefully to a cold solution (0 °C of freshly distilled phosphoryl chloride (22.5 g, 141.3 mmol) pyridine (13.5 g, 172.1 mmol), and acetonitrile (25.9 g 630 mmol). Predried tiazofurin (9.0 g, 34.6 mmol) was added, and the mixture was stirred at 0 °C for 4.5 h. The reaction mixture was poured into ice-water (350 mL), stirred, and the pH was adjusted to 2.0 with 2 *N* sodium hydroxide. The solution was stirred for 1.5 h with preswelled, acid-washed carbon-Celite mixture (1.5:1). The column was washed thoroughly with water until the eluate was salt-free. The column was eluted with a solution of ethanol-water-concentrated ammonium hydroxide (10:10:1), and 25 mL fractions were taken. The fractions containing the nucleotide were combined and evaporated to dryness in vacuum. This anhydrous solid was dissolved in water and passed through a column of Dowex 50W-X8 (50-100 mesh, H^+ form, 200 mL). Fractions containing the nucleotide were combined, concentrated under reduced pressure, and lyophilized: yield 7.17 g (60%). This product was converted to the sodium salt by passing its water solution through Dowex 50W-X8 resin (50-100 mesh, Na^+ form, 200 mL). The fractions containing the nucleotide were lyophilized to give the product which was contaminated with a small amount of sodium chloride. This impure product (6.45 g) was dissolved in water and passed through a column of Dowex 50W-X8 (50-100 mesh, H^+ form, 200 mL) to give product fractions which were combined, concentrated, and lyophilized to give a solid. This product was taken up in ethanol and precipitated by adding ether to give an oil that solidified after trituration in acetonitrile. The product was dried *in vacuo*: yield 4.85 g (41%); mp <80 °C; MS (FAB) 341 (M + 1); IR (KBr) 3340 (broad), 2975, 2940, 1660 1580, 1210, 1030, 476; ^1H NMR (Me_2SO-d_6) δ 3.92 (m, 2, CH_2-5′), 4.04 (m, 2, H-4′,3′), 4.11 (t, 1, H-2′), 4.98 (d, 1, H-1′), 7.57 (2 br s, 2, NH_2-4), 8.23 (s, 1, H-5) *Anal.* Calcd for $C_8H_{13}N_2O_8PS \cdot 0.33C_2H_5OH \cdot 0.45H_2O$: C, 31.91; H, 4.40; N, 7.71. Found: C, 31.91; H, 4.75; N, 8.06.

1-β-D-Ribofuranosyl-5′-phosphate-1,2,4-triazole-3-carboxamide, Diammonium Salt (151). A cold 0 °C stirred solution of phosphoryl chloride (3.3 mL, 32.6 mmol) in 66 mL of trimethylphosphite was treated with ribavirin (2.68 g 11 mmol). This suspension was stirred at 0 °C for 6 h. Most of the solid dissolved after the first 2 h of stirring. The reaction solution was then kept in the refrigerator overnight. The solution was poured into 120 mL of water (0 °C), and the pH was adjusted to 2 with 2 *N* sodium hydroxide. The solution was extracted with two 150 mL portions of chloroform. This aqueous solution was applied to a plug column of activated carbon (acid-washed) and Celite (60 mL:30 mL). The column was washed with water until salt-free. The nucleotide was eluted with a solution of ethanol-water-conc ammonium hydroxide (10:10:1). The solvent was removed under reduced pressure, and the residue was dissolved in dilute ammonia Ethanol was

added to the solution and the precipitate was collected and dried *in vacuo*: yield, 1.97 g (38%). IR (KBr) 3500-2800 (broad), 1680, 1475 (broad), 1295, 1065 (broad), 970 cm^{-1}; UV λ_{max} 206 (11,236) at pH 1; 207 (11,236) at pH7. ^1H NMR (Me_2SO-d_6) δ 3.70 (t, 2, CH_2-5′), 4.07 (d, 1, H-4′), 4.23 (t, 1, H-3′), 4.48 (t, 1, H-2′), 5.77 (d, 1, H-1′), 7.64 (s, 2, NH_2-3), 7.96 (s, 1, NH_2-3), 8.96 (s, 1, H-5). *Anal.* Calcd for $C_8H_{13}N_4O_8P \cdot 0.25C_2H_5OH \cdot 2NH_3 \cdot 2H_2O$: C, 25.16: H, 6.08; N, 20.71. Found: C, 25.14; H, 5.89; N, 20.62.

1-β-D-Ribofuranosyl-5′-*O*-methylphosphate-1,2,4-triazole-3-carboxamide, Ammonium Salt (152). The 5′-phosphate of ribavirin (3.24 g, 10 mmol) was dissolved in a solution of methanol (400 mL) containing triethylamine (7.5 mL). Dicyclohexylcarbodiimide (16.6 g, 82 mmol) was added, and this solution was kept at 37 °C overnight. The solution was first concentrated to about 150 mL under reduced pressure and then was diluted with water, stirred for 4 h, chilled, and filtered to remove the dicyclohexylurea. The filtrate was concentrated to an oil under reduced pressure and then dried *in vacuo*. This residue was dissolved in water (50 mL), filtered, and the clear filtrate was passed through a column of Dowex 50Wx2 resin (NH_4^+, 200 mL). The product-containing eluates were combined, and evaporated *in vacuo*. The semi-solid residue was stirred in ethanol (50 mL), and the white solid product was collected, and dried *in vacuo*: yield 2.18 g (55%). IR (KBr) 3600-2800 (broad), 1685, 1615, 1470, 1290, 1215, 1060, 820 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.30 (d, J = 11 Hz, 3, CH_3OP), 3.78 (m, 2, CH_2-5′), 4.05 (q, 1, H-4′), 4.2 (t, 1, H-3′), 4.41 (t, 1, H-2′), 5.83 (d, 1, H-1′), 6.19 (d, 1, H-1′), 7.39 (s, 4, NH_4^+-5′), 7.65 (s, 2, NH_2-3), 8.05 (s, 2, NH_2-3), 8.20 (s, 2, NH_2-3), 8.92 (s, 1, H-5), 8.94 (s, 1, H-5). *Anal.* Calcd for $C_9H_{18}N_5O_8P \cdot 0.75C_2H_5OH \cdot 0.5H_2O$: C, 31.62; H, 5.93; N, 17.56. Found: C, 31.90; H, 6.21; N, 17.52.

1-β-D-Ribofuranosyl-5′-*O*-diphosphate-1,2,4-triazole-3-carboxamide, Dilithium Salt (154). The triethylammonium salt of ribavirin 5′-phosphoromorpholidate dihydrate (800 mg, 1.5 mmol) was dried by two repetitions of dissolution in pyridine (15 mL) and evaporation *in vacuo*. Orthophosphoric acid (85%) (0.3 mL, 4.5 mmol) was dissolved in pyridine (15 mL) containing tri-*n*-butylamine (1.07 mL, 4.5 mmol), and evaporated *in vacuo*. Three evaporations with pyridine (3 x 15 mL) rendered this mixture anhydrous.

Both of the above residues were dissolved in pyridine, combined, and the evaporation procedure was repeated two more times. The residue was dissolved in dry pyridine (20 mL), and stirred for 3 days (until no morpholidate remained). The solvent was removed *in vacuo* and the residue was evaporated several times with water. The pH of the aqueous solution was adjusted to pH 6.5 with 0.5 *M* LiOH, and the aqueous solution was washed several times with ether. The pH of the aqueous phase was adjusted to 12 with LiOH (total volume, 45 mL). This suspension was chilled at 0 °C for 0.5 h, and the lithium phosphate was removed by filtration, and washed with a small amount of 0.01N LiOH. The pH of the aqueous solution was adjusted to pH 8 with Dowex 50 (H^+)-resin, and applied to a column of Dowex 2-X8 (Cl^- resin (2.5 x 15 cm). The column was washed with water and then eluted with increasing concentrations of lithium chloride in 0.003 *N* HCl: 0.0125 *N*, 0.025 *N*, 0.075 *N*, 0.1 *N*, 0.25 *N*, and 0.5 *N* for over 2 L. Fractions containing the product were combined and evaporated *in vacuo*. The residue was treated with methanol, diluted with acetone, centrifuged, and the liquid was decanted to remove the LiCl. This procedure was repeated several times. The residue (250 mg) was dissolved in water and freeze-dried to give the nucleoside diphosphate dilithium salt:

yield 230 mg (26%). IR (KBr) 3600-3100 (broad), 1685, 1640, 1490, 1300, 1220, 1110 (broad), 940 cm^{-1}; ^{31}P NMR (1.6 mL Hepes Buffer, pH 7.4; 0.4 mL D_2O and 0.05 mL EDTA) δ -5.96 (2, 1 P, d, $^3J_{1,2}$ = 22.1 Hz) and -9.97 (1, 1 P, d qt). *Anal.* Calcd for $C_8H_{12}N_4O_{11}P2Li_2 \cdot 4.5H_2O \cdot 2LiCl$: C, 16.51; H, 3.64; N, 9.63. Found: C, 16.51; H, 3.56; N, 9.61.

1,2,4-Triazole-3-carboxamide, 1-β-D-Ribofuranosyl-5′-triphosphate, Disodium Salt, with Water and Disodium Pyrophosphate (155). Ribavirin (671 mg, 2.53 mmol) was added to a cold (0 °C) stirred solution of phosphorus oxychloride (0.76 ml, 8.19 mmol) in trimethylphosphate (10 mL). The reaction suspension was stirred at 0 °C for 2 h before complete dissolution occurred. This solution was treated with a solution of bis-tri-*n*-butylammonium pyrophosphate (8.69 g, 15,86 mmol) and tributylamine (3.2 mL, 13.45 mmol) in 15 mL of DMF. This reaction solution was stirred at 0 °C for 20 min, and was then poured into 350 mL of ice water. The pH was adjusted to 8 with triethylamine before the solution was lyophilized, and the residue was washed with ether and dried. The solid was dissolved in water, applied to an activated carbon-Celite-sand column, and eluted with EtOH-H_2O-concentrated NH_4OH (10:10:1). The fractions containing the desired triphosphate were combined and freeze-dried. This solid was dissolved in water and passed through a column of Bio-Rad Ag 50W-X4 (50 mL), Na^+ form (100-200 mesh). The fractions containing the nucleotide were collected and lyophilized: yield 308 mg; MS (FAB) *m/e* 483 (M + 1); IR (KBr) 3100-3600 (broad), 1690, 1255, 1095, 985, 890 cm^{-1}; ^{13}P NMR (1.6 mL Hepes Buffer, pH 7.4, containing 0.4 mL D_2O and 0.05 mL EDTA, 150 mg/10 mL, with H_3PO_4 as external reference): δ 21.2 (t), 10.3 (d t), 6.0 (d). *Anal.* Calcd for $C_8H_{13}N_4O_{14}Na_2P_3 \cdot H_2O \cdot Na_2H_2P_2O_7$: C, 10.13; H, 1.81; N, 5.90. Found: C, 10.31; H, 1.94; N, 5.87.

Formycin B. (Pyrazolo[4,3-*d*]-6*H*-7-pyrimidone, 3-β-D-ribofuranosyl (164). Formycin B was synthesized following a 14 step reaction sequence by L. Kalvoda)[55]; mp 248-251 °C cap; UV λ_{max} 276 nm (7,700) at pH 1; 278 (7,700) at pH 7; 292 (8,400) at pH 13; MS (FAB) *m/e* 269 (M + 1); IR (KBr) 1700, 1668, 1587, 1530, 1122, 1115, 1076, 1014, 930, 900 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.48, 3.62 (2 m, 2, CH_2-5′), 3.88 (q, 1, H-4′), 4.60 (s, 1, H-3′), 4.43 (apparent q, 1, H-2′), 4.90 (d, 1, H-1′), 7.89 (s, 1, H-5), 12.3, 14.06 (2 br s, 2, H-NH).

2′,3′,5′-*O*-Acetylformycin B [3-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidin-7-one] (165). Formycin B (164) was suspended with stirring in 100 mL of dry pyridine and 100 ml of acetic anhydride. The reaction mixture was protected from moisture with an argon atmosphere. (No exothermic heat was detectable.) The reaction mixture was chilled briefly in an ice bath, stored in the refrigerator, and shaken occasionally. Complete solution was achieved in less than 24 h. Since TLC indicated the reaction was complete, the solvents were removed at reduced pressure. The resulting syrup was treated with 50 mL of ethanol and refluxed for 15 min. The ethanol was evaporated, and additional portions of ethanol were evaporated until a foam was obtained. The foam was dissolved in chloroform and washed with 2 x 50 mL portions of 1 *N* HCl, water, saturated $NaHCO_3$, and brine. The $CHCl_3$ solution was dried, filtered, and evaporated to a foam. The foam was dissolved in 50 mL of hot water, filtered, and allowed to cool. Because oiling occurred, the mixture was warmed and the solution was decanted. The warm solution was cooled slowly, and the sides of the flask were scratched with a glass rod to induce crystallization. The white product was collected and dried over phosphorus pentoxide: yield, 5.3 g (36%); mp 171-172 °C cap; UV λ_{max} 274 nm (7,600), 217 (15,400) at pH 1; 277 (7,600), 217 (15,700) at pH 7; 291 (8,700), 229 (15,900) at pH 13; MS

(FAB) *m/e* 394 (M + 1); IR (KBr) 1745, 1728, 1699, 1679, 1590, 1377, 1254, 1230, 1041, 924 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.00, 2.02, 2.09 (3 s, 9, $COCH_3$), 4.10, 4.34 (2 m, 2, CH_2-5'), 4.27 (apparent q, 1, H-4'), 5.21 (d, 1, H-1'), 5.48 (t, 1, H-3'), 5.78 (t, 1, H-2'), 7.92 (s, 1, H-2). *Anal.* Calcd for $C_{16}H_{18}N_4O_8$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.66; H, 4.74; N, 14.26.

6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (171a). 4-Ethoxyacetophenone (16.4 g, 0.1 mol) was dissolved in 50 mL ethanol. Sodium borchydride (1.9 g, 0.05 mol) was slowly added and the mixture was refluxed for 2 h. Water (10.2 mL) was added and the solution was cooled to give a precipitate which was collected by filtration. The remaining mother liquor was evaporated to an oil which also solidified to a white solid (17.6 g). The combined solid products were refluxed for 5 h with sesamol (13.8, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL). An excess of water was added to cause the separation of an oil which was extracted with ether. Solvent removal under vacuum gave a brown solid which was recrystallized with cyclohexane. Cooling resulted in the formation of fine white needle-like crystals (1.8 g, mp 845-855 °C) which were collected from the top of the precipitated mass. The remaining light-brown solid was recrystallized using hot benzene and ether. The resulting off-white needle-like crystals were collected by filtration (5.5 g); mp 84.5-85.5 °C; MS (EI) *m/e* 286 (M); ^1H NMR (Me_2SO-d_6) δ 9.04 (s, 1, OH), 7.12 (m, 2, Ar-H), 6.78 (m, 2, Ar-H), 6.58 (s, 1, Ar-H), 6.38 (s, 1, Ar-H), 5.85, 5.83 (2 d, 2, OCH_2O), 4.34 (q, 1, CH_2CH_3), 3.96 (q, 2, OCH_2CH_3), 1.42 (d, 3, CH_3), 1.30 (t, 3, OCH_2CH_3); IR (KBr) 3463, 1510, 1436, 1248, 1230, 1199, 1179, 1040, 930, 853 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 156.4, 148.4, 145.0, 140.0, 138.2, 128.1, 124.7, 113.8, 106.8, 100.2 97.4, 62.8, 35.6, 20.8, 14.6 ppm. *Anal.* Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.14; H, 6.48.

6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (171b). 4-Methoxyacetophenone (15 g, 0.1 mol) was added to 50 mL of stirring ethanol. Sodium borohydride (1.9 g, 0.5 mol) was then slowly added and the mixture was stirred for 3 h. An excess of water was added to precipitate an oil which was isolated by extracting with ether. The resulting oil (21.8 g) was refluxed with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL) and water (2.5 mL) for 5 h. An excess of water was again added to cause separation of an oil. Extracting with ether, drying with sodium sulfate, and solvent evaporation gave an oil which was crystallized using hexane-benzene-pet. ether, giving a brown solid (22.7 g). The solid (4 g) was further purified by recrystallization with ether-hexane, giving brown needle-like crystals (2.3 g); mp 90-92 °C; MS (EI) *m/e* 272 (M); ^1H NMR (Me_2SO-d_6) δ 9.04 (s, 1, OH), 7.13 (m, 2, Ar-H), 6.81 (m, 2, Ar-H), 6.61 (s, 1, Ar-H), 6.41 (s, 1, Ar-H), 5.84, 5.83 (s, d, 2, OCH_2O), 4.35 (q, 1, $CHCH_3$), 3.69 (s, 3, OCH_3), 1.43 (d, 3, CH_3); IR (KBr) 3471, 1510, 1437, 1248, 1231, 1200, 1178, 1039, 926, 854 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.1, 148.4, 144.9, 139.6, 138.3, 128.0, 124.6, 113.3, 106.8, 100.2, 97.3, 54.8, 35.5, 20.8 ppm. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.45; H, 5.94.

6-[1-(4-Methylphenyl)ethyl]-1,3-benzodioxol-5-ol (171c). 4-Methylacetophenone (13.4 g, 0.1 mol) was dissolved in 50 mL of ethanol. Sodium borohydride (1.9 g, 0.05 mol) was slowly added, and the mixture was stirred for 3 h. An excess of water was added to precipitate an oil which was isolated by extracting with ether to give 169b. The ether was removed by vacuum evaporation, and the resulting oil (13.5 g) was refluxed with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL) for 5 h. An

excess of water was again added to precipitate a solid. Extracting with ether, drying with sodium sulfate, and solvent evaporation gave an off-white solid (6.4 g); mp 116-118 °C; MS (EI) *m/e* 256 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.05 (s, 1, OH), 7.12 (m, 2, Ar-H), 7.05 (m, 2, Ar-H), 6.62 (s, 1, Ar-H), 6.41 (s, 1, Ar-H), 6.36, 6.34 (2 d, 2, OCH_2O), 4.36 (q, 1, $CHCH_3$), 2.24 (s, 3, CH_3Ar), 1.44 (d, 3, $CHCH_3$); IR (KBr) 3462, 1512, 1437, 1253, 1182, 1175, 1039, 925, 854, 823 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 148.6, 145.0, 143.4, 139.6, 134.3, 128.5, 127.1, 124.5, 106.9, 100.3, 97.4, 20.7, 20.5. *Anal.* Caled for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C,74.99; H, 6.43.

6-[1-(4-Fluorophenyl)ethyl]-1,3-benzodioxol-5-ol (171d). 4-Fluoroacetophenone (13.8 g, 0.1 mol) was dissolved in 50 mL of ethanol. Sodium borohydride (1.9 g, 0.05 mol) was slowly added and the mixture was stirred overnight. An excess of water was added to precipitate an oil which was isolated by extracting with ether. The resulting oil was refluxed overnight with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 m). An excess of water was added to precipitate a solid which was isolated by filtration. Toluene (200 mL) was then added and evaporated to remove residual acetic acid. The solid was then recrystallized with ether-petroleum ether to give the desired compound as a brown solid (1.4 g); mp 109.5-111.0 °C; MS (EI) *m/e* 260 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.09 (s, 1, OH), 7.25 (m, 2, Ar-H), 7.06 (m, 2, Ar-H), 6.69 (s, 1, Ar-H), 6.41 (s, 1, Ar-H), 5.85 (d, 2, OCH_2O), 4.39 (q, 1, $CHCH_3$), 1.45 (d, 3, $CHCH_3$); IR (KBr) 3436, 1508, 1434, 1218, 1169, 1143, 1037, 836, 816, 543 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 162.0, 158.8 ($^1J_{C,F}$ = 241.3 Hz), 148.7, 145.4, 142.7, 142.6 ($^4J_{C,F}$ = 2.95 Hz), 139.9, 128.9, 128.8 ($^3J_{C,F}$ =7.8 Hz), 124.2, 114.6, 114.4 ($^2J_{C,F}$ = 20.9 Hz), 106.9, 100.4, 97.7, 36.1, 20.7. *Anal.* Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.71; H, 7.18.

5-Methoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxol (172a). 6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (1.9 g, 0.007 mol) and methyl iodide (3.3 mL, 0.041 mol) was added to acetone (20 mL). Potassium carbonate (7 g, 0.05 mol) was slowly added and the mixture was refluxed for 24 h. The potassium salts were removed by filtration and rinse thoroughly with acetone. Evaporation of solvent gave an oil. Water was added and the oil was extracted with ether. Removal of ether by evaporation gave an oil, which was purified on a silica gel column using ethyl acetate-pet. ether (1:15). The desired compound was isolated as a yellow oil (1.2 g); MS (EI) *m/e* 286 (M); ^{1}H NMR (Me_2SO-d_6) δ 7.12 (m, 2, Ar-H), 6.82 (m, 2, Ar-H), 6.72 (2 s, 2, Ar-H), 5.92, 5.89 (2 d, 2, OCH_2O), 4.37 (q, 1, $CHCH_3$), 3.70 (s, 3, OCH_3), 3.68 (s, 3, OCH_3), 1.44 (d, 3, $CHCH_3$); IR (KBr) 1511, 1483, 1465, 1423, 1246, 1191, 1170, 1038, 854, 831 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.2, 151.1, 145.6, 140.6, 138.1, 128.0, 127.0, 113.4, 107.0, 100.7, 95.2, 56.5, 54.8, 35.6, 20.9 ppm. *Anal.* Calcd for $C_{17}H_8O_4$: C, 71.31; H, 6.33. Found: C, 70.91; H, 6.27.

5-Ethoxy-6-[1-(4-ethoxyphenyl)ethyl]-1,3-benzodioxol (172b). 6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (2 g, 0.007 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Then potassium carbonate (6 g, 0.04 mol) was added, and the mixture was refluxed for 48 h. The potassium salts were removed by filtration and rinsed thoroughly with acetone. The solution was evaporated to an oil, and water was added to dissolve any remaining K_2CO_3. The crude product was isolated by extracting with ether followed by solvent evaporation. The crude compound was then purified by column chromatography using ethyl acetate-pet. ether (1:15). The desired compound was isolated as an oil, which after several days,

solidified as an off-white clump (1.6 g); mp 47-49 °C; MS (EI) *m/e* 314 (M); ^{1}H NMR (Me_2SO-d_6) δ 7.12 (m, 2, Ar-H), 6.80 (m, 2, Ar-H), 6.74 (s, 1, Ar-H), 6.68 (s, 1, Ar-H), 5.90, 5.89 (2 d, 2, OCH_2O), 4.37 (q, 1, $CHCH_3$), 3.95 (q, 2, OCH_2CH_3), 3.89 (m, 2, OCH_2CH_3), 1.44 (d, 3, $CHCH_3$), 1.28 (t, 3, OCH_2CH_3), 1.25 (t, 3, OCH_3CH_3); IR (KBr) 1510, 1504, 1486, 1477, 1233, 1225, 1185, 1049, 1034, 928 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 156.4, 150.2, 145.4, 140.5, 138.1, 128.0, 127.4, 113.8, 106.9, 100.6, 96.2, 64.5, 62.7, 35.8, 20.9, 14.6 ppm. *Anal.* Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.51; H, 7.02.

5-Methoxy-6-[1-(4-ethoxyphenyl)ethyl]-1,3-benzodioxol (172c). 6-[1-(4-Ethoxyphenyl)ethyl]-1,3-benzodioxol-5-ol (2 g, 0.007 mol) was refluxed for 48 h with methyl iodide (3 mL, 0.014 mol), acetone (6 mL), and potassium carbonate (7 g, 0.05 mol). The solution was cooled and the potassium salts were removed by filtration. The filtered salts were further rinsed with acetone, and the combined acetone solutions were then evaporated to dryness. Water was added to the residue and the resulting solid was collected by filtration. Recrystallization using hot methanol gave brown, thick needle-like crystals (1.7 g); mp 67-69 °C; MS (EI) *m/e* 300 (M); ^{1}H NMR (Me_2SO-d_6) δ 7.10 (m, 2, Ar-H), 6.80 (m, 2, Ar-H), 6.72 (2 s, 2, Ar-H), 5.91, 5.89 (2 d, 2, OCH_2O), 4.35 (q, 1, $CHCH_3$), 3.95 (g, 2, OCH_2CH_3), 3.67 (s, 3, OCH_3), 1.43 (d, 3, $CHCH_3$), 1.29 (t, 3 OCH_2CH_3); IR (KBr) 1505, 1482, 1478, 1470, 1241, 1202, 1180, 1170, 1042, 856 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 156.4, 151.0, 145.5, 140.5, 137.9, 128.0, 127.0, 113.9, 107.0, 100.6, 95.2, 62.7, 56.5, 35.6, 20.9, 14.6 ppm. *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.64; H, 6.90.

5-Ethoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxol (172d). 6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-6-ol **171b** (1.9 g, 0.007 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the reaction mixture was refluxed for 48 h. The potassium salts were then removed by filtration and rinsed thoroughly with acetone. Evaporation of the solvent gave a brownish solid which was recrystallized using hot methanol. The desired compound was isolated as white, needle-like crystals (1.3 g); mp 90-90.5 °C; MS (EI) *m/e* 300 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 7.13 (m, 2, Ar-H), 6.80 (m, 2, Ar-H), 5.90, 5.92 (2 d, 2, OCH_2O), 4.37 (q, 1, $CHCH_3$), 3.88 (m, 2, OCH_2CH_3), 3.70 (s, 3, OCH_3), 1.45 (d, 3, $CHCH_3$), 1.26 (t, 3, OCH_2CH_3); IR (KBr) 1504, 1484, 1478, 1430, 1178, 1041, 986, 853, 819, 349 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.1, 150.2, 145.4, 140.6, 138.2, 128.0, 127.3, 113.3, 106.9, 100.6, 96.1, 64.5, 54.8, 35.9, 20.9, 14.7. *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.84.

5-Ethoxy-6-[1-methylphenyl)ethyl]-1,3-benzodioxol (172f). 6-[1-(4-Methylphenyl)ethyl]-1,3-benzodioxol-5-ol **171c** (1.8 g, 0.007 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) while stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the reaction mixture was refluxed for 48 h. The potassium salts were removed by filtration and rinsed thoroughly with acetone. Evaporation of the solvent gave a dark oil. Water (50 mL) was added, the oil was extracted with ether, dried with sodium sulfate, and the solvent evaporated to give the desired compound as a golden oil (1.3 g); MS (EI) *m/e* 284 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 7.10 (m, 2, Ar-H), 7.04 (m, 2, Ar-H), 6.76 (s, 1, Ar-H), 6.69 (s, 1, Ar-H), 5.91, 5.89 (2 d, 2, OCH_2O), 4.37 (q, 1, $CHCH_3$), 3.89 (m, 2, OCH_2CH_3), 2.24 (s, 3, CH_3Ar), 1.45 (d, 3, $CHCH_3$), 1.25 (t, 3, OCH_2CH_3); IR (KBr) 1504, 1484, 1478, 1431, 1178, 1041, 936, 853, 819, 349 cm^{-1}; ^{13}C NMR (Me_2SO-d_6)

δ 150.2, 145.5, 143.2, 140.6, 134.3, 128.5, 127.1, 127.0, 106.9, 100.6, 96.1, 64.5, 36.3, 20.8, 20.5, 14.6. *Anal.* Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.71; H, 7.18.

5-(2-Propenyloxy)-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole (172g). 6-[1-(4-Methoxyphenyl)ethyl]-1,3-benzodioxol-5-ol **171b** (1.9 g, 0.007 mol) and allyl iodide (1.17 g, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (1.74 g, 0.012 mol) was added, and the reaction mixture was refluxed for 24 h. An excess of water was added to precipitate an oil which was extracted with ether. The ether solution was dried with sodium sulfate and evaporated to give an oil. The desired compound was isolated as an off-white solid (0.7 g); mp 50-51 °C; MS (EI) *m/e* 312 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 7.12 (d, 2, Ar-H), 6.80 (d, 2, Ar-H), 6.74 (s, 1, Ar-H), 6.71 (s, 1, Ar-H), 5.98 (d, 1, CH=CH_2), 5.90 (d, 2, OCH_2O), 5.35 (d, 1, CH=CH_2), 5.21 (d, 1, CH=CH_2), 4.43 (m, 2, OCH_2-CH=CH_2), 4.39 (q, 1, $CHCH_3$), 3.68 (s, 3, OCH_3), 1.44 (d, 3, $CHCH_3$); IR (KBr) 1508, 1485, 1429, 1271, 1235, 1196, 1182, 1037, 929, 835 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 157.2, 149.7, 145.4, 140.8, 138.1, 133.8, 128.0, 127.5, 116.7, 113.4, 107.0, 100.6, 96.5, 69.5, 54.9, 35.8, 20.9; *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 72.81; H, 6.80. Found: C, 73.06; H, 6.45.

6-[1-(2-(3,4-Dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxol-5-ol (174). 3,4-Dimethoxybenzyl alcohol (16.8 g, 0.1 mol) was refluxed with sesamol (13.8 g, 0.1 mol), oxalic acid (1 g, 0.008 mol), acetic acid (30 mL), and water (2.5 mL) for 5 h. An excess of water was added to precipitate an oil. Extraction with ether, drying with sodium sulfate, filtering, and solvent evaporation gave an off-white solid (5.4 g); mp 132-133 °C; MS (EI) *m/e* 438 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.18 (s, 1, OH), 6.80 (d, 1, Ar'' H), 6.75 (s, 1, Ar'-H), 6.73 (s, 1, Ar'-H), 6.68 (s, 1, Ar-H), 6.57 (m, 1, Ar''-H), 6.44 (s, 1, Ar-H), 6.18 (s, 1, Ar-H), 5.81 (2 d, 2, OCH_2O), 3.75 (s, 4, CH_2), 3.57 (m, 12, OCH_3); IR (KBr) 1514, 1506, 1436, 1257, 1232, 1228, 1176, 1159, 1138, 1028 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 149.1, 148.6, 147.11, 147.10, 145.4, 139.6, 133.6, 131.4, 131.1, 120.3, 118.9, 114.4, 114.3, 112.5, 111.8, 108.8, 100.4, 97.4, 55.6, 55.5, 55.4, 55.3, 37.2, 31.5. *Anal.* Calcd for $C_{25}H_{26}O_7$: C, 68.48; H, 5.98. Found: C, 68.45; H, 6.07.

5-Methoxy-6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxole (175a). 6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodiol-5-ol (**174**, 2.0 g, 0.004 mol) and methyl iodide (3 mL, 0.041 mol) were added to acetone (20 mL) with stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the mixture was stirred for 48 h. An excess of water was added to precipitate a yellow solid which was collected by filtration. The solid was recrystallized using hot methanol. The desired product was isolated as white crystals (1.7 g); mp 107-108 °C; MS (EI) *m/e* 452 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 6.79 (d, 1, Ar''-H), 6.79 (s, 1, Ar'-H), 6.78 (s, 1, Ar-H), 6.71 (s, 1, Ar'-H), 6.68 (s, 1, Ar''-H), 6.55 (d, 1, Ar''-H), 6.28 (s, 1, Ar-H), 5.90 (s, 2 OCH_2O), 3.70 (m, 19, OCH_3 and CH_2); IR (KBr) 1515, 1508, 1484, 1262, 1222, 1196, 1163, 1139, 1024, 869 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 151.5, 148.2, 147.0, 146.9, 145.8, 140.3, 133.4, 131.2, 130.6, 120.9, 120.1, 114.3, 114.2, 112.4, 111.7, 108.9, 100.7, 94.8, 56.2, 55.55, 55.48, 55.4, 55.3, 37.1, 31.4; *Anal.* Calcd for $C_{26}H_{28}O_7$: C, 69.01; H, 6.24. Found: C, 68.95; H, 6.61.

5-Ethoxy-6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxole (175b). 6-[1-(2-(3,4-dimethoxybenzyl)-4,5-dimethoxyphenyl)methyl]-1,3-benzodioxole (**174**, 2.0 g, 0.004 mol) and ethyl iodide (3.3 mL, 0.041 mol) were added to acetone (20 mL) while stirring. Potassium carbonate (7 g, 0.05 mol) was added, and the reaction mixture was refluxed for 72 h. An excess of water was added to precipitate a solid

which was filtered and recrystallized with hot methanol. The desired compound was isolated as a white solid (1.2 g); mp 105-106 °C; MS (EI) *m/e* 466 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 6.79 (d, 1, Ar''-H), 6.75 (s, 1, Ar'-H), 6.72 (s, 1, Ar-H), 6.70 (s, 1, Ar'-H), 6.65 (m, 1, Ar''-H), 6.52 (m, 1, Ar''-H), 6.30 (s, 1, Ar-H), 5.87 (s, 2, OCH_2O), 3.94 (q, 2, CH_2CH_3), 3.78, 3.70 (2 s, 4, CH_2), 3.66 (m, 12, OCH_3), 1.24 (t, 3, OCH_2CH_3); IR (KBr) 1514, 1489, 1475, 1254, 1229, 1148, 1138, 1101, 1038, 1030 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 150.6, 148.5, 146.9, 146.88, 145.7, 140.3, 133.4, 131.1, 130.7, 121.3, 120.1, 114.2, 112.3, 111.7, 108.9, 100.6, 95.8, 64.3, 55.53, 55.46, 55.42, 55.3, 37.1, 31.4, 14.7. *Anal.* Calcd for $C_{27}H_{30}O_7$: C, 69.51; H, 6.48. Found: C, 69.35; H, 6.76.

3-Phenylbenzo-1,4-thiazin-2-one oxime (179a).[57-59] α-Chloroisonitrosoacetophenone (2 g, 0.011 mol) and 2-aminothiophenol (1.38 g, 0.011 mol, 1.17 mL) were dissolved in benzene, and the mixture was cooled in an ice bath. Sodium methoxide (0.65 g, 0.012 mol) was slowly added with stirring, and the reaction mixture was allowed to slowly warm to room temperature. The mixture was then heated at reflux for 2 h and cooled. The yellow solid was collected and dried. Recrystallization from boiling ethanol gave yellow needle-like crystals (3.7 g); mp 220-221 °C; MS (FAB) *m/e* 255 (*M* + 1); ^{1}H NMR (Me_2SO-d_6) δ 12.92 (s, 1, OH or NH), 7.78 (m, 2, Ar-H), 7.60 (m, 1, Ar-H), 7.46 (m, 4, Ar-H), 7.36 (m, 2, Ar-H); IR (KBr) 3053, 3037, 3024, 2904, 2768, 2730, 1145, 1004, 994, 696 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 153.5 (C-5'), 140.5 (C-2), 137.9 (C-3'), 137.6 (Ar-C-1), 131.2 (C-5), 129.5 (Ar-C-4), 129.2 (Ar-C-2), 128.5 (C-6), 127.5 (Ar-C-3), 127.1 (C-7), 125.7 (C-8), 122.5 (C-8'). *Anal.* Calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.01. Found: C, 65.94; H, 4.28; N, 11.09.

3-(4-Fluorophenyl)-benzo-1,4-thiazin-2-one oxime (179b).[57-59] 2-Aminothiophenol (1.25 g, 0.01 mol) was added to methanol (100 mL) with stirring. The solution was cooled in an ice bath, and sodium methoxide (0.54 g, 0.01 mol) and α-chloroisonitroso-4'-fluoroacetophenone (2 g, 0.01 mol) were slowly added. After 24 h of stirring, the solvent was removed by distillation, leaving a solid which was recrystallized with ethanol. The desired compound was isolated as a yellow solid (2.3 g); mp 243-244 °C; MS (EI) *m/e* 272 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 12.92 (s, 1, OH or NH), 7.86 (m, 2, Ar-H), 7.60 (m, 1, Ar-H), 7.47 (m, 1, Ar-H), 7.36 (m, 2, Ar-H), 7.26 (m, 2, Ar-H); IR (KBr) 3049, 3024, 2763, 1600, 1508, 1412, 1238, 998, 831, 754 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 164.4, 162.2, 152.3, 140.5, 137.8, 133.94, 133.90, 131.7, 131.6, 131.2, 128.5, 127.1, 125.7, 122.6, 114.6, 114.3. *Anal.* Calcd for $C_{14}H_9FN_2OS$: C, 61.75; H, 3.33; N, 10.29. Found: C, 61.73; H, 3.57; N, 10.18.

3-[4-Methoxyphenyl]-benzo-1,4-thiazin-2-one oxime (179c).[57-59] 2-Aminothiophenol (1.12 g, 0.009 mol) was added to methanol (100 mL) with stirring. The solution was cooled in an ice bath, before sodium methoxide (0.48 g, 0.009 mol) and α-chloroisonitroso-4'-fluoroacetophenone (2 g, 0.01 mol) were slowly added. After 24 h of stirring, the solvent was removed by distillation, leaving a solid which was recrystallized with methanol. The desired compound was isolated as a yellow solid (1.2 g); mp 199-200 °C; MS (EI) *m/e* 284 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 12.88 (s, 1, OH or NH), 7.74 (m, 2, Ar-H), 7.59 (m, 1, Ar-H), 7.46 (m, 1, Ar-H), 7.32 (m, 2, Ar-H), 7.00 (m, 2, Ar-H), 3.83 (s, 3, CH_3); IR (KBr) 3137, 3057, 2908, 1606, 1510, 1442, 1253, 1179, 994, 828 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) δ 160.6, 152.4, 140.6, 138.2, 131.2, 131.0, 129.8, 128.0, 126.9, 125.6, 122.5, 112.9, 55.2. *Anal.* Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.26; N, 9.85. Found: C, 63.08; H, 4.57; N, 10.07

Chloromethanesulfonic Acid, 1,4-Butanediyl Ester (184a). Into a 100-mL three-necked round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and a calcium sulfate drying tube was added chloromethanesulfonyl chloride[62-65] (15.5 g, 0.105 mmol) dissolved in ethyl acetate (50 mL), with stirring and chilling in a salt-ice bath. A solution of triethylamine (17.3 mL, 0.125 mmol) and 1,4-butanediol (4.7 g, 0.052 m) was dissolved in ethyl acetate (10 mL) and added dropwise over 45 min with stirring. The reaction mixture was stirred for 2 h and then stored in a refrigerator overnight. The triethylamine hydrochloride was removed by filtration and washed with ethyl acetate. The filtrate was washed with brine solution (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated. The solid residue was triturated with ethyl acetate and dried over phosphorus pentoxide; yield, 5.4 g (39%); IR (KBr) 1361, 1172, 1141, 1137, 1029, 937, 882, 855, 544 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.80 (m, 4, $OCH_2CH_2CH_2CH_2O$), 4.37 (m, 4, $OCH_2CH_2CH_2CH_2O$), 5.35 (s, 4, $ClCH_2SO_2$). *Anal.* Calcd for $C_6H_{12}Cl_2O_6S_2$: C, 22.86; H, 3.84. Found: C, 22.96; H, 3.97.

(Methylsulfonyl)methanesulfonic Acid, 1,4-Butanediyl Ester (184b). Into a 100-mL round-bottomed flask equipped with an addition funnel, calcium sulfate drying tube, and a magnetic stirring bar was added methylsulfonylmethanesulfonyl chloride[62-65] (7 g, 36.3 mmol) and ethyl acetate (50 mL). The reaction solution was chilled in an ice bath and a solution of 1,4-butanediol (1.64 g, 18.2 mmol) and triethylamine (4.4 g, 43.6 mmol) in ethyl acetate (10 mL) was added dropwise over 10-15 min. The mixture was stirred for 4 h in the ice bath before the insoluble precipitate was collected and washed with more ethyl acetate. The filtrate was washed with brine (3 x 25 mL), dried over $MgSO_4$, filtered, and evaporated, yield 1.0 g (14 %). The previously separated EtOAc insoluble residue was treated with water, and the insoluble material was collected, washed again with water, and dried, yield 4.4 g (60%). The two crops were combined, dissolved in acetonitrile, filtered, diluted with benzene until cloudy, and scratched to initiate crystallization. The product was collected and dried at room temperature over phosphorus pentoxide, yield, 3.6 g (49%); mp 135-137 °C $_{cap}$; IR (KBr) 1350, 1333, 1319, 1229, 1183, 1175, 1170, 1123, 929, 865 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.98 (m, 4, $OCH_2CH_2CH_2CH_2O$), 3.25 (s, 6, SO_2CH_3), 4.53 (m, 4, $OCH_2CH_2CH_2CH_2O$), 5.25 (s, 4, $SO_2CH_2SO_2$). *Anal.* Calcd for $C_8H_{18}O_{10}S_4$: C, 23.87; H, 4.51. Found: C, 23.73; H, 4.70.

Chloromethanesulfonic Acid, 4-[(Methanesulfonyl)oxy]butyl Ester (189a). 4-Benzyloxybutanol[65] (10 g, 55.6 mmol), and triethylamine (6.73 g, 66.7 mmol) dissolved in ethyl acetate (10 mL) was added dropwise over 40 min to a chilled solution of methanesulfonyl chloride [62-65](6.37 g, 55.6 mmol) in ethyl acetate (20 mL). The mixture was stirred in an ice bath for 4 h before the triethylamine hydrochloride was removed by filtration. The residue was washed with ethyl acetate, and the filtrate and washings were washed with brine, dried over $MgSO_4$, filtered, and evaporated. A yellow oil was obtained which was passed through a column of silica gel (300 g) and eluted with 2:1 hexane-ethyl acetate. The appropriate fractions, as identified by TLC, were combined and evaporated, giving 9.2 g of **189a** from two crops. Both crops were dissolved in ethyl acetate (100 mL), and the benzyl group was removed by hydrogenation at atmospheric pressure using 10% Pd/C as catalyst. The catalyst was removed by filtration through a Celite pad. The filtrate was then chilled in an ice bath and treated with triethylamine (4.3 g, 42.5 mmol). A solution of chloromethanesulfonyl chloride (5.2 g, 0.035 mol) in ethyl acetate (10 mL) was added dropwise over 25 min. The mixture was stirred for 0.5 h and stored at 6-10 °C overnight. The triethylamine hydrochloride was removed by filtration and washed with

ethyl acetate. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and evaporated; crude yield 7.4 g.

After two recrystallizations from ethyl acetate: hexane, 2.6 g (27%) of pure product was obtained; mp 44-46 °C cap; IR (KBr) 1364, 1351, 1338, 1170, 982, 938, 925, 879, 856, 532 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9 (m, 4, $OCH_2CH_2CH_2CH_2O$), 3.02 (s, 3, SO_2CH_3); 4.29, 4.46 (2 m, 4, $OCH_2CH_2CH_2CH_2O$), 4.62 (s, 2, SO_2CH_2Cl). *Anal.* Calcd for $C_6H_{13}ClO_6S_2$: C, 25.67; H, 4.67. Found: C, 25.80; H, 4.75.

(Methylsulfonyl)methanesulfonic Acid, 4-[(Methylsulfonyl)oxy] Butyl Ester (189b). 4-Benzyloxybutanol **186**[65] (10 g, 55.6 mmol) and triethylamine (6.7 g, 66.7 mmol) were dissolved in ethyl acetate (15 mL) and added dropwise with stirring to a cold solution of methanesulfonyl chloride[62-65] in ethyl acetate (25 mL) in an ice bath. The reaction mixture was stirred for 2 h and stored overnight in a refrigerator. The triethylamine hydrochloride was removed by filtration and washed with ethyl acetate. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified with a silica gel (300 g) column using 2:1 hexane-ethyl acetate, yield 5.2 g (64 %). The sulfonate ester was dissolved in ethyl acetate (100 mL) and hydrogenated at atmospheric pressure with 10% Pd/C. The catalyst was removed by filtration through a Celite pad. Triethylamine (4.3 g, 42.5 mmol) was added to the filtrate (and washings) with good stirring in an ice bath followed by the addition of a solution of (methylsulfonyl)methanesulfonyl chloride[62-64] (5.4 g, 28.3 mmol) in ethyl acetate (25 mL). The reaction mixture was stirred for 1 h at 0 °C and stored overnight in the refrigerator. The triethylamine hydrochloride was removed by filtration, washed with ethyl acetate, and the filtrate (and washings) was washed with brine, dried over $MgSO_4$, filtered, and evaporated. After two recrystallizations from ethyl acetate-hexane, a pure product was obtained, yield, 3.6 g (39 %) mp 97-98.5 °C; IR (KBr) 1370, 1351, 1339, 1330, 1309, 1177, 1160, 934 (broad), 854, 527 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.92 (m, 4, $OCH_2CH_2CH_2CH_2O$), 3.19 (s, 3, OSO_2CH_3), 3.25 (s, 3, $CH_2SO_2CH_3$), 4.31, 4.51 (2 m, 4, $OCH_2CH_2CH_2CH_2O$), 5.22 (s, 2, $CH_3SO_2CH_2$). *Anal.* Calcd for $C_7H_{16}O_8S_3$): C, 25.92; H, 4.97. Found: C, 26.02; H, 4.94.

[For the syntheses of compounds **191-194**, we relied only on MS and ^{1}HNMR for confirmation of their identifications. We felt that full characterization of all intermediates was unnecessary since we were closely following a procedure provided by J. Bronson of Bristol-Myers. However, in the following experimental descriptions, we have included all of the analytical data supplied to us in the Bronson procedure.]

2-Chloromethoxyethyl Acetate (191). Into a 500-mL round-bottomed flask a solution of acetyl chloride (17.4 g, 220 mmol) in 80 mL of anhydrous ether was added dropwise via an additional funnel, over 1 h to a mixture of 1,3-dioxolane (15 g, 202 mmol) and zinc chloride (0.109 g, 80 mmol) in 100 mL of anhydrous ether at room temperature under nitrogen. [The 1,3-dioxolane was predistilled to remove any triethylamine inhibitor.] The reaction mixture was then stirred at room temperature for 25 h and evaporated *in vacuo* to remove any volatile materials. The resulting light-brown oil was purified by distillation under reduced pressure to afford a colorless oil (21.2 g, bp 54-55 °C at 0.8 mm Hg); MS (EI) *m/e* 152 (M^+); ^1H NMR (200 MHz, $CDCl_3$) δ 5.50 (s, 2, CH_2Cl), 4.25 (t, 2, J = 7 Hz, CH_2), 3.80 (t, 2, J = 7 Hz, CH_2), and 2.05 (s, 3, CH_3); IR (thin film): 2980, 2950, 1740(s), 1460, 1380, 1235, 1140, 1080, and 650 cm^{-1}.

2-(Diisopropylphosphonylmethoxy)ethyl Acetate (192). 2-(Chloromethoxy)ethyl acetate (**191**) (21.2 g, 0.150 mol) and triisopropyl phosphite (25 g, 25.8 mL, 0.139 mol) were combined in a 200-mL three-necked round-bottomed flask equipped with a reflux condenser and a gas inlet adapter. The reaction mixture was heated at around 100-110 °C for 18 h. (Bubbling was noted when the temperature initially reached 105 °C.) The reaction mixture was then allowed to cool to room temperature and the volatile residuals were removed *in vacuo*. The residual oil was purified by vacuum distillation (bp 133-138 °C, 0.7-0.8 mmHg) yielding a colorless liquid (16.5 g); MS (EI) *m/e* 282 (M^+): ^{1}H NMR ($CDCl_3$) δ 4.79 (apparent octet, 2, J = 6.5 Hz, CH), 4.24 (t, 2, J = 4.5 Hz, CH_2), 3.81 (t, 2, J = 4.5 Hz, CH_2), 3.79 (d, 2, J = 8.2 Hz, CH_2), 2.08 (s, 3, CH_3), and 1.35 (d, 12, J = 6.5 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.85, 71.10 (d, J = 7 Hz), 70.88 (d, J = 11 Hz), 65.99 (d, J = 170 Hz), 63.28, 24.09 (d, J = 4 Hz), 23.96 (d, J = 4 Hz), and 20.84; IR (thin film) 2981, 2938, 2880, 1742(s), 1468, 1456, 1387, 1377, 1242(s), 1180, 1132, 1109, 1057, 991(s), and 890 cm^{-1}.

2-Diisopropylphosphonylmethoxy-1-ethanol (193). A solution of 2-diisopropylphosphonylmethoxyethyl acetate (**192**) (79.9 g) in 500 mL of acetone-water (4:1) was treated with concentrated HCl (42.8 mL). The reaction mixture was stirred at 50-55 °C for 72 h. The resulting solution was concentrated *in vacuo* and the residue was co-evaporated with toluene (3 x 150 mL) to afford a crude dark-yellow oil (80 g) which was used without further purification.

2-(Diisopropylphosphonylmethoxy)ethylmethanesulfonate (194). 2-Diisopropylphosphonylmethoxy-1-ethanol (**193**) (100 g, 0.471 mol, accumulated from combined runs) was dissolved in 850 mL of anhydrous methylene chloride (dried over activated molecular sieves) and the solution was cooled to 0 °C. After 15 min, the methanesulfonyl chloride was added rapidly (55.8 g, 37.5 mL, 0.490 mol) followed by dropwise addition of triethylamine (81.56 g, 125 mL, 0.806 mol) over 1 h. The resulting clear-yellow solution was stirred at room temperature for 18 h and then 200 mL water was added. The reaction mixture was stirred for 10 min before the organic layer was separated and the aqueous layer was extracted with 300 mL methylene chloride. The combined organic portions were washed with saturated sodium chloride solution (2 x 300 mL). The compound was isolated by evaporation *in vacuo* to yield a yellow oil and was purified by column chromatography in silica gel (5:1), eluting with a gradient of 3-5% methanol-methylene chloride. MS (FAB) *m/e* 319 (M + 1); ^{1}H NMR ($CDCl_3$) δ 4.78 (d of septet, 2, J = 5, 6.2 Hz, CH), 4.38-4.42 (m, 2, CH_2), 3.86-3.90 (m, 2, CH_2), 3.80 (d, 2, J = 8.5 Hz, CH_2), 3.09 (s, 3, CH_3), and 1.36 (d, 12, J = 6.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 71.21 (d, J = 7 Hz), 70.75 (d, J = 11 Hz), 68.71, 66.12 (d, J = 170 Hz), 37.73, 24.07 (d, J = 4 Hz), and 23.99 (d, J = 4 Hz); IR (thin film) 2983, 2937, 2881, 1739, 1468, 1456, 1414, 1376, 1355 (s), 1253, 1177 (s), 1133, 1108, 988(s), 926, 836, 808, 755, and 727 cm^{-1}.

9-(2-Diisopropylphosphonylmethoxyethyl)adenine (195). Sodium hydride (1.2 g, 0.05 mol) was added to a stirred slurry of adenine (2.0 g, 0.014 mol) in 100 mL of anhydrous dimethylformamide in a 200-mL three-necked round-bottomed flask equipped with an overhead mechanical stirrer and an argon inlet adapter. The reaction mixture was heated at 80 °C for 2 h to give a thick, white slurry. A solution of 2-(diisopropylphosphonylmethoxy)ethylmethanesulfonate (**194**) (7.7 g, 0.024 mol) in 10 mL of anhydrous DMF was then added over 10 min to the hot slurry and the reaction mixture was raised to 100 °C. The reaction mixture was stirred at 100-105 °C for 14 h, allowed to cool to room temperature, and filtered to remove insoluble material.

The filtrate was concentrated *in vacuo* and the gummy, semi-solid residue was suspended in 100 ml of 10% isopropanol in methylene chloride. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give an orange, viscous residue. Purification by column chromatography on silica gel (10:1), eluting with a gradient of 3-10% methanol in methylene chloride afforded 2.11 g (24.6% yield) of a white crystalline solid. This material was purified further by recrystallization from ethyl acetate-toluene. MS (EI) *m/e* 358 (M^+); ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1), 8.09 (s, 1), 7.21 (br s, 2), 4.50 (apparent octet, 2, J = 6.5 Hz, CH), 4.34 (t, 2, J = 4.8 Hz, CH_2), 3.91 (t, 2, J = 4.8 Hz, CH_2), 3.79 (d, 2, J = 8.4 Hz, CH_2), 1.18 (d, 6, J = 6.5 Hz, CH_3), and 1.13 (d, 6, J = 6.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.86, 152.23, 149.46, 140.90, 118.57, 70.22 (d, J = 10 Hz), 70.05 (d, J = 12 Hz), 64.50 (d, J = 165 Hz), 42.35, 23.61 (d, J = 7 Hz), and 23.52 (d, J = 7 Hz).

9-(2-Phosphonylmethoxyethyl)adenine (196). A solution of 9-(2-diisopropylphosphonylmethoxyethyl)adenine (**195**) (2.11 g, 0.060 mol) in 20 mL of anhydrous acetonitrile was treated with bromotrimethylsilane (8.29 g, 0.054 mol), and the resulting clear, yellow solution was stirred at room temperature under argon for 16 h. The reaction mixture was concentrated *in vacuo* and the yellow residue was placed under high vacuum for 5 h. Water (15 mL) was added next, causing immediate formation of a white precipitate. Acetone (15 mL) was added, and the pale yellow slurry was stirred at room temperature for 14 h. The solid was collected by filtration, washed twice with 10 mL of acetone and once with 10 mL of anhydrous ether. An additional portion of solid was collected from the filtrate. The combined solids were recrystallized from water to afford 1.41 g (86%) of an off-white crystalline solid; mp >250 °C; MS (EI) *m/e* 273 (M^+); ^{1}HNMR (Me_2SO-d_6) δ 8.14 (s, 1), 8.13 (s, 1), 7.2' (br s, 2), 4.32 (t, 2, J = 5 Hz, CH_2), 3.87 (t, 2, J = 5 Hz, CH_2, and 3.59 (d, 2, J = 8.8 Hz, CH_2); ^{13}C NMR (Me_2SO-d_6) δ 151.10, 148.70, 146.28, 143.80, 118.05, 69.94 (d, J = 10 Hz), 66.27 (d, J = 160 Hz), and 43.15. *Anal.* Calcd for $C_8H_{12}N_5O_4P \cdot 0.5\ H_2O$: C, 34.04; H, 4.54; N, 24.82. Found: C, 33.90; H, 4.76; N, 24.86.

9-[2-(Diethylphosphonylmethoxy)ethyl]-2-amino-6-chloropurine (209). To a heterogeneous mixture of 2-amino-6-chloropurine (5 g, 29 mmol) and K_2CO_3 (6 g, 43 mmol) in DMF (80 mL) was added 2-(diethylphosphonylmethoxy)ethyl-1-tosylate (8.75 g, 23 mmol). The reaction mixture was stirred at room temperature under argon for 72 h, and then the reaction was heated at 60 °C for 4 h. The reaction mixture was filtered, and the filtrate was evaporated *in vacuo* to a gummy yellow residue. The semisolid residue was suspended in 600 mL of 30% *n*-propyl alcohol in $CHCl_3$. The mixture was filtered and the filtrate was concentrated to give a dark yellow viscous residue (14 g). Purification by column chromatography on silica gel, eluting with a gradient of 5→10→14→16% MeOH in $CHCl_3$, yielded pale yellow crystals (7.8 g); MS (FAB) *m/e* 349 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 1.15 (t, 6, CH_2CH_3), 3.82-3.88 (m, 4, NCH_2CH_2O, CH_2P), 3.92 (m, 4, OCH_2CH_3), 4.25 (m, 2, NCH_2), 6.91 (s, 2, NH_2), 8.1 (s, 1, =CH).

Methyl 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxylate (211). Methyl 1,2,4-triazole-3-carboxylate (**210**) (3.81 g, 0.075 mol), 2-(diethylphosphonylmethoxy)ethane-1-tosylate (6.3 g, 0.083 mol), and anhydrous potassium carbonate (5.6 g, 0.04 mol) were added to 150 mL dry DMF under argon. The mixture was stirred at room temperature with periodic checking by TLC ($CHCl_3$-MeOH, 9:1). After 2 days, the reaction seemed to stall, and therefore the mixture was heated at 90 °C for two 8 hr installments. The reaction mixture was then cooled to room temperature and filtered to remove insoluble materials. The DMF

was then evaporated and the resulting semisolid sludge was chromatographed on silica gel ($CHCl_3$-MeOH, 9:1). Among the isolated products were the desired intermediate (Rf = 0.5), a structural isomer (Rf = 0.6), and a product (Rf = 0.45) whose MS corresponded to the decarboxylated analog, diethylphosphonylmethoxylethyl-1,2,4-triazole with the actual site of alkylation not being determined. Only a small amount of (**210**) was rigorously purified for structure verification. We have provided analytical data for (**210**) which was isolated as a light golden oil. For the conversion of the carboxylic ester to the carboxamide, the mixture of products was used. Separation of the decarboxylated analog (**213**) from the resulting amide (**214**) was much easier than from the corresponding ester (**211**). MS (FAB) *m/e* 321 (M + 1); ^{1}H NMR (Me_2SO-d_6) δ 8.68 (s, 1, triazole H), 4.48 (t, 2, *J* = 5 Hz, NCH_2), 3.98 (apparent q, 4, *J* = 8 Hz, OCH_2CH_3), 3.92 (m, 2, CH_2P), 3.36 (s, m, 5, OCH_3, NCH_2CH_2), 1.18 (t, 6, *J* = 7 Hz, OCH_2CH_3). *Anal.* Calcd for $C_{10}H_{19}N_4O_5P \cdot 0.5H_2O$: C, 38.10; H, 6.39; N, 17.77. Found: C, 37.97; H, 6.16; N, 18.16.

1-[2-(Diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide (214). The mixture of products (0.75 g) containing **211** and **213** from the previous reaction were added to concentrated ammonium hydroxide (50 mL) and stirred overnight at room temperature. The solvent was then removed under vacuum and the resulting viscous light yellow oily residue was chromatographed (silica gel, $CHCl_3$-MeOH, 9:1) to separate the mixture of products, carboxamide (**214**) (0.6 g, Rf = 0.25) and the decarboxylated triazole analog (**213**) (0.1 g, Rf = 0.45), both as almost colorless, viscous oils. MS (FAB) *m/e* 303 (M + 1); IR (KBr) 3315, 3184, 1685, 1479, 1291, 1239, 1121, 1047, 1026, 974 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.56 (s, 1, triazole H), 7.74, 7.54 (2 br s, 2, NH_2), 4.42 (t, 2, J = 5 Hz, NCH_2CH_2), 3.97 (apparent q, 4, J = 7 Hz, OCH_2CH_3), 3.96-3.88 (m, 2, NCH_2CH_2O), 3.35 (d, 2, J = 8 Hz, CH_2P), 1.17 (t, 3, J = 8 Hz, OCH_2CH_2); IR (KBr) 3412, 1688, 1476, 1291, 1236, 1122, 1048, 1026, 975, 349 cm^{-1}. *Anal.* Calcd for $C_{10}H_{19}N_3O_5P \cdot 0.5H_2O$: C, 38.10; H, 6.39; N, 17.77. Found: C, 38.05; H, 6.39; N, 17.91.

1-[2-(Phosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxylamide (215). The 1-[2-(diethylphosphonylmethoxy)ethyl]-1,2,4-triazole-3-carboxamide (**214**) (1.0 g, 0.0033 mol) was dissolved in anhydrous acetonitrile under an inert atmosphere (N_2). Bromotrimethylsilane (3.0 mL, 3.5 g, 0.023 mol) was then added dropwise with stirring at room temperature. The mixture was stirred for 14 h, and then the solvent and volatile reactants were removed under vacuum to give a golden oil. The oil was further vacuumed overnight before an aqueous acetone solution (10 mL, 1:9) was added. Since no precipitation could be induced, the solvents were removed under vacuum. The residue was then dissolved in MeOH. After 3 days at room temperature, a small amount of white solid precipitated. After another day, the solid was collected, washed with MeOH (2 x 5 mL), and dried to give 95 mg of analytically pure **215**; mp 167-169 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.68 (s, 1, triazole H), 7.76, 7.04 (2 br s, 2, NH_2), 4.42 (t, 2, *J* = 5 Hz, NCH_2CH_2), 3.90 (t, 2, *J* = 5 Hz, NCH_2CH_2), 3.60 (d, 2, *J* = 9 Hz, CH_2P). *Anal.* Calcd for $C_6H_{11}N_4O_5P \cdot 0.2H_2O$: C, 28.41; H, 4.52; N, 22.08. Found: C, 28.69; H, 4.54; N, 21.79.

Additional compound **215** could be isolated after its conversion to its ammonium salt **216** by the following procedure. Dilute ammonium hydroxide was added to 47 mg of the mixture containing **215**. The solution was then filtered and evaporated under vacuum, giving a hygroscopic foam. When allowed to absorb

moisture from the air, 27 mg of the hydrated ammonium salt was isolated as a white solid. *Anal.* Calcd for $C_6H_{11}N_4O_5P \cdot 2.5NH_3 \cdot 1HBr \cdot 2H_2O$: C, 17.59; H, 5.78; N, 22.22. Found: C, 17.22; H, 5.45; N, 22.08.

5′-Deoxyadenosine, 5′-*N*,*N*-Diethylthiocarbamate [AVS-4618] (218). Sodium diethyldithiocarbamate trihydrate (3 g) and 2′,3′-*O*-methylethylidene-5′-tosyladenosine (4.5 g) was added to dry DMF (200 mL) and the solution was refluxed for 3 h in a Dean-Stark water separation set-up. The reaction mixture was concentrated under reduced pressure to a gummy solid. The product was purified by silica gel column chromatography, eluting with 5% methanol in chloroform (3.68 g) [MS (FAB) 439 (M + 1)]. A solution of this compound in ethanol (10 mL) was stirred with 1 *N* H_2SO_4 (30 mL) at room temperature for 3 days. The reaction mixture was then triturated several times with ethanol. The residue obtained was taken up in ethanol (200 mL) and pH of the solution was brought to 7.0. The solid obtained was filtered. The filtrate was concentrated, charged on a silica gel column, eluting with 10% methanol in chloroform. Product obtained was further purified by crystallization from methanol (1.65 g); mp 101-102 °C; MS (FAB) 399 (M + 1). UV λ_{max} 258 (20,600), 206 (23,400); IR (KBr) 3500, 3129, 2975, 2925, 3450-2800 (broad) (NH_2, OH and CH), 1672 (C=S), 1642, 1602 (aromatic), 1575, 1489, 1470, 1421, 1415, 1335, 1295, 1270, 1206 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.37 (s, 1, H-8), 8.16 (s, 1, H-2), 7.3 (br s, 2, NH_2), 5.9 (d, 1, H-1′, J = 6 Hz), 5.53 (d, 1, OH-2′, J = 6 Hz), 5.4 (d, 1, OH-3′, J = 5 Hz), 4.86 (d d, 1, H-2′), 4.18 (d d, 1, H-3′), 4.14-4.04 (m, 1, H-4′), 3.97 (q, 2, CH_2N), 3.87-3.68 and 3.68-3.52 (m, 4, H-5′ and CH_2N), 1.18 and 1.15 (t, 6 H, CH_3); ^{13}C NMR (Me_2SO-d_6) δ 193.2 (C=S), 156.0 (C-NH_2, $^3J_{C_6,H_2}$ = 11.3 Hz), 152.5 (C-2, $^1J_{C_2,H_2}$ = 198.9 Hz), 149.3 (C-4, $^3J_{C_4,H_8}$ = 12.4 Hz, $^3J_{C_4,H_2}$ = $^3J_{C_4,H_{1'}}$ = 4 Hz), 140.0 (C-8, $^1J_{C_8,H_8}$ = 212.8 Hz, $^3J_{C,H_{1'}}$ = 4.2 Hz), 119.2 (C-5, $^3J_{C_5,H_8}$ = 11.6 Hz, $^3J_{C_5NH}$ = 3.6 Hz), 87.4 (C-1′, $^1J_{C_{1'},H_{1'}}$ = 164.9 Hz), 82.5 (C-4′), 72.7 (C-3′), 72.5 (C-2′), 49.2 and 46.4 (CH_2NCH_2), 39.1 (C-5′), 12.3 and 11.2 (CH_3) ppm. *Anal.* Calcd for $C_{15}H_{22}N_6S_2O_3 \cdot 0.5H_2O \cdot 0.5EtOH$: C, 44.64; H, 6.09; N, 19.53; S, 14.90. Found: C, 44.87; H, 5.80; N, 19.51; S, 14.90.

5′-Deoxyadenosine, 5′-*N*,*N*-Diethylthiocarbamate (218). A hot, stirred solution of 5′-*O*-tosyladenosine (3.15 g, 7.47 mmol) in ethanol (300 mL) was treated with sodium diethyldithiocarbamate (2.36 g, 10.46 mmol). This reaction solution was heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residual solid was stirred in cold water (50 mL). The white solid product was collected, washed with cold water, and dried *in vacuo* (P_2O_5): yield, 2.34 g, (78%); mp 168-170 °C; MS (FAB) *m/e* 399 (M + 1); UV λ_{max} 258 (23,470) at pH 7, 258 (24,400) at pH 13; IR 3500, 3129, 2975, 2925, 3450-2800 (broad) [NH_2, OH and CH], 1672 (C=S), 1642, 1602 (aromatic), 1575, 1489, 1470, 1421, 1415, 1335, 1295, 1270, 1206 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.37 (s, 1, H-8), 8.16 (s, 1, H-2), 7.3 (br s, 2, NH_2), 5.9 (d, 1, H-1′, J = 6 Hz), 5.53 (d, 1, J = 6 Hz, OH-2′), 5.4 (d, 1, J = 5 Hz, OH-3′), 4.86 (d d, 1, H-2′), 4.18 (d d, 1, H-3′), 4.14-4.04 (m, 1, H-4′), 3.97 (q, 2, CH_2N), 3.87-3.68 and 3.68-3.52 (m, 4, H-5′ and CH_2N), 1.18 and 1.15 (t, 6, CH_3). *Anal.* Calcd for $C_{15}H_{22}N_6O_3S_2 \cdot 0.75H_2O \cdot 0.25EtOH$: C, 43.95; H, 5.95; N, 19.84. Found: C, 43.97; H, 6.34; N, 19.99.

1-Morpholinomethyltetrahydro-2(1*H*)-pyrimidinethione (219). Tetrahydro-2(1*H*)-pyrimidinethione (10.8 g, 0.1 mol), 37.7% formalin (8.9 mL, 0.1 mol), and morpholine (8.7 g, 0.1 mol) were added to methanol (250 mL) and heated at 60 °C for 4 h. The reaction mixture was cooled, and the solvent was removed under

vacuum. The resulting residue was washed with ether and recrystallized from ethyl acetate, ethanol, and three more times from ethyl acetate to give the desired product as colorless plates (2.5 g). TLC (silica gel, chloroform:methanol. iodine chamber) showed that the mother liquors still contained the desired product. However, no more effort was directed toward the isolation and purification of additional product; mp 143-145 °C; MS (FAB) *m/e* 200 (M + 1); IR (KBr) 3225, 2938, 2926, 2871, 2855, 2820, 1650, 1647, 1514, 1460, 1445, 1426, 1397, 1302, 1285, 1278, 1220, 1207, 1189, 1167, 1128,1116, 862, 770 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.22 (br s, 1, NH), 3.88 (s, 2, NCH_2N), 3.54 (m, 4, OCH_2), 3.24 (m, 2, pyrm NCH_2), 3.10 (m, 2, $NHCH_2$), 2.36 (m, 4, morph NCH_2), 1.76 (m, 2, pyrm $CH_2CH_2CH_2$); ^{13}C NMR (Me_2SO-d_6) δ 155.35 (C=O), 67.79 (NCH_2N), 66.05 (OCH_2), 50.51 (morph $NHCH_2$), 44.82 (pyrm NCH_2), 39.61 (pyrm $NHCH_2$), 21.91 (pyrm $CH_2CH_2CH_2$). *Anal.* Calcd for $C_9H_{17}N_3O_5$: C, 54.30; H, 8.60; N, 21.10. Found: C, 54.07, H, 8.88; N, 20.92.

1,3-Bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinone (220). A solution of 37.7 % formalin (8.9 g, 0.1 mol), morpholine (8.7 g, 0.1 mol), and tetrahydro-2(1*H*)-pyrimidinone (10 g) was refluxed in 250 ml MeOH for 2 h. The solvent was then evaporated under reduced pressure, the residue washed with dry ether and boiled with ethyl acetate. The undissolved material was filtered, and crude monomorpholinomethylated product was obtained from the ethyl acetate. The bis-(morpholinomethyl)-tetrahydro-2(1*H*)-pyrimidinoine was obtained from the mother liquid after evaporation and column chromatography (silica gel, CH_3OH-MeOH 9:1, iodine) followed by recrystallization from ethyl acetate: yield, 0.6 g; mp 120-122 °C (reported 121-123 °C); MS (FAB) *m/e* 299 (M + 1); ^1H NMR (Me_2SO-d_6) δ 3.94 (s, 4, NCH_2N), 3.55 (m, 8, OCH_2), 3.32 (m, 4, pyrm NCH_2), 2.38 (m, 8, morph NCH_2), 1.84 (m, 2, pyrm $CH_2CH_2CH_2$); IR (KBr) 2933, 2913, 2867, 2851, 2818, 1645, 1632, 1497, 1459, 1438, 1430, 1291, 1276, 1211, 1202, 1118, 1111, 1003, 921, 864, 757 cm^{-1}. *Anal.* Calcd for $C_{14}H_{26}N_4O_3$: C, 56.35; H, 8.78; N, 18.78. Found: C, 56.69; H, 8.92; N, 18.87.

1-Morpholinomethyl-tetrahydro-2(1*H*)-pyrimidinethione (221). Tetrahydro-2(1*H*)-pyrimidinethione (5.8g, 0.05 mol), 37.7% formalin (9.2 mL, 0.11 mol), and morpholine (9 g, 0.104 mol) were added to methanol (60 mL) and refluxed for 2 h. Removal of the solvent and crystallization from ethanol (x3) gave two crops of colorless needles (1.2 g and 1.7 g). Only the former of these was found to be analytically pure; mp 160-162 °C (reported, 156-158 °C); MS (FAB) *m/e* 216 (M + 1); IR (KBr) 3346, 2950, 2919, 2871, 2863, 2818, 2802, 1535, 1510, 1357, 1285,1266, 1202, 1170, 1109, 1002, 861, 851 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.98 (br s, 1, NH), 4.50 (s, 2, CH_2), 3.54 (m, 4, OCH_2), 3.31 (m, 2, pyrm NCH_2), 3.10 (m, 2, $NHCH_2$), 2.48 (m, 4, morph NCH_2), 1.32 (m, 2, pyrm $CH_2CH_2CH_2$). *Anal.* Calcd for $C_9H_{17}N_3O_5$: C, 50.20; H, 7.96; N, 19.52. Found: C, 50.17; H, 8.03; N, 19.62.

5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (226). 5-Chloro-3-(2',3',5'-tri-*O*-acetyl-β-*D*-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**225**) (300 mg) was suspended in a solution of 10 mL acetone and 90 mL 0.1 *M* NH_4HCO_3 with good stirring and heating at 35-37 °C. Porcine esterase (0.1 mL) was added and the mixture was stirred for 3 days. Since the reaction was incomplete, another 0.1 mL more esterase was added and the heating was continued for 4 more hours. The reaction mixture was evaporated to dryness *in vacuo*, and azeotroped with EtOH-benzene. The sample was purified by passing it through a 50 g silica gel flash chromatography column, eluting with 12:1 chloroform-methanol. The appropriate fractions were combined and evaporated. This residue (~100 mg) was dissolved in hot EtOH, cooled, scratched to induce

crystallization, and stored in the freezer. The product was collected and dried, yielding 52 mg (24%). Retreatment of a faster eluting fraction with esterase followed by the same workup led to the isolation of an additional 52 mg (24%) of product.

Ethanolic ammonia deblocking: Into a stainless steel bomb were placed 250 mg (**225**) and ~50 ml of saturated NH_3-EtOH. The reaction was stirred at room temperature overnight and then evaporated. The residue was then chromatographed on a 50 g flash chromatography column and eluted with 12:1 chloroform:methanol. The product (60 mg) was combined with the two products from the esterase deblocking and was blended, yielding 164 mg of the desired product; mp 167-169 °C cap; UV λ_{max} 283 nm (12,500) at pH 1, pH 7, and pH 13; MS (FAB) *m/e* 303 (M + 1); IR (KBr) 1710, 1689, 1669, 1586, 1548, 1512, 1502, 1103, 1095, 1070 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60, 3.74 (2 m, 2, CH_2-5′), 3.98 (m, 1, H-4′), 4.17 (apparent q, 1, H-3′), 4.42 (apparent q, 1, H-2′), 5.19 (t, 1, OH-5′), 5.24 (d, 1, OH-3′), 5.69 (d, 1, OH-2′), 5.77 (d, 1, H-1′), 6.26 (s, 1, H-6), 9.19 (s, 1, H-2).

4-Amino-2,6-dithiouracil (229).[79] To a solution of 4-amino-6-hydroxy-2-mercaptopyrimidine (**228**, predried, 5 g, 31 mmol) and anhydrous pyridine (150 mL) was added P_2S_5 (15 g, 67.4 mmol). The mixture was heated under argon at reflux for 3 h, during which a red-orange solution formed. The pyridine was removed under pressure to give a crude solid. Water (75 mL) was added carefully and the aqueous mixture was refluxed for 4 h or until all H_2S(g) had been given off. The reaction mixture was filtered and the remaining precipitate was taken up in NH_4OH-H_2O (1:1) and boiled until a clear solution formed. The solution was cooled to room temperature and treated with decolorizing carbon. The solution was filtered through celite, and the filtrate was taken to pH 2 with 1 *M* HCl which caused the precipitation of yellow crystals. Recrystallization with DMF-water (1:9) yielded 3.1 g; mp > 280 °C; MS (FAB) *m/e* 160 (M + 1); ^1H NMR (Me_2SO-d_6) δ 5.8 (s, 1, vinyl H), 6.9 (br s, 2, NH_2), 12.18 (s, 1, SH), 12.38 (s, 1, SH); IR (KBr) 1642.2, 1607.2, 1571.9, 1555.4, 1188.9, 1101.6, 1059.8, 820.4, 802.6, 689.8 cm^{-1}. *Anal.* Calcd for $C_4H_5N_3S$: C, 30.17; H, 3.16; N, 26.39. Found: C, 30.17; H, 3.49; N, 26.39.

6-Aza-4-thiouridine, 2′,3′,5′-Triacetate (231).[80] Into a 100-mL round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and drying tube was added with stirring, 5 g (13.5 mmol) of 6-azauridine, 2′,3′,5′-triacetate (**230**), and dry pyridine (50 mL). Phosphorus pentasulfide (2.1 g, 4.7 mmol) was then added quickly, the system was flushed with argon, and the reaction was heated at gentle reflux for 3 h. The reaction was then cooled, and the solution was decanted from the dark gum and evaporated at reduced pressure. The residue was dried *in vacuo* over P_2O_5 to remove pyridine. The residue was taken up in EtOH, treated with charcoal, filtered, and evaporated. The dark residue was dissolved in $CHCl_3$, washed with water, dried filtered, and evaporated. A portion of the product was purified by flash chromatography on 100 g of silica gel, using $CHCl_3$ as the eluate. The product was isolated as an orange foam; yield, 580 mg; UV λ_{max} 325 nm (14,400), 242 (6,10) at pH 1; 335 (13,000), 247 (7,700) at pH 7; 335 (13,300), 247 (7,300) at pH 13; MS (FAB) *m/e* 388 (M + 1); IR (KBr) 1748, 1729, 1580, 1375, 1200 (broad), 1132, 1100, 1074, 1047 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.11 (m, 9, $COCH_3$), 4.17, 4.39 (2 m, 2, H-5′), 4.40 (m, 1, H-4′), 5.43 (t, 1, H-3′), 5.66 (q, 1, H-2′), 6.25 (d, 1, H-1′); 7.67 (s, 1, H-5), 10.40 (s, 1, NH). *Anal.* Calcd for $C_{14}H_{17}N_3O_8S \cdot 0.1EtOH \cdot 0.1H_2O$: C, 43.31; H, 4.56; N, 10.67. Found: C, 43.26; H, 4.80; N, 10.66.

6-Aza-4-thiouridine (232).[80] A solution of 6-aza-4-thiouridine, 2',3',5'-triacetate (231, 1 g, 2.58 mmol) was dissolved in 50 mL of MeOH and slowly passed through a column of Dowex 1 resin (OH^- form). The column was washed with about 300 mL of MeOH and the product was eluted using 5% HOAc in MeOH. The appropriate fractions were combined, evaporated, the residual HOAc removed by evaporation from water (2 x 50 mL), followed by evaporation from 50 mL EtOH-benzene. The product was purified by chromatography through a flash column of 100 g of silica gel with $CHCl_3$-MeOH (7:1). The appropriate fractions were combined, evaporated, and the residue was washed with ether (2 x 30 mL) and dried at 56 °C over phosphorus pentoxide: yield, 140 mg; mp 104-115 °C dec; UV λ_{max} 328 nm (13,700), 243 (5,600) at pH 1; 334 (12,600), 247 (7,000) at pH 7; 336 (12,700), 247 (7,100) at pH 13; MS (FAB) *m/e* 262 (M + 1); IR (KBr) 1704, 1575, 1283, 1050 (broad), 990, 590 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.39, 3.50 (2 m, 2, H-5'), 3.80 (apparent q, 1, H-4'), 4.02 (apparent q, 1, H-3'), 4.24 (apparent q, 1, H-2'), 4.65 (t, 1, OH-5'), 5.04 (d, 1, OH-3'), 5.30 (d, 1, OH-2'), 5.84 (d, 1, H-1'), 7.75 (s, 1, H-5), 13.7 (br s, 1, NH). *Anal.* Calcd For $C_8H_{11}N_3O_5S \cdot 0.3H_2O \cdot 0.07Et_2O$: C, 36.58; H, 4.56; N, 15.46. Found: C, 36.63; H, 4.84; N, 15.38.

4-Amino-5-glycosylamino-2-thiouracil (234). In a 50-mL round-bottomed flask equipped with a reflux condenser and drying tube were mixed 4,5-diamino-2-thiouridine (500 mg, 3.16 mmol) and α-glucose (570 mg, 3.16 mmol). DMSO (25 mL) was added, and the flask was then quickly flushed with argon. The reaction mixture was heated at 70 °C for 3 h, with complete solution occurring after less than an hour. The reaction was cooled, evaporated to a brown gum at reduced pressure below 50 °C, and the residue was triturated with ether (2 x 30 mL). The gummy residue was then treated with EtOH, ground to a powder, collected, washed with EtOH, and then dried, giving 1.0 g of crude product. A portion (700 mg) of the crude product was dissolved in hot EtOH, then filtered, cooled, and precipitated by the addition of hexane. The product was collected, washed with hexane, and dried at room temperature over phosphorus pentoxide: yield, 300 mg (43%); mp 135-142 °C dec; IR (KBr) 1624, 1562, 1250, 1175, 1080, 1015 cm^{-1}, all peaks rounded and broad; MS (FAB) *m/e* 321 (M + 1); ^1H NMR (Me_2SO-d_6) δ 2.8°-3.0 (m, 2, H-2',4'), 3.05-3.15 (m, 1, H-5'), 3.34 (m, 2, H-6'b), 3.65 (m, 2, H-6'a), 3.81 (d d d, 1, H-3', $J_{2',3'} = J_{3',4'} = 4.0$ Hz), 4.29 (d, 1, OH-3', $J_{3',3'\text{-}OH} = 4.4$ Hz), 4.50 (t, 1, OH-6', $J_{6',6'\text{-}OH} = 6.0$ Hz), 4.88 and 4.86 (2 d, 2, OH-2',5', $J_{2',2'\text{-}OH}$, $J_{5',5'\text{-}OH} = 5.5$ Hz), 5.32 (d, 1, H-1', $J_{1',2'} = 3.2$ Hz), 6.13 (apparent s, 2, NH_2), 11.62 (br s, 1, NH), 11.95 (br s, 1, NH). *Anal.* Calcd for $C_{10}H_{16}N_4O_6S \cdot 0.75H_2O \cdot 0.25EtOH$: C, 36.52; H, 5.55; N, 16.22. Found: C, 36.36; H, 5.62; N, 16.10. *This compound was found to be very hydrolytically unstable.*

4-Amino-5-mannosylamino-2-thiouracil (239). In a 50 mL round-bottomed flask equipped with a reflux condenser and drying tube were mixed 4,5-diamino-2-thiouridine (500 mg, 3.16 mmol) and mannose (570 mg, 3.16 mmol). DMSO (25 mL) was added, and the flask was then quickly flushed with argon. The reaction mixture was heated at 70 °C for 3 h with complete solution occurring after less than an hour. The reaction was cooled, evaporated to a brown gum at reduced pressure below 50 °C, and the residue was triturated with ether (2 x 30 mL). The gummy residue was then treated with EtOH, ground to a powder, collected, washed with EtOH and dried. The crude product was dissolved in hot EtOH, filtered, cooled, and precipitated by the addition of hexane. The product was then collected, washed with hexane, and dried at room temperature over phosphorus pentoxide: yield, 380 mg; mp 128-132 °C dec; IR (KBr) 1625, 1560, 1440, 1375, 1250, 1170, 1065

cm^{-1}, all peaks rounded and broad; MS (FAB) *m/e* 321 (M + 1); ^1H NMR (Me_2SO-d_6) spectrum peaks will be assigned later. *Anal.* Calcd for $C_{10}H_{16}N_4O_6S \cdot 0.90H_2O$ 0.2EtOH: C, 36.13; H, 5.54; N, 16.21. Found: C, 35.97; H, 5.42; N, 16.34. *This compound was found to be very hydrolytically unstable.*

2,4-Dithio-6-azauridine, 2',3',5'-triacetate (246, R = Ac). The preparation for 2,4-dithio-6-azauridine 2',3',5'-triacetate was patterned after the procedure of Beranek and Sorm.[7] Under an argon atmosphere in a 100-mL round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and drying tube was placed 2',3',5'-triacetyl-2-thio-6-azauridine (1.75 g, 4.52 mmol) and 50 mL of dry pyridine. As soon as a homogeneous solution was obtained, P_2S_5 (6.0 g, 13.6 mmol) was added in one portion. The system was flushed with argon, and the reaction was heated at gentle reflux for 3 h before it was cooled and filtered. The residue was washed well with ether, and the filtrate and washings were combined and evaporated *in vacuo*. The resulting dark residue was extracted with EtOAc (75 mL) and ether (3 x 75 mL). The extracts were washed further with very dilute aqueous HCl to remove residual pyridine, then they were washed with saturated salt solution, dried, filtered, and evaporated. The crude product was purified by flash column chromatography (300 g silica gel) eluting with 98:2 methylene chloride-MeOH. An orange crystalline foam (550 mg, 30 %) was obtained; mp 52-56 °C; UV λ_{max} 321 nm (13,700); 281 (24,600) at pH 1; 341 (15,300); 287 (17,500) at pH 7; 340 (16,100) at pH 13; IR (KBr) 1750, 1578, 1497, 1372, 1283, 1235 (broad), 1131, 1102, 1079, 1046 cm^{-1}; MS (FAB) *m/e* 404 (M + 1); ^1H NMR (Me_2SO-d_6) δ 4.09 (m, 1, H-4'), 4.33 (m, 2, H-5'), 5.37 (t, 1, H-3'), 5.59 (m, 1, H-2'), 6.97 (d, 1, H-1'), 8.12 (s, 1, H-5). *Anal.* Calcd for $C_{14}H_{17}N_3O_7S_2$: C, 41.68; H, 4.25; N, 10.42. Found: C, 41.52; H, 4.37; N, 10.68.

2,4-Dithio-6-azauridine (246, R = H). A solution of 2,4-dithio-6-azauridine, 2',3',5'-triacetate (246, R = Ac) (2 g, 4.96 mmol) dissolved in ~100 mL MeOH was slowly passed through a column of Dowex 1 resin (OH^- form). The column was washed with at least 300 mL of MeOH, then with about 300 mL 5% HOAc in MeOH, and finally with 5% formic acid in MeOH. The appropriate fractions were determined by TLC and combined, evaporated, azeotroped with benzene-ethanol (2 x 30 mL), and dried over phosphorus pentoxide at room temperature; yield 610 mg (45%); mp 180-188 °C dec; UV λ_{max} 322 nm (13,050), 280 (23,660) at pH 1; 339 (15,230), 283 (17,970) at pH 7; 340 (15,500), 284 (17,700) at pH 13; IR (KBr) 1588, 1543, 1360, 1288, 1248, 1171, 1111, 1098, 1040 (broad), 969 cm^{-1}; MS (FAB) *m/e* 278 (M + 1); ^1H NMR (Me_2SO-d_6) δ 3.41, 3.55 (2 m, 2, H-5'), 3.83 (m, 1, H-4'), 4.03 (t, 1, H-3'), 4.22 (apparent t, 1, H-2'), 4.65 (br s, 1, OH-5'), 5.05 (br s, 1, OH-3'), 5.35 (br s, 1, OH-2'), 6.71 (d, 1, H-1'), 8.01 (s, 1, H-5), 14.60 (br s, 1, NH-3). *Anal.* Calcd for $C_8H_{11}N_3O_4S_2 \cdot 0.25MeOH$: C, 34.73; H, 4.24; N, 14.73. Found: C, 34.78; H, 4.50; N, 14.71.

5'-*O*-[[[[2',3',4',6'-Tetra-*O*-benzyl-α-D-glucopyranosyl)oxy]carbonyl]amino]sulfonyl]-2',3'-isopropylidene-6-azauridine (249, R = O). A solution of D-glucopyranose (1.2 g, 2.2 mmol) in dry methylene chloride (18 mL) was cooled to -30 °C under argon and treated with chlorosulfonylisocyanate (0.311 g, 2.2 mmol). The mixture was stirred at -30 °C for 3 h, and then a solution of 2',3'-isopropylidine-6-azauridine (0.565 g, 1.46 mmol) in anhydrous acetonitrile was added. The reaction mixture was stirred at room temperature for 8 h, and then dry pyridine (0.17 mL, 2.2 mmol) was added. The reaction mixture was further stirred for 10 h at room temperature before it was evaporated under reduced pressure, and the resulting yellow residue was

column chromatographed (silica gel), eluting with $CHCl_3$-MeOH (gradient 100% $CHCl_3$ → 95%). The fifth major band afforded the desired compound as a white foam; yield 80 mg (6%); mp 80-85 °C; MS (FAB) *m/e* 931 (M + 1) and (neg FAB) *m/e* 929 (M + 1); IR (KBr) 3235, 3100, 3065, 2990, 2945 (CH, NH), 1757, 1731, 1699 (C=O), 1454, 1384, 1265, 1240, 1211, 1185, 1159, 1130, 1103, 1071, 1051, 1027, 984, 863, 751, 736, 698 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.24, 1.40 (2 s, 6, isopropylidine) 3.52-3.85 (m, 6, H-2'', H-3'', H-4'', H-5'', H-6''), 4.28 (m, 2, H-5'), 5.00-4.60 (m, 10, CH_2Ph), 4.48 (m, 1, H-4'), 4.72 (m, 1, H-3'), 5.00 (d, 1, H-2'), 6.12 (s, 1, H-1'), 6.24 (d, 1, H-1''), 7.14-7.30 (m, 20, Ph-H's), 7.48 (d, 1, H-3, vinyl H), 12.3 (s, 1, NH). *Anal.* Calcd for $C_{46}H_{50}N_4O_{15}S \cdot 0.4H_2O$: C, 58.33; H, 5.62; N, 6.51 Found: C, 58.45; H, 5.52; N, 6.22.

4-Acetyl-4-phenylpiperidine Hydrochloride. 4-Acetyl-4-penylpiperidine (10 g) was chromatographicaly purified by elution with $CHCl_3$-MeOH (95:5) through silica gel. Dissolution of the crystallizable clear oil in EtOH (125 mL) followed by bubbling HCl gas, solvent evaporation (x3), charcoaling in hot ethanol, and solvent evaporation to about 20% of the original volume gave a white granular solid (4.0 g). (Further evaporation gave 0.8 g of a slightly impure sample of 39.) Mp (darkens at 150 °C) 229-230 °C; partial, 239-240 °C; ^1H NMR (Me_2SO-d_6) δ 9.20 (s, 2, $\overset{\oplus}{N}H_2$), 7.40 (m, 5, Ar-H's), 3.10 (m, 2, H-2 eq), 2.95 (m, 2, H-2 ax), 2.52 (m, 2, H-3 eq), 2.24 (m, 2, H-3 ax), 1.94 (s, 3, CH_3). *Anal.* Calcd for $C_{13}H_{18}ClNO$: C, 65.12; H, 7.58; N, 5.84. Found: C, 64.74; H, 7.58; N, 5.84.

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