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CONTRACT NO: DAMD17-87-C-7171

TITLE: SUICIDE INHIBITORS OF REVERSE TRANSCRIPTASE IN THE
THERAPY OF AIDS AND OTHER RETROVIRUSES

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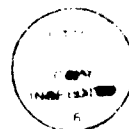
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13. ABSTRACT (Maximum 200 words) The final year of the contract has been quite productive and significant advances have been made in a number of areas. Groups of compounds were synthesized as potential suicide inhibitors of viral polymerases. Test results from compounds submitted to the U.S. Army antiviral screening program have been received and are summarized below. Full details of active compounds are given in the Appendix to this report. Of the 40 compounds tested to date, significant antiviral activity against one or more of the 11 test viruses have been observed for a surprisingly high proportion. 16 compounds in all have shown some antiviral activity. Several of these have low cytotoxicity and small animal test are planned in collaboration with the Army antiviral screening program if the current (residual) funding proves sufficient.				
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SUMMARY

1. The final year of the contract has been quite productive and significant advances have been made in a number of areas.
2. Groups of compounds were synthesized as potential suicide inhibitors of viral polymerases. Test results from compounds submitted to the U.S. Army antiviral screening program have been received and are summarized below. Full details of active compounds are given in the Appendix to this report. Of the 40 compounds tested to date, significant antiviral activity against one or more of the 11 test viruses have been observed for a surprisingly high proportion. 16 compounds in all have shown some antiviral activity. Several of these have low cytotoxicity and small animal test are planned in collaboration with the Army antiviral screening program if the current (residual) funding proves sufficient.
3. Cellular components have been identified that produce up to a 1,000-fold increase in the sensitivity of HIV-reverse transcriptase to the pyrophosphate analog phosphonoformate (Foscarnet).
4. The following table summarizes the compounds found to have antiviral activity and the target virus against which they were effective.

<u>Virus</u>	<u>Compounds showing significant antiviral activity</u> <u>(AVS #'s)</u>				
HIV	6460	6457	6455	6466	
Vaccinia	6462	6467			
Punta Toro	6442 6443	6444	6445	6449	6462
Yellow Fever	6456	6458	6444	6445	

Further details for each compound are given in the Appendix Section.

A. INTRODUCTION

The principle that inhibitors of reverse transcriptase will inhibit replication of retroviruses is well established. For example, 3'-azido-3' deoxythymidine, the triphosphate of which inhibits the RT activity of HIV, is a potent inhibitor of virus replication in cultured H-9 cells in the range of 1-10 micromolar and is being used successfully in patients with AIDS. Prolonged administration may cause serious side effects. Another agent which has shown promise is phosphonoformate (PFA, Foscarnet) which inhibits the RT activity of HIV with an I_{50} of only 0.1 micromolar. However, much higher concentrations of up to 340 micromolar are required for complete inhibition of HIV replication in H-9 cells. Other drugs including the dideoxycytidines which are also based upon inhibition of RT by chain termination of the viral template are in clinical trial. Since none of these drugs permanently inactivate the reverse transcriptase and since they do not accumulate intracellularly in significant amounts, virus replication will resume when blood levels of the drugs decrease.

This project represents a collaborative effort between groups of investigators with expertise in virology, cell biology, enzymology, drug design and organic synthesis, to develop new types of antiviral drugs. Novel anti-HIV drugs are being developed based upon the principles of (i) compounds designed to accumulate intracellularly at the sites of viral replication (ii) slow release lipid soluble prodrugs having a long biological half life and capability to accumulate in brain tissues (iii) synergistic combination drugs designed to reduce side effects and development of drug resistance during long-term therapy.

B. WORK ACCOMPLISHED

1. Cellular Pharmacokinetics of Sterol Phosphonoformates.

The first class of compounds are lipid soluble sterol derivatives of the pyrophosphate analog PHOSPHONOCFORMIC ACID (PFA). This compound is an excellent *in vivo* inhibitor of reverse transcriptase with I_{50} 's as low as 0.1 μ M for the HIV-RT when transcribing from the viral template. The drug is also relatively non-toxic and acute dosage blood levels of up to 300 μ M have been reported without serious side effects. The antiviral potency of the compound however is low with concentrations up to 330 μ M being required for complete inhibition of HIV replication in tissue culture. Simple esterification derivatives do not improve the antiviral potency.

The sterol phosphonoformates which we have developed thus represent a significant advance in the pharmacology of antiviral drug delivery to cells. They are replication-site directed inhibitors designed to enter and accumulate in cells via the endocytotic pathway normally used for cholesterol esters. Subsequent hydrolysis by lysosomal sterol esterases results in slow release of PFA at the intracellular sites where the first critical steps in HIV replication take place. Some of the cholesterol phosphonoformate derivatives we have synthesized display a 20-30 fold increase in potency against virus replication in tissue culture, compared to the parent compound PFA.

One of the major goals of this project is the further development of this class of compounds into effective therapeutic agents. These studies will include synthesis and evaluation of ligands which enhance cellular accumulation, those which regulate hydrolysis, and those which enhance anti-viral activity against HIV replication in a standardized tissue culture assay system. A novel and potentially useful therapeutic property which has been observed is the ability of these sterol analogs to accumulate intracellularly and protect cells against virus for up to 8 days following drug removal. The pharmacokinetic studies we are proposing on blood-brain and tissue distribution and half life of these compounds *in vivo* are designed to investigate their suitability as potential agents for long-term antiviral therapy.

2. Sterol Carboxylate Diesters of AZT, DDC and nucleoside spiroxiranes (NSO):

An extension of this strategy which has proved successful with PFA is being applied to improve the pharmacokinetic properties of AZT, dideoxycytidine (DDC) and nucleoside spiroxiranes. The nucleoside spiroxiranes are a new class of mechanism based (suicide) inhibitors of the reverse transcriptase. These nucleoside analogs are effective inhibitors of reverse transcriptase and viral replication but have very short blood half lives and do not accumulate intracellularly. Virus replication probably recovers soon after blood levels of the drugs fall. Here the problem is not to

increase the cellular permeability of the compounds which is adequate, but to enhance the intracellular accumulation in a slow-release form.

The effect on their pharmacokinetic properties of modifying these compounds by conversion to the 5' sterol dicarboxylates will therefore be investigated. These compounds are designed to incorporate into the lipoprotein and chylomicron particles in the same manner as the long-chain cholesterol esters and phospholipids. Cholesteryl sebacylchloride has been used previously to make synthetic lipoproteins. Sterol and ester hydrolases are present in the lysosomes which will regenerate the active compounds. In pilot studies ³H-AZT cholesteryl sebacylate has been synthesized and uptake by cultured lymphocytes confirmed (see preliminary data section). Appropriate changes in the sterol and linker moieties will be made and the effects on cell accumulation, intracellular release and prolongation of antiviral protection will be evaluated. In addition, the unlabelled AZT-cholesteryl sebacate, succinate and carbonate esters have been synthesized and inhibited viral replication in tissue culture.

3. Development of Synergistic Combination Drugs:

The basic hypothesis underlying this approach is that drug dosages and side effects can be reduced and antiviral potency increased by suitable combinations of drugs directed at different facets of the viral replicative process. In addition, combination drugs lessen the opportunity for drug resistant variants of the virus to appear because of the low probability of simultaneous mutations against two mechanistically different inhibitors. This approach therefore has required basic information on the effects of different drugs on the various steps involved in intracellular replication of the HIV virus, using the purified HIV-RT to obtain detailed information on the kinetic interactions of the HIV reverse transcriptase with potential inhibitors. As an example of the application of this type of information, the nucleotide and template specificity of the RT has been studied with respect to inhibition by PFA. PFA inhibits only the step in viral replication in which TTP is being incorporated into the viral template. Incorporation of dCTP is relatively insensitive to PFA. Furthermore PFA inhibition is not competitive with respect to TTP for the HIV-RT, indicating that mutations that confer AZT resistance are unlikely to result in co-resistance to PFA.

Part of the antiviral potency of AZT in addition to inhibiting RT has been attributed to its ability to inhibit thymidine kinase, thus lowering intracellular TTP levels. These results taken together suggest that additive or synergistic effects should be observed in joint therapy of the sterol phosphonoformates with AZT, DDC or NSO. Since the side effects of these drugs are directed in part at different facets of cell metabolism: whereas the antiviral effects are focussed on the viral reverse transcriptase, a combination of drugs at levels insufficient to impair cell metabolism may nevertheless give complete inhibition of virus replication. The successful development of the sterol dicarboxylates of AZT renders this approach particularly attractive, since all three types of inhibitor are now potentially available in slow-release and long acting forms.

4. Expression of HIV-Reverse Transcriptase In Different Cell Lines.

In order to determine if the recombinant HIV-reverse transcriptase was expressed in different forms depending upon the cell type, the vaccinia VCF-21 construct was grown in a number of different cell lines of both human, monkey and rodent origin. The expressed reverse transcriptase was tested for inhibition by Foscarnet at two different levels (1 and 10 nanomolar) and compared to the E. Coli recombinant HIV-RT (Kindly donated by Dr. Steven Hughes Fort Detrick M.D.) and the wild type HIV-RT. Both the wild type and E. Coli HIV-RT's were resistant to PFA showing essentially no inhibition at the 10nM level. Previous studies have shown that both enzymes have I_{50} 's for PFA in the 200-400 nM range. The recombinant HIV-RT expressed in eukaryotic cells however showed a range of phenotypes as indicated in figures 3 and 4 below. Both U-937 and Vero cells expressed enzyme sensitive to 1 nanomolar PFA, whereas human embryo lung and A-498 cells expressed RT-enzyme having wild-type sensitivity. Hela, HuTK- and CV-1 cells as observed previously expressed enzyme having intermediate PFA sensitivity (Figure 1).

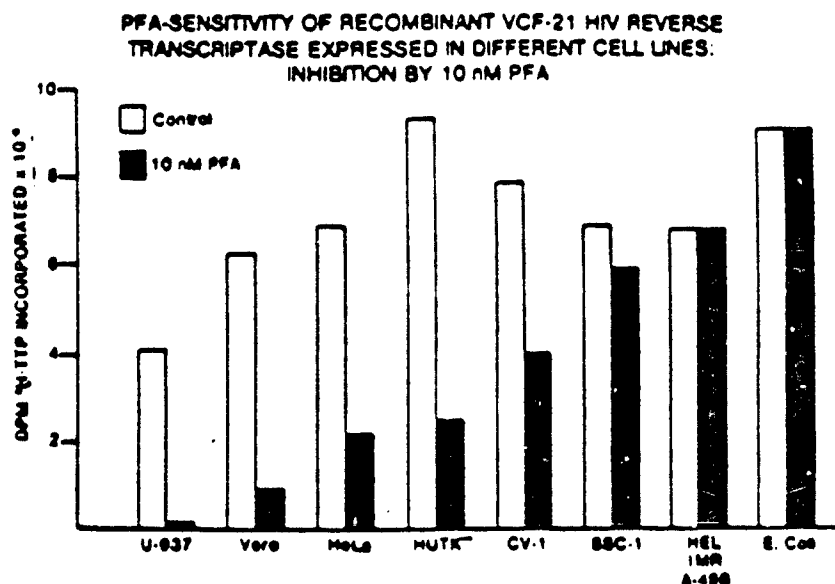


Figure 1: Sensitivity of Recombinant HIV-Reverse Transcriptases to 10 Nanomolar PFA.

The VCF-21 vaccinia construct was grown in the indicated cell lines and the activity of the expressed reverse transcriptase was measured in the presence (dark blocks) or absence (open blocks) of 10 nanomolar PFA.

5. Sensitivity of Recombinant HIV-Reverse Transcriptase to Foscarnet.

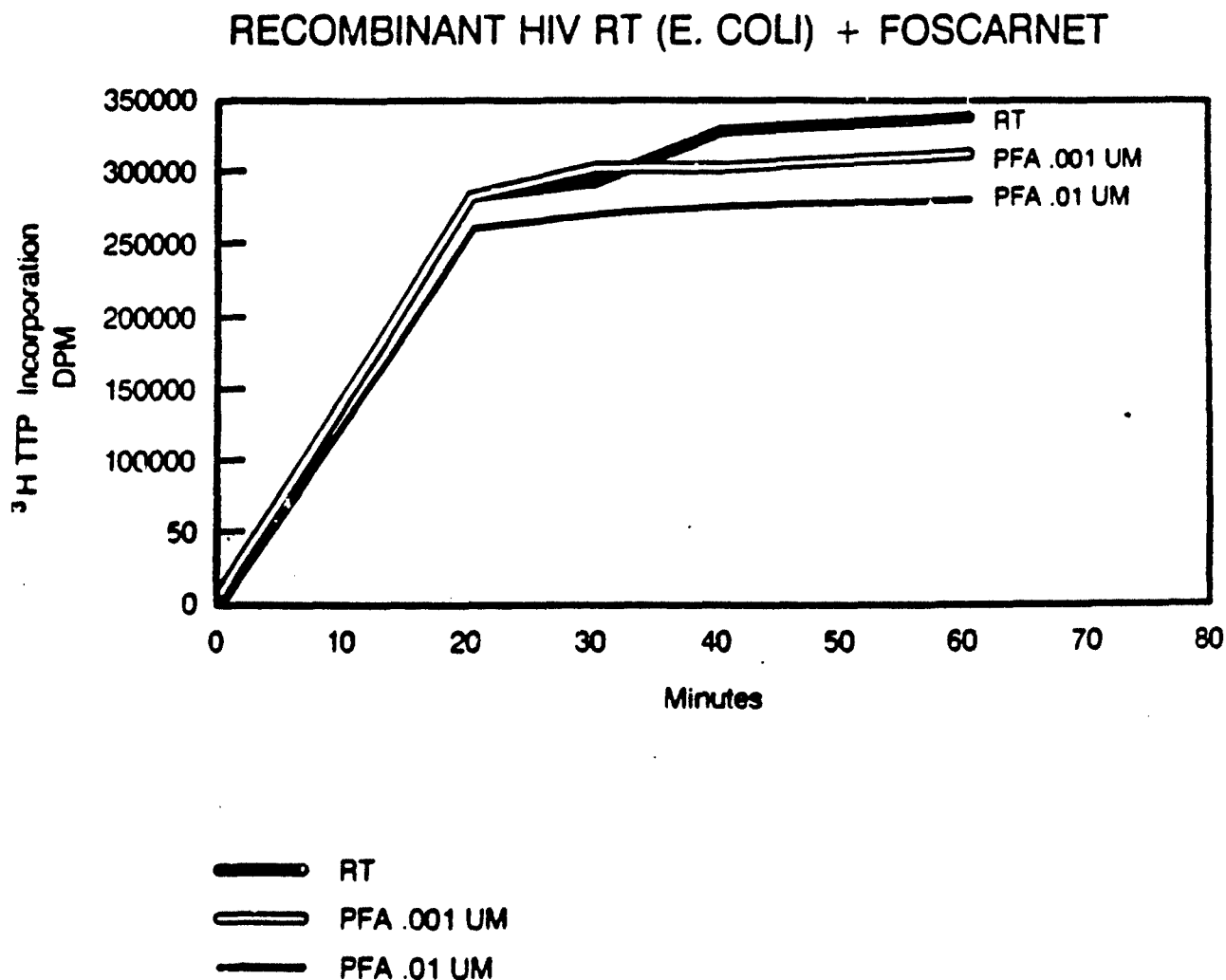


Figure 2. Activity of a recombinant (E. Coli produced) HIV-RT was assayed using ^3H -dTTP and poly rAdT₁₀ template both without inhibitor PFA and in the presence of 0.001 μM and 0.01 μM PFA. Note the relative insensitivity of the enzyme to these low concentrations. The I_{50} of the E. Coli recombinant HIV-RT for PFA was shown to be 0.4 μM which is similar to that of the wild type HIV-RT.

SENSITIVITY TO FOSCARNET INHIBITION OF HIV REVERSE TRANSCRIPTASE (PURIFIED) IN THE PRESENCE OF CELL LYSATES

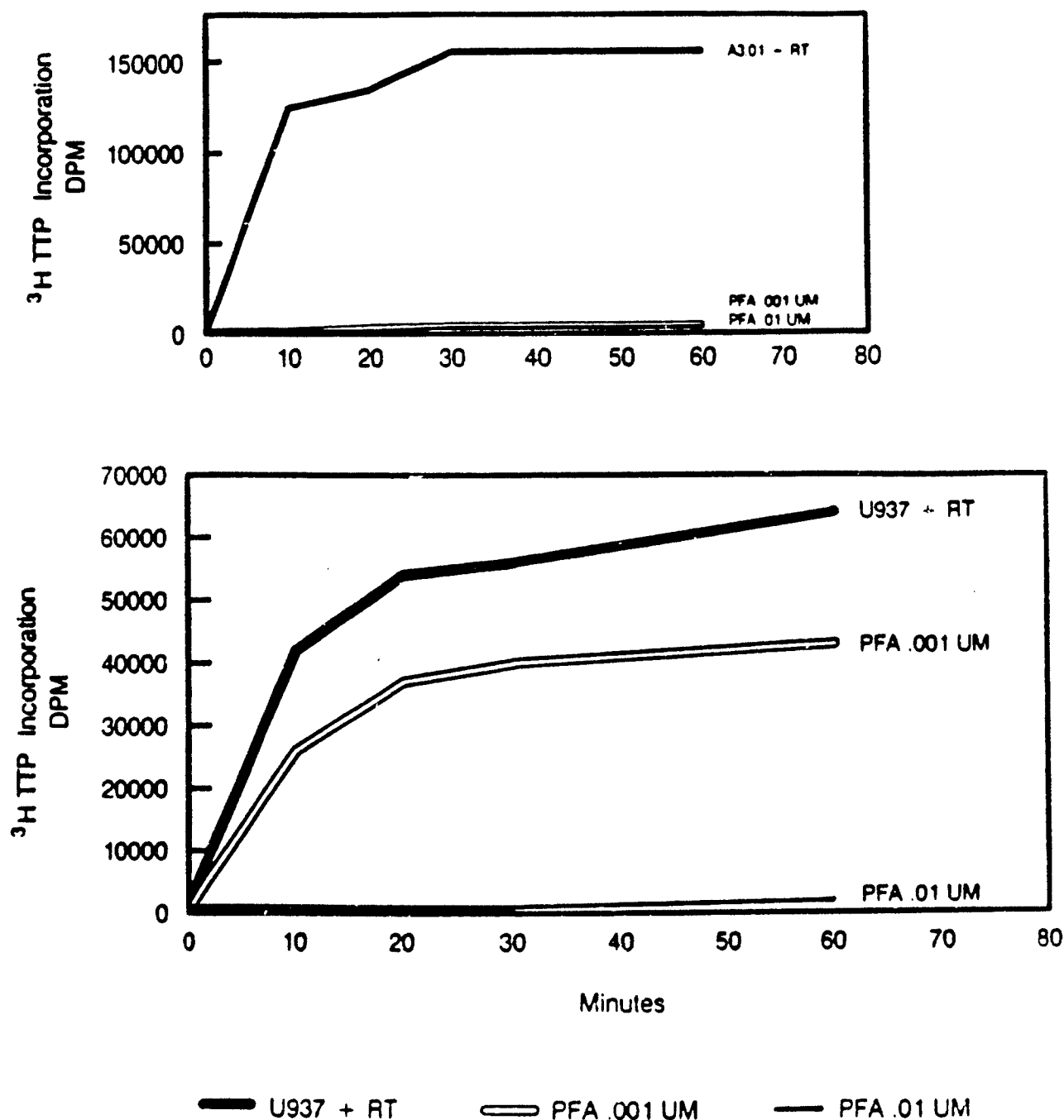


Figure 3. The E. Coli recombinant HIV-RT was incubated with PFA under the same conditions as Figure 1R, with the addition of lysates from A.301 cells (upper panel) or U937 cells (bottom panel). Note that the lysates markedly increase the sensitivity of the reverse transcriptase to inhibition by PFA.

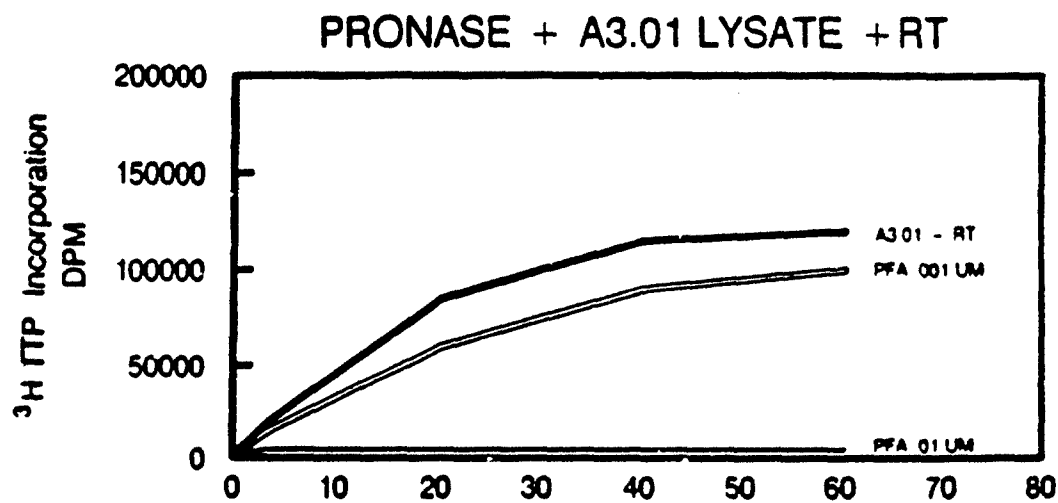
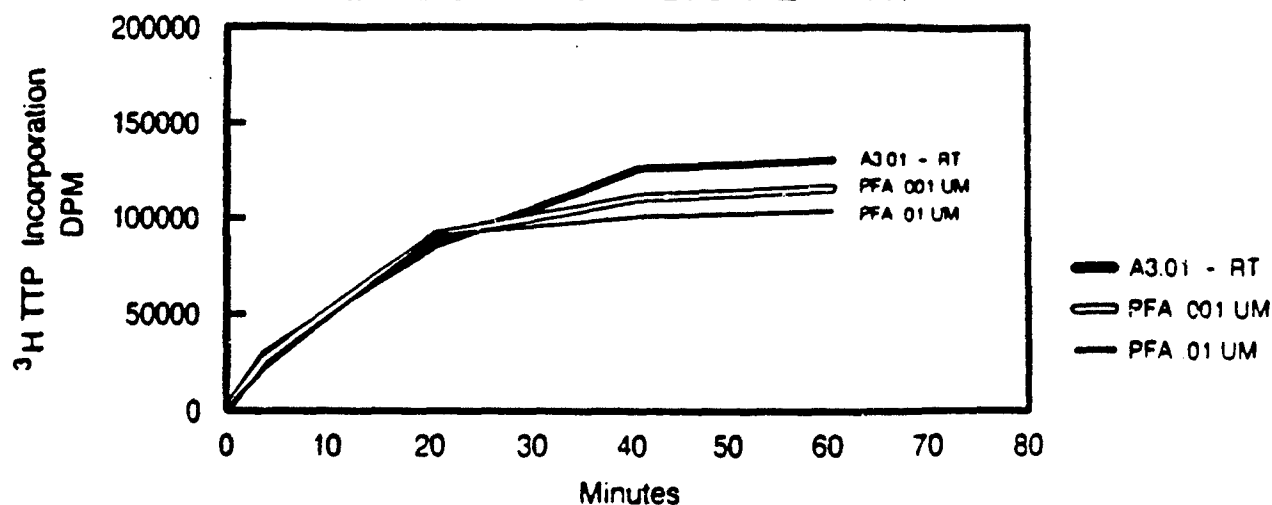


Figure 4. The E. Coli recombinant HIV-RT was incubated with PFA and cell lysates under the same conditions as in Figure 2R with the exception that the lysates were preincubated with pronase for 30 minutes and heat inactivated. Note that neither treatment destroyed the PFA sensitizing activity of the cell extracts.

SENSITIVITY TO FOSCARNET INHIBITION OF HIV REVERSE TRANSCRIPTASE (PURIFIED) IN THE PRESENCE OF CELL LYSATES

RNASE + A.3.01 LYSATE + RT



RNASE + U937 LYSATE + RT

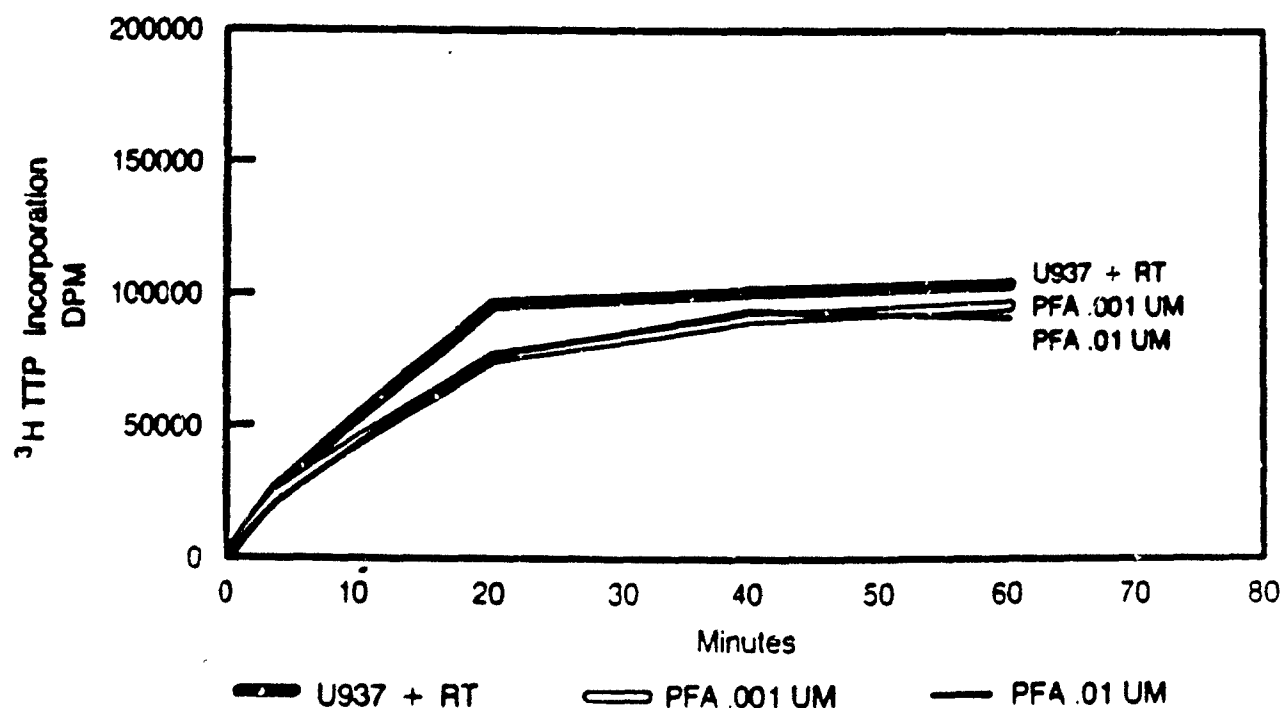


Figure 5. The E. Coli recombinant HIV-RT was incubated with PFA and cell lysates under the same conditions as Figure 2R with the exception that the lysates were preincubated with pancreatic ribonuclease for 30 minutes. Note that the RNase treatment completely destroyed the PFA sensitizing activity of the extracts.

Since the molecular weight of the sensitized, purified recombinant RT prepared from sensitizing cell lines was not substantially different from that of wild type enzyme, these observations suggest that the sensitizing activity may be associated with a copurifying RNase sensitive material of relatively low molecular weight.

6. Drug Screening Results.

Test results from 26 of the compounds submitted to the U.S. Army antiviral testing facility have been received. A number of compounds were identified that have activity against one or more of the 11 viruses in the test battery. Of these 4 were active against HIV (Appendix III), and 9 were active against Vaccinia, Punta Toro and Yellow Fever viruses (Appendix IV).

Several of these compounds have very favorable therapeutic indices and have been selected for further testing and development to the limit of currently available funding.

Appendix I.

PUBLICATIONS

PROJECT: DAMD 17-87-C-7171

TITLE: SUICIDE INHIBITOR OF REVERSE TRANSCRIPTASE IN THERAPY OF AIDS AND OTHER RETROVIRUSES.

PRINCIPAL INVESTIGATOR: Dr. J.M. Bailey, Ph.D., D.Sc.
Professor of Biochemistry

PRODUCTIVITY REPORT

Publications:

1. Enhanced sensitivity to Foscarnet of first-strand viral replication by recombinant HIV-reverse transcriptase. M.M. Lightfoote and J.M. Bailey. *FASEB J.* 4:1318 (1990).
2. Differential sensitivity of wild-type and recombinant HIV-Reverse transcriptase to inhibition by Foscarnet. M.M. Lightfoote and J.M. Bailey. *Proc Vth Int. AIDS conf. Montreal* 5:515 (1989).
3. M.M. Lightfoote and J.M. Bailey. Somatic Cell Modulation of HIV-Reverse Transcriptase Expression. *Antiviral Chem. and Chemotherapy*. (1989) in preparation.
4. Nucleotide and template selectivity for inhibition of reverse transcriptase by PFA: Implications for retroviral therapy. J.M. Bailey and M.M. Lightfoote. *Proc. IVth Int. AIDS Conf. Montreal.* 4:3223 (1988).
5. Differential sensitivity of wild-type and recombinant HIV-reverse transcriptase to inhibition by foscarnet. M.M. Lightfoote and J.M. Bailey. *Proc. IVth Int. AIDS Conf. Montreal.* (1989).
6. Antiviral activities of some sterol phosphonoformate diester. J.M. Bailey, K. Nelson, M. Lightfoote. *J. Clin. Exp. Ther.* in preparation.
7. Nucleoside spiroxiranes: A new class of retroviral inhibitor. J.M. Bailey, K. Nelson, M. Lightfoote. *J. Virol.* in preparation.
8. Synthesis and antiviral activities of some sterol dicarboxylate esters of 3'-Azido thymidine (AZT). J.M. Bailey, R.M. Mook, M. Lightfoote. *J. Clin. Exp. Ther.* in preparation.
9. Synthesis of mono and di-substituted cholesterol phosphonoformates by the Arbuzov reaction. J.M. Bailey and Keith Nelson. *Tetrahedron Letters.* in preparation.

Appendix II

COMPOUNDS SYNTHESIZED:

Compounds synthesized and prepared for shipment to USAMRIID for antiviral testing.

1. 2',0²-Anhydrouridine
2. 2',0²-Anhydrocytidine hydrochloride
3. 3',5'-Di-0-benzoyl-2'-0²-anhydrouridine
4. 5'-0- γ -Butyldimethylsilyl-3'-0-benzoyl-2',0'-anhydrouridine
5. 2',3'-Anhydro-5'-0-trityluridine
6. 3'-Deoxy-2'-thymidine
7. N³-Benzyl-2',5'-di-0-trityluridine
8. 5'-0- γ -Butyldimethylsilylanhydrouridine
9. N⁴-Benzoylcytidine
10. 2',3'-Di-0-mesyl-5'-0-trityluridine
11. 5'-0- γ -Butyldimethylsilyl-2',3'-isopropylideneuridine
12. 2',3'-Isopropylideneuridine
13. 2',3'-0-Sulfinyluridine
14. 2',3'-Benzylideneuridine
15. N⁴-Benzoyl-2',3'-0-Sulfinylcytidine
16. 2',3'-0-Sulfinylcytidine
17. 3',5'-Di-0-trityl-2'-deoxy-2'-oxouridine
18. 3',5'-Di-0- γ -butyldimethylsilyl-2'-deoxy-2'-oxouridine
19. 2',5'-Di-0- γ -butyldimethylsilyl-3'-deoxy-3'-oxouridine
20. Diethyl (cholesteryl oxycarbonyl) phosphonate
21. Disodium (cholesteryl oxycarbonyl) phosphonate
22. Di-[1-(3-carboethoxypropyl)] cholesteryl oxycarbonyl
23. Di-(2,3-isopropylidene glyceryl) cholesteryl oxycarbonyl phosphonate
24. Di-[1-(3-methylbutyl)] cholesteryl oxycarbonyl phosphonate
Di-[1-(lithium 3-carboxypropyl)] cholesteryl oxycarbonyl phosphonate
25. Sodium ethyl (cholesteryl oxycarbonyl) phosphonate

-
26. Sodium 1-(3-carboxypropyl) 1-(30 carboethoxypropyl) [cholesteryloxycarbonyl] phosphonate
 27. Adenosine 2',3'-Riboepoxide
 28. Thymidine 5'-(1,3,2-dioxaphosphorin-2-oxide)
 29. Thymidinene 5'-(1,3,2-dioxaphosphorin-2-oxide)
 30. Thymidinene
 31. 2-Ethoxy-5-chloro-6-methyl-1,3,2-dioxaphosphorin-5-ene-2-oxide
 32. 2-Ethoxy-5-chloro-1,2-oxaphosphol-4-ene-2-oxide
 33. 2,4-dichloro-5-methyl-1,3,2-dioxaphosphole-2-oxide
 34. 2-methoxy-4,5-dimethyl-1,3,2-dioxaphole-2-oxide
 35. Thymidine 3',5'-oxetane

Appendix III

TEST DATA ON ANTI HIV DRUGS



DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
FORT DETRICK, FREDERICK, MARYLAND 21701-5011

May 10, 1990

REPLY TO
ATTENTION OR

Department of Antiviral Studies

Dr. J. Martyn Bailey
Professor of Biochemistry and Molecular Biology
The George Washington University
Department of Biochemistry
2300 Eye Street, NW
Washington, DC 20037

Dear Dr. Bailey:

Enclosed please find results of the antiviral activity screening on the U.S. Army's Antiviral Drug Development Program. The enclosed data summarizes the in vitro results of the screening done to date.

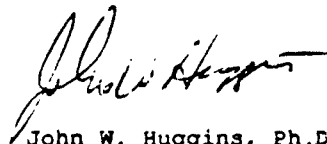
•Older assay methodologies have been reviewed in relation to current program status and predictability. As a result of this review, current data sheets may reflect new data as well as the removal of previously reported data now thought to be supplanted by new assay techniques.

•Data have not been previously reported for compounds showing antiviral activity prior to confirmation. I feel this procedure has unnecessarily slowed the reporting of data to suppliers; hence, we will now report data as it is received. Please do not make corporate or business decisions based on a preliminary, unconfirmed result without discussing this data with the undersigned or a designated member of the Virology Division.

Our intent with these changes is to decrease the length of time required to get data to you for review. Please let me know if the new approach to reporting is improved, and if additional modifications might further enhance collaboration.

Correspondence regarding the evaluation of your compounds or the interpretation of screening results should be addressed to the undersigned at U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21701-5011, (301) 663-7494, FAX (301) 698-0854. Alternatively, you may contact Dr. Edward L. Stephen, P.O. Box 248, Monrovia, Maryland 21770, (301) 874-5533.

Sincerely,



John W. Huggins, Ph.D.
Department of Antiviral Studies
Virology Division

Enclosures

CF: Edward L. Stephen, D.V.M.
Antiviral Information, Compound
Solicitation and Repository

USAMRIID

Antiviral Drug Screening Program

08/06/90

STRUCTURE

CHIRAL

SUBMITTER
01141.01CTR NO
KN-II-55AVS NO
AVS-006466DATE RECD
12-28-89AMT RECEIVED [mg]
53.30MOL WT (au)
224.213

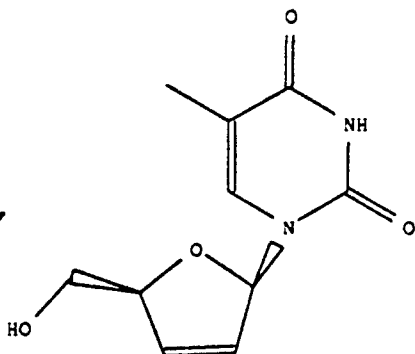
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-DIDEOXYTHYMIDINENE



COMPOUND NAME

2',3'-DIDEOXYTHYMIDINENE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST VH RTE DOSE MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR+	DOSE	CELL	MTC	TI	TI+	LAB	PRT	DATE
HIV			4.99	MT2	66.4	13.29		SO	MTT04-APR-90	
HIV			.32	CEM	71.1	> 222.13		SO	MTT26-APR-90	
JE			NOT ACT	VERO	184	0		SO	MTT06-MAR-90	
PT			NOT ACT	VERO	182	0		SO	MTT06-MAR-90	
SF			NOT ACT	VERO	171	0		SO	MTT06-MAR-90	
VEE			NOT ACT	VERO	> 320	0		SO	MTT09-MAR-90	
YF			NOT ACT	VERO	173	0		SO	MTT06-MAR-90	

IN VIVO SCREEN [Dose = mg/kg]

VIR HST VR VR+ DOSE MTC VEH RTE D TOX SP L PR DATE

PLATE 1Q9
DRUG 6460

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6460
TAI: >30.24 SI: 2.79

	1	2	3	4	5	6	7	8	9	10	11	12
A	reagent background						plate background					
	0.302	0.273	0.281	0.414	0.402	0.296	0.079	0.081	0.255	0.252	0.130	0.071
B		curve					tox	drug 6460 experimental		curve		tox
C		1.940					1.999	0.798	0.734	0.680	2.096	2.160
D		1.881					1.993	0.697	0.802	0.720	1.992	1.693
E		1.776					1.987	0.947	0.994	0.879	1.856	1.943
F		0.557					2.067	1.159	0.949	0.911	0.423	2.060
G		0.423					2.018	0.930	1.338	1.309	0.365	1.921
H		0.478					1.223	0.719	0.614	0.637	0.500	0.881
							drug 6460 colorimetric background					
							0.354	0.270	0.282	0.268	0.273	0.313

24-well titer assay control control virus control BOLD = highest drug conc values shown are optical densities

VIRUS
CELLS
SHIPMENT NUMBER
STRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

HIVCRF
CEM Satisfactory: Active: Retest
63
RF2
0.328
0.130
1.596
1.466

PROJECT # 6520-2
SPONSOR USAMRIID
TEST DATE 06/12/90
DATE READ 06/19/90

DRUG 6460	25%	50%	95%
TC (uG/mL)	82.48	89.38	100.00
IC (uG/mL)	1.18	22.40	
ANTIVIRAL INDEX (AI)	62.61	4.14	

DRUG 6460		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN CPE	MEAN O.D.	% CELL VIABILITY	
low B	0.32	0.295	20%	1.767	100%	-0.015
C	1	0.337	23%	1.570	98%	-0.055
D	3.2	0.542	37%	1.697	100%	-0.060
E	10	0.595	41%	1.782	100%	-0.046
F	32	0.793	54%	1.700	100%	-0.058
high G	100	0.173	12%	0.698	44%	0.026

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6460 vs. HIVCRF (06/12/90)

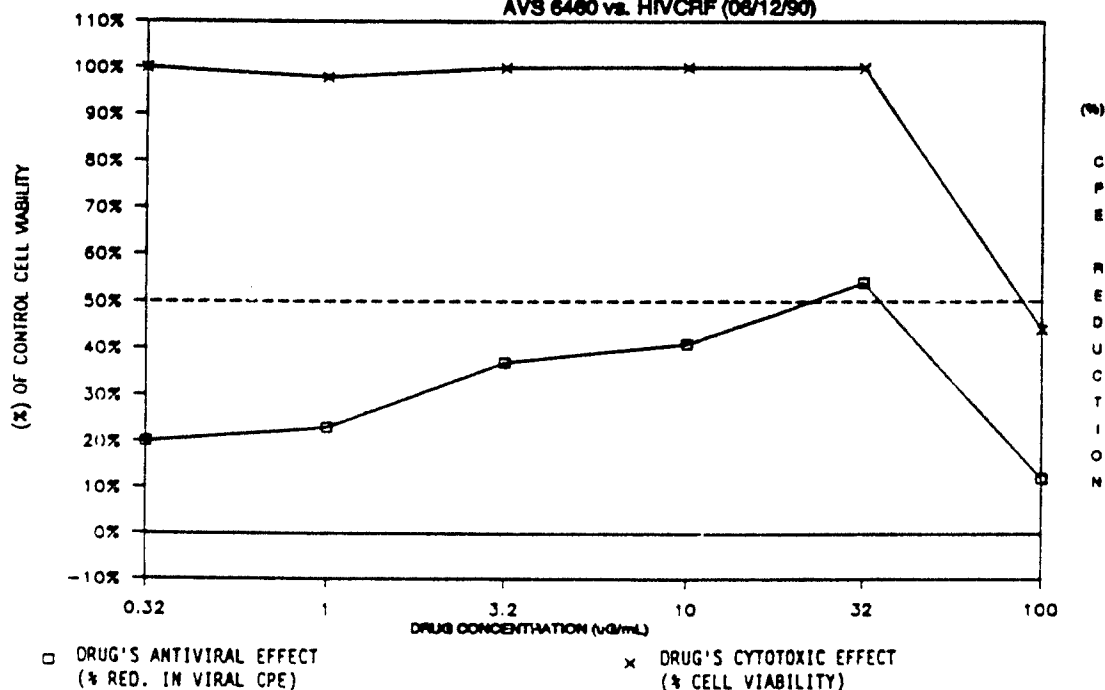


PLATE 108
DRUG 6457

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6457
TAI: >27.78 SI: >1.29

	1	2	3	4	5	6	7	8	9	10	11	12
A	reagent background						plate background					
	0.433	0.373	0.552	0.655	0.447	0.451	0.103	0.100	0.191	0.442	0.104	0.087
B	1.739	1.747	drug 0457 experimental			1.972					1.841	
C	1.606	1.765	0.674	0.715	1.069	1.794					1.750	
D	1.871	1.913	0.555	0.799	1.037	1.806					2.012	
E	1.782	0.522	0.965	0.990	0.742	1.916					0.811	
F	1.783	0.541	0.894	0.662	1.126	1.899					0.583	
G	1.691	0.602	1.069	1.161	1.241	1.811					0.652	
H	drug 0457 colorimetric background											
	0.345	0.405	0.387	0.396	0.393	0.382						
test-cell turbidity control control +virus control BOLD = highest drug conc values shown are optical densities												

low-well toxicity cell-well control no-virus control BOLD = highest drug conc values shown are optical densities

VIRUS
CELLS
SHIPMENT NUMBER
STRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

HIVCRF
CEM Satisfactory; Active; Retest
63
RF2
0.485
0.133
1.353
1.220

PROJECT # 6520-2
SPONSOR USAMRIID
TEST DATE 06/12/90
DATE READ 06/19/90

DRUG 6457	25%	50%	95%
TC (uG/mL)	> 180.00	> 180.00	> 180.00
IC (uG/mL)	4.88	77.00	-----
ANTIVIRAL INDEX (AI)	> 21.37	> 1.29	-----

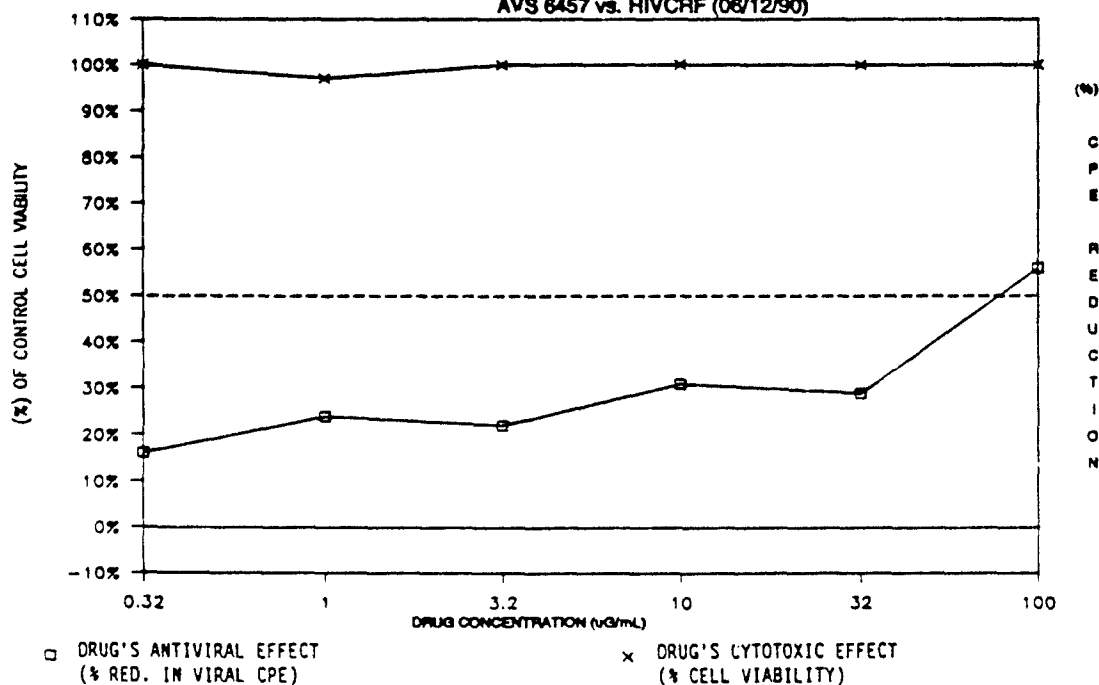
DRUG 6457		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	0.32	0.190	16%	1.473	100%	-0.103
C	1	0.293	24%	1.307	97%	-0.092
D	3.2	0.269	22%	1.442	100%	-0.089
E	10	0.379	31%	1.462	100%	-0.098
F	32	0.356	29%	1.436	100%	-0.080
high G	100	0.679	56%	1.406	100%	-0.140

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6457 vs. HIVCRF (06/12/90)



PRINTED 08/21/90

SOUTHERN RESEARCH INSTITUTE

PLATE 1Q7
DRUG 6455

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6455
TAI: >38.98 SI: >5.71

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.463	0.349	0.539	0.566	0.386	0.388	0.253	0.256	0.399	0.448	0.239	0.199
B	1.916	1.590	0.861	0.677	0.813	1.889					1.783	
C	1.340	1.486	0.820	0.986	0.873	2.017					1.588	
D	1.800	2.193	0.764	0.557	0.841	1.849					1.641	
E	2.057	0.462	0.856	0.811	1.334	2.016					0.539	
F	1.959	0.636	0.944	1.071	1.242	1.830					0.548	
G	2.003	0.374	1.269	1.478	1.180	1.913					0.607	
H	0.328	0.243	0.480	0.459	0.455	0.448						

VIRUS
CELLS
SHIPMENT NUMBER
STRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

HIVCRF
CEM Satisfactory; Active; Retest
63
RF2
0.449
0.079
1.265
1.186

PROJECT # 6520-2
SPONSOR USAMRIID
TEST DATE 06/12/90
DATE READ 06/19/90

DRUG 6455	25%	50%	95%
TC (uG/mL)	> 100.00	> 100.00	> 100.00
IC (uG/mL)	0.49	17.50	-----
ANTIVIRAL INDEX (AI)	> 203.84	> 5.71	-----

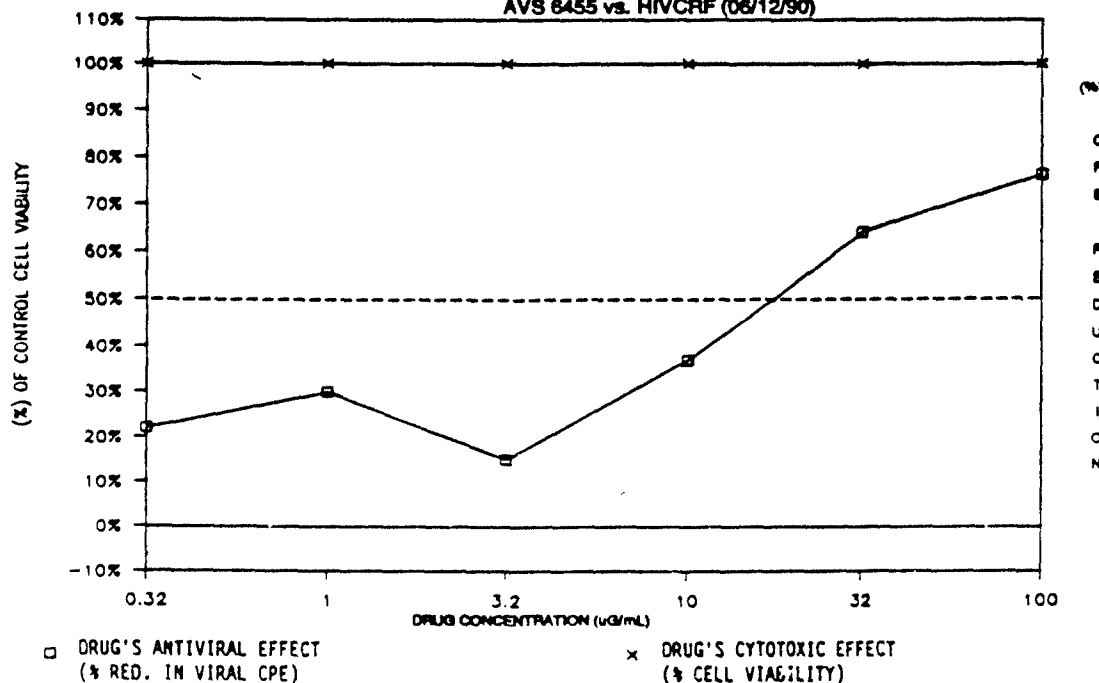
DRUG 6455		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% RED. IN VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	0.32	0.256	22%	1.454	100%	0.000
C	1	0.358	30%	1.473	100%	0.007
D	3.2	0.182	15%	1.365	100%	0.011
E	10	0.442	37%	1.557	100%	0.031
F	32	0.764	64%	1.652	100%	-0.206
high G	100	0.902	76%	1.631	100%	-0.120

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6455 vs. HIVCRF (06/12/90)



PRINTED 06/21/90

SOUTHERN RESEARCH INSTITUTE

Appendix IV
TEST DATA AGAINST OTHER VIRUSES

USAMRIID

Antiviral Drug Screening Program

03/26/90

STRUCTURE

CHIRAL

SUBMITTER

01141.01

CTR NO

KN-V-99

AVS NO

AVS-006442

DATE RECD

12-28-89

AMT RECEIVED [mg]

74.00

MOL WT (au)

290.253

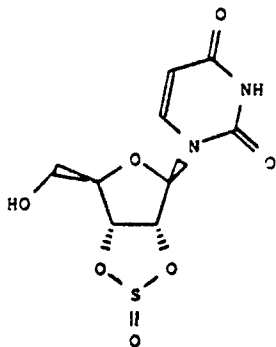
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-O-SULFINYL URIDINE



COMPOUND NAME

2',3'-O-SULFINYL URIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VR RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

R	VR	VR*	1039	CELL	MTC	TI	TI*	LAB PR	DATE
1	NOT ACT	VERO	183			0		SO MTT	90-03-01
2	NOT ACT	VERO	170		2.39			SO MTT	90-03-01
3	NOT ACT	VERO	172			0		SO MTT	90-03-01
4	NOT ACT	VERO	38.3			0		SO MTT	90-03-02
5	NOT ACT	VERO	171			0		SO MTT	90-03-01

VR	RST	VR	VR*	DOSE	MTC	VEN	RTE	D	TOX	SP	L	PR	DATE
----	-----	----	-----	------	-----	-----	-----	---	-----	----	---	----	------

PLATE USA
DRUG 6442

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6442
TAI: 15.38 SI: 1.70

	1	2	3	4	5	6	7	8	9	10	11	12
reagent background						plate background						
A	0.042	0.041	0.040	0.042	0.039	0.042	0.001	0.001	0.001	0.001	0.001	0.001
B	0.898	0.951	0.392	0.299	0.337	0.956					0.746	
C	0.938	1.033	0.389	0.295	0.345	0.912					0.972	
D	1.011	1.139	0.419	0.423	0.434	1.020					0.800	
E	1.034	0.329	0.559	0.504	0.542	1.102					0.334	
F	1.115	0.389	0.663	0.626	0.656	1.181					0.342	
G	0.243	0.553	0.227	0.227	0.219	0.229					0.396	
drug 6442 colorimetric background												
H	0.049	0.038	0.038	0.037	0.038	0.039						
test-cell toxicity			cell-control		virus-virus control		BOLD = highest drug conc			values shown are optical densities		

VIRUS
CELLS
SHIPMENT NUMBER
SITE
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

PT
VERO Satisfactory: Active; Retest
63
ACAMES
0.041
0.316
0.899
0.583

PROJECT # 5975-1
SPONSOR USAMRIID
TEST DATE 03/01/90
DATE READ 03/09/90

DRUG 6442	25%	50%	95%
TC (ug/mL)	170.00	239.00	> 320.00
IC (ug/mL)	22.20	100.00	-----
ANTIVIRAL INDEX (AI)	7.65	2.39	-----

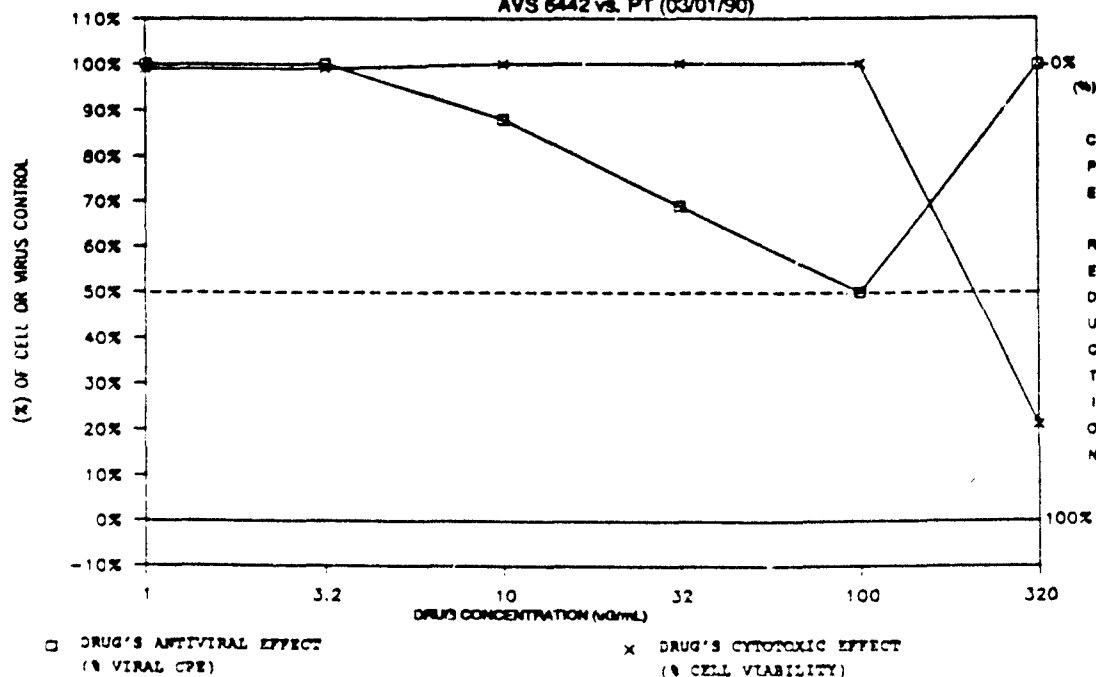
DRUG 6442		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW OR PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	-0.013	100%	0.888	99%	-0.002
C	3.2	-0.011	100%	0.887	99%	-0.003
D	10	0.072	88%	0.979	100%	-0.004
E	32	0.181	69%	1.030	100%	-0.003
F	100	0.294	50%	1.110	100%	-0.003
high G	320	-0.161	100%	0.187	21%	0.008

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6442 vs. PT (03/01/90)



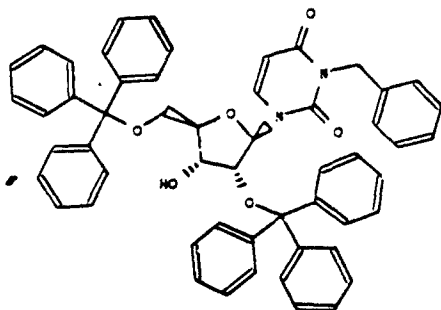
USAMRIID

Antiviral Drug Screening Program

03/26/90

STRUCTURE

CHIRAL



SUBMITTER

01141.01

CTR NO

KN-V-109

AVS NO

AVS-006443

DATE RECD

12-28-89

AMT RECEIVED [mg]

86.00

MOL WT (au)

818.979

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

4POUND NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AQ2>VSV

HOST VR RTE DOSE MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VR	VR*	DOSE	CELL	MTC	TI	TI*	LAB PR	DATE
NOT ACT	VERO	24.7		0			50 MTT	90-03-01
77.1	VERO	210		> 4.15			50 MTT	90-03-01
NOT ACT	VERO	> 320		0			50 MTT	90-03-01
NOT ACT	VERO	> 320		0			50 MTT	90-03-02
NOT ACT	VERO	> 320		0			50 MTT	90-03-01

VIR HOST VR VR* DOSE MTC VEH RTE D TOX SP L PR DATE

PLATE U9A
DRUG 6443

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6443
TAI: >10.57 SI: 2.72

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						passive background					
A	0.042	0.041	0.040	0.042	0.039	0.042	0.001	0.001	0.001	0.001	0.001	0.001
B		curve					low	drug 6443 experimental			curve	low
C		0.951					0.830	0.378	0.357	0.334	0.746	0.879
D		1.033					0.911	0.386	0.324	0.297	0.972	0.771
E		1.139					1.015	0.406	0.436	0.343	0.800	0.866
F		0.329					0.800	0.493	0.491	0.497	0.334	0.814
G		0.389					0.734	0.695	0.713	0.683	0.342	0.716
H		0.353					0.696	0.560	0.632	0.599	0.396	0.751
							drug 6443 colorimetric background					
							0.059	0.044	0.040	0.039	0.040	0.040
	low=cell toxicity		co=cell control		vo=virus control		BOLD = highest drug conc		values shown are optical densities			

VIRUS
CELLS

PT

VERO

Satisfactory; Active; Retest

PROJECT #

5975-1

SHIPMENT NUMBER

63

SPONSOR

USAMRIID

STRN

ADAMES

TEST DATE

03/01/90

DATE READ

03/09/90

REAGENT

0.041

VIRUS CONTROL

0.316

CELL CONTROL

0.899

DIFFERENTIAL

0.583

DRUG 6443	25%	50%	95%
TC (ug/mL)	210.00	> 320.00	> 320.00
IC (ug/mL)	34.20	77.10	-----
ANTIVIRAL INDEX (AI)	6.15	> 4.15	-----

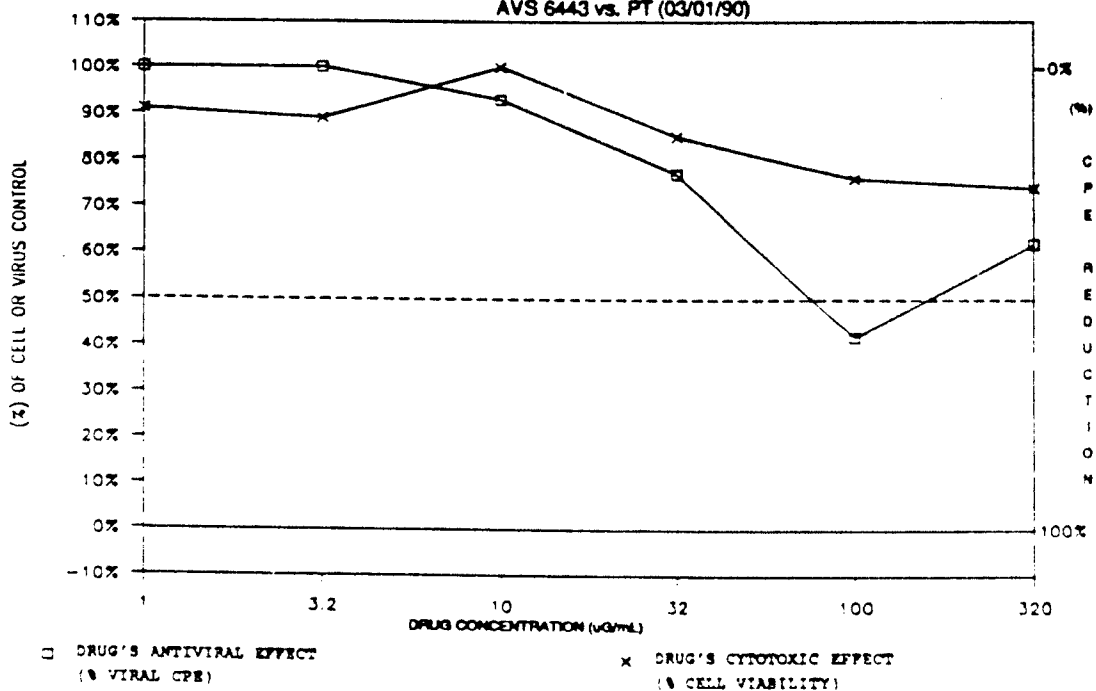
DRUG 6443		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	-0.001	100%	0.815	91%	-0.001
C	3.2	-0.021	100%	0.801	89%	-0.001
D	10	0.040	93%	0.902	100%	-0.002
E	32	0.137	77%	0.767	85%	-0.001
F	100	0.337	42%	0.681	76%	0.003
high G	320	0.222	62%	0.665	74%	0.010

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6443 vs. PT (03/01/90)



USAMRIID

Antiviral Drug Screening Program

01/26/90

STRUCTURE

CHIRAL

SUBMITTER

01141.01

CTR NO

KN-VII-83

AVS NO

AVS-006444

DATE RECD

12-29-89

AMT RECEIVED [mg]

79.00

MOL WT (g)

726.837

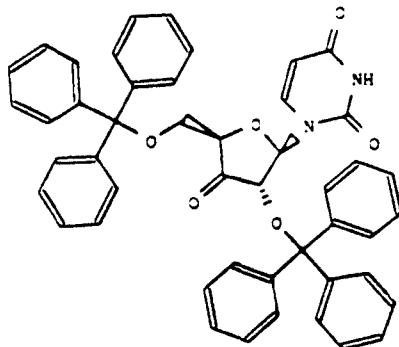
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE



COMPOUND NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>XF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST VH RTE DOSE MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR*	DOSE	CELL	MTC	TI	TI*	LAB PR	DATE
JE		NOT ACT	VERO		51	0		50 MTT	90-03-01
PT		19.2	VERO		> 320	> 4	04	50 MTT	90-03-01
SF		NOT ACT	VERO		30	0		50 MTT	90-03-01
VEE		NOT ACT	VERO		> 320	0		50 MTT	90-03-02
VF		NOT ACT	VERO		> 320	0		50 MTT	90-03-01

IN VIVO SCREEN [Dose = mg/kg]

VIR MTT VR VR* DOSE MTC VEH RTE 2 TOX SP 1 PR DATE

PLATE U98
DRUG 6444

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6444
TAI: >24.65 SI: >4.04

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.043	0.042	0.045	0.041	0.040	0.042	0.001	0.001	0.001	0.001	0.001	0.001
B	1.033	0.918	0.365	0.330	0.321	0.884					0.837	
C	0.959	0.946	0.304	0.333	0.381	0.999					0.734	
D	0.936	1.054	0.433	0.451	0.414	0.883					0.631	
E	0.811	0.295	0.382	0.411	0.490	0.810					0.339	
F	0.753	0.355	0.577	0.706	0.655	0.748					0.369	
G	0.962	0.382	0.952	0.924	0.879	0.981					0.358	
H	drug 6444 colorimetric background											
	0.041	0.043	0.042	0.039	0.039	0.039						

lowest toxicity control control virus control SOLD = highest drug dose values shown are optical densities

VIRUS CELLS

SHIPMENT NUMBER

STRN

REAGENT

VIRUS CONTROL

CELL CONTROL

DIFFERENTIAL

PT

VERO

63

ADAPES

0.042

0.308

0.811

0.504

Satisfactory/ Active/ Retest

PROJECT #

5975-1

SPONSOR

USAMRIID

TEST DATE

03/01/90

DATE READ

03/09/90

DRUG 6444	25%	50%	95%
TC (ug/mL)	> 320.00	> 320.00	> 320.00
IC (ug/mL)	41.50	79.20	278.00
ANTIVIRAL INDEX (AI)	> 7.72	> 4.04	> 1.15

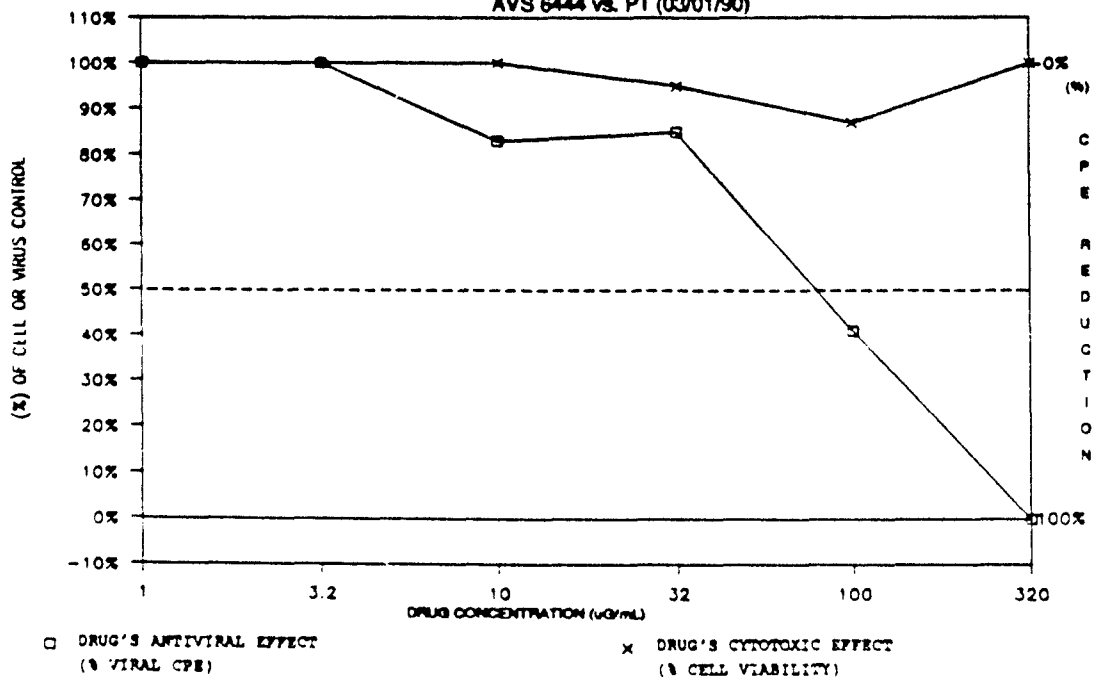
DRUG 6444		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	-0.008	100%	0.909	100%	-0.003
C	3.2	-0.007	100%	0.940	100%	-0.003
D	10	0.086	83%	0.870	100%	-0.003
E	32	0.078	85%	0.768	95%	-0.000
F	100	0.295	41%	0.707	87%	0.001
high G	320	0.570	0%	0.940	100%	-0.001

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6444 vs. PT (03/01/90)



USAMRIID

Antiviral Drug Screening Program

03/26/90

STRUCTURE

CHIRAL

SUBMITTER

01141.01

CTR NO

KN-VII-21

AVS NO

AVS-006445

DATE RECD

12-28-89

AMT RECEIVED [mg]

74.00

MOL WT (au)

726.837

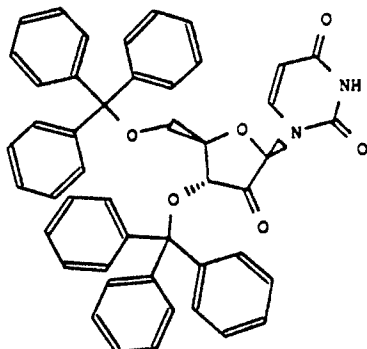
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE



COMPOUND NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VH RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VR	VR*	LD50	CELL	MTC	TI	TI*	LAB PR	DATE
JZ			NOT ACT	VERO	23.2	0		50 MTT	90-03-01
PT			22.6	VERO	49	2.92		50 MTT	90-03-01
SF			NOT ACT	VERO	43.3	0		50 MTT	90-03-01
VEE			NOT ACT	VERO	32	0		50 MTT	90-03-02
YF			18.9	VERO	48	3.45		50 MTT	90-03-01

VIR MST VR VR* DOSE MTC VCH RTE D TOX SP L PR DATE

PLATE U98
DRUG 6445

IN VITRO ANTIVIRAL RESULTS MIT ASSAY

DRUG: AVS 6445
TAI: >17.14 SI: 2.17

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.043	0.042	0.045	0.041	0.040	0.042	0.001	0.001	0.001	0.001	0.001	0.001
B		0.918					0.833	0.402	0.373	0.379	0.837	0.871
C		0.946					1.074	0.286	0.430	0.407	0.734	0.870
D		1.054					0.830	0.567	0.567	0.534	0.631	0.816
E		0.295					0.882	0.656	0.606	0.590	0.339	0.890
F		0.355					0.033	0.036	0.036	0.035	0.369	0.033
G		0.382					0.035	0.036	0.036	0.036	0.358	0.037
H							drug 6445 colorimetric background					
							0.038	0.044	0.043	0.040	0.039	0.039

low-cell toxicity control control virus-virus control BOLD = highest drug done values shown are optical densities

VIRUS
CELLS

PT

PROJECT #

5975-1

SHIPMENT NUMBER

63

SPONSOR

USAMRIID

STIRN

ADAMAS

TEST DATE

03/01/90

REAGENT

0.042

DATE READ

03/09/90

VIRUS CONTROL

0.308

CELL CONTROL

0.811

DIFFERENTIAL

0.504

DRUG 6445	25%	50%	95%
TC (ug/mL)	49.00	66.00	96.60
IC (ug/mL)	5.74	22.60	-----
ANTIVIRAL INDEX (AI)	8.53	2.92	-----

DRUG 6445		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	0.038	92%	0.813	100%	-0.003
C	1.2	0.028	94%	0.933	100%	-0.003
D	10	0.215	57%	0.783	97%	-0.002
E	32	0.267	47%	0.843	100%	0.001
F	100	-0.315	100%	-0.011	0%	0.002
high G	320	-0.310	100%	-0.002	0%	-0.004

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6445 vs. PT (03/01/90)

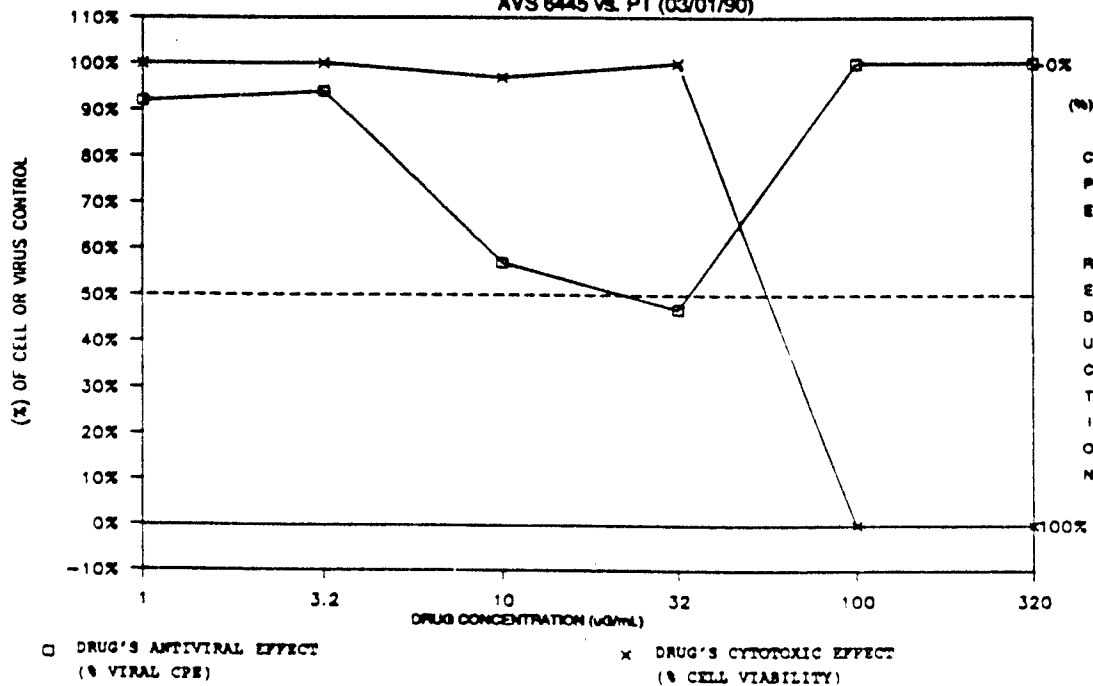


PLATE UAR
DRUG 6445

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6445
TAI: >19.99 SI: 2.53

	1	2	3	4	5	6	7	8	9	10	11	12
reagent background						plate background						
A	0.042	0.040	0.039	0.038	0.039	0.039	0.001	0.001	0.001	0.001	0.001	0.001
B		co/ve					100	drug 6445 experimental			co/ve	100
C		0.847					0.912	0.290	0.356	0.317	0.926	0.943
D		1.048					0.867	0.433	0.438	0.426	0.782	0.925
E		0.922					0.767	0.426	0.441	0.474	0.882	0.834
F		0.213					0.857	0.621	0.700	0.670	0.218	0.916
G		0.293					0.034	0.033	0.034	0.034	0.176	0.042
H		0.297					0.035	0.036	0.035	0.035	0.190	0.038
drug 6445 colorimetric background						0.038	0.041	0.044	0.039	0.040	0.042	

100=cell toxicity co=cell control vo=virus control BOLD = highest drug conc values shown are optical densities

VIRUS
CELLS
SHIPMENT NUMBER
STRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

YF
VERO Satisfactory; Active; Retest
63
ASIBI
0.040
0.185
0.862
0.677

PROJECT # 5975-1
SPONSOR USAMRIID
TEST DATE 03/01/90
DATE READ 03/09/90

DRUG 6445	25%	50%	95%
TC (ug/mL)	48.00	65.30	96.50
IC (ug/mL)	2.22	18.90	-----
ANTIVIRAL INDEX (AI)	21.56	3.45	-----

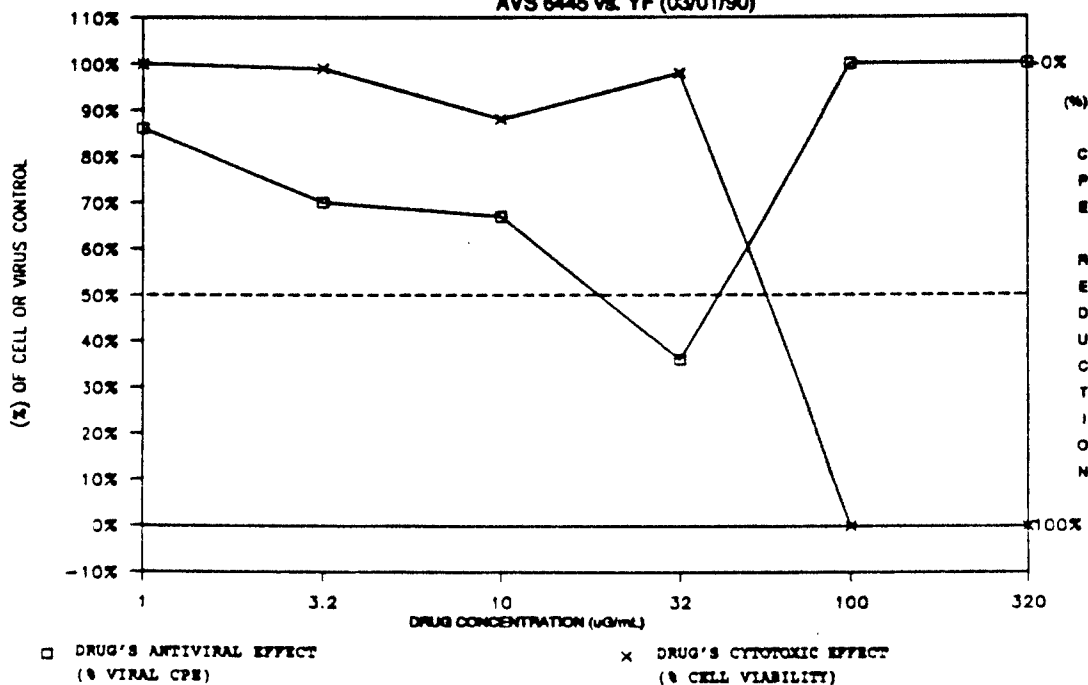
DRUG 6445		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	0.094	86%	0.885	100%	0.003
C	3.2	0.204	70%	0.856	99%	0.001
D	10	0.224	67%	0.762	88%	-0.001
E	32	0.435	36%	0.843	98%	0.004
F	100	-0.193	100%	-0.003	0%	0.002
high G	320	-0.187	100%	-0.001	0%	-0.002

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6445 vs. YF (03/01/90)



USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL

SUBMITTER

01141.01

CTR NO

KN-V-109

AVS NO

AVS-006443

DATE RECD

12-28-89

AMT RECEIVED [mg]

86.00

MOL WT (a.u.)

818.979

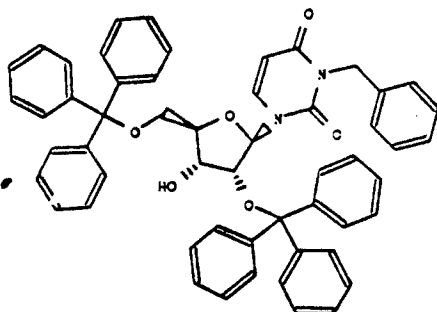
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE



COMPOUND NAME

N3-BENZYL-2',5'-DI-O-TRITYLURIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY-PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VM RTE LOSS MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VR	VR*	IPSO	CELL	MTC	TI	TI*	LAB	PRT	DATE
HIV			NOT ACT	MT2	> 100	0		SO	MTT	90-03-20
JE			NOT ACT	VERO	531	0		SO	MTT	90-03-22
JE			NOT ACT	VERO	24.7	0		SO	MTT	90-03-01
PT			77.1	VERO	210	> 4.15		SO	MTT	90-03-01
PT			NOT ACT	VERO	335	0		SO	MTT	
SF			NOT ACT	VERO	441	0		SO	MTT	90-03-22
SF			NOT ACT	VERO	> 320	0		SO	MTT	90-01-01
VEE			NOT ACT	VERO	773	0		SO	MTT	90-03-23
VEE			NOT ACT	VERO	> 320	0		SO	MTT	90-03-02
VV			NOT ACT	VERO	124	0		SO	MTT	90-03-22
YF			NOT ACT	VERO	427	0		SO	MTT	90-03-22
YF			NOT ACT	VERO	> 320	0		SO	MTT	90-03-01

VIR HST VR VR* DOSE MTC VM RTE D TOX SP L PR DATE

PLATE UQ9
DRUG 6443

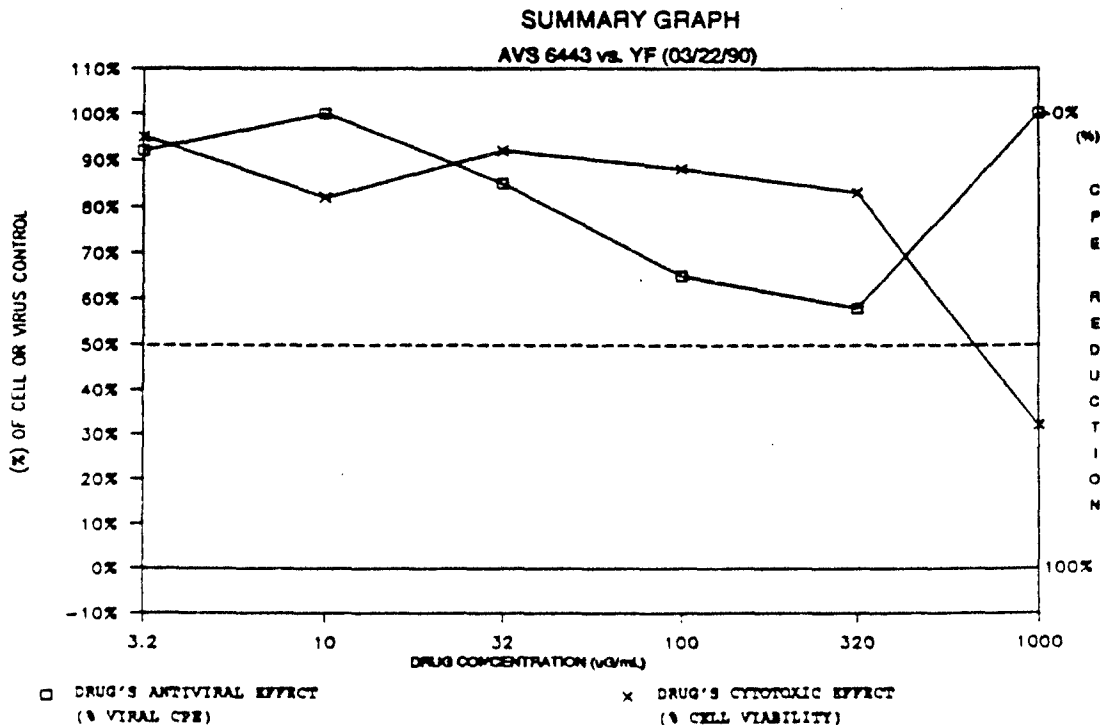
IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6443
TAI: >8.74 SI: 0.00

	1	2	3	4	5	6	7	8	9	10	11	12
reagent background						plate background						
A	0.061	0.061	0.061	0.059	0.059	0.062	0.001	0.001	0.002	0.002	0.001	0.002
drug 6443 experimental												
B	1.421	1.475	0.417	0.536	0.571	1.230					1.590	
C	1.514	1.258	0.406	0.411	0.448	0.783					0.962	
D	1.327	1.605	0.658	0.571	0.499	1.230					1.398	
E	1.281	0.452	0.761	0.771	0.763	1.170					0.434	
F	1.222	0.408	0.872	0.841	0.865	1.158					0.366	
G	0.678	0.466	0.284	0.271	0.382	0.582					0.425	
drug 6443 colorimetric background												
H	0.207	0.089	0.068	0.064	0.064	0.064						
10x=cell toxicity 0x=cell control 10x=virus control BOLD = highest drug conc values shown are optical densities												

VIRUS CELLS	YF	VERO	Satisfactory; Active; Retest	PROJECT #	5975-1
SHIPMENT NUMBER	63	TOXICITY RUN		SPONSOR	USAMRIID
STRN	ASIBI			TEST DATE	03/22/90
REAGENT	0.061			DATE READ	03/30/90
VIRUS CONTROL	0.365				
CELL CONTROL	1.321				
DIFFERENTIAL	0.956				
		DRUG 6443	25%	50%	95%
		TC (ug/mL)	427.00	780.00	> 1000.00
		IC (ug/mL)	56.60	-----	-----
		ANTIVIRAL INDEX (AI)	7.54	0.00	0.00

DRUG 6443		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	3.2	0.079	92%	1.261	95%	0.004
C	10	0.008	100%	1.084	82%	0.004
D	32	0.147	85%	1.214	92%	0.004
E	100	0.332	65%	1.157	88%	0.008
F	320	0.405	58%	1.101	83%	0.029
high G	1000	0.260	100%	0.423	32%	0.147
		* highest drug concentration tested		values shown are final adjusted numbers		



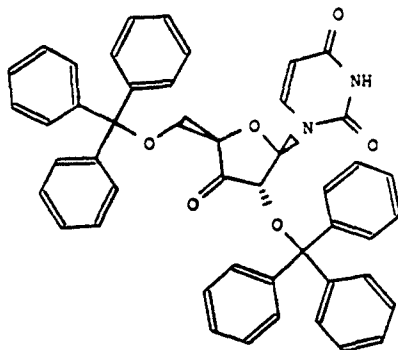
USAMRIID

Antiviral Drug Screening Program

05/19/90

STRUCTURE

CHIRAL

SUBMITTER
01141.01CTR NO
KN-VII-83AVS NO
AVS-006444DATE RECD
12-28-89AMT RECEIVED [mg]
79.00MOL WT (au)
726.837

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

COMPOUND NAME

3'-DEOXY-2',5'-DI-O-TRITYL-3'-OXOURIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VN RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VR	VR+	LD50	CELL	MTC	TI	TI+	LAB	PRT	DATE
HIV		NOT ACT		MT2	> 100	0		SO	MTT	90-03-20
JZ		NOT ACT		VERO	51	0		SO	MTT	90-03-01
JZ		NOT ACT		VERO	547	0		SO	MTT	90-03-22
PT		79.2		VERO	> 320	> 4.04		SO	MTT	90-03-01
PT		NOT ACT		VERO	257	0		SO	MTT	
SF		NOT ACT		VERO	30	0		SO	MTT	90-03-01
SF		NOT ACT		VERO	365	0		SO	MTT	90-03-22
VEE		NOT ACT		VERO	680	0		SO	MTT	90-03-23
VEE		NOT ACT		VERO	> 320	0		SO	MTT	90-03-02
VV		NOT ACT		VERO	116	0		SO	MTT	90-03-22
YF		29.8		VERO	410	24.55		SO	MTT	90-03-22
YF		NOT ACT		VERO	> 320	0		SO	MTT	90-03-01

VIR RST VR VR+ DOSE MTC VEN RTE D TOX SP L PR DATE

PLATE UQO
DRUG 6444

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6444
TAI: 3.21 SI: _____

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.077	0.073	0.071	0.070	0.072	0.072	0.001	0.001	0.002	0.001	0.002	0.002
B		oocyte					low	drug 6444 experimental		oocyte		low
C		1.519					1.517	0.509	0.325	0.554	1.544	1.671
D		1.478					1.483	0.458	0.481	0.478	1.484	1.577
E		1.487					1.474	0.462	0.467	0.492	1.537	1.384
F		0.607					1.542	0.621	0.651	0.640	0.589	1.615
G		0.615					1.327	0.845	0.897	0.927	0.619	1.517
H		0.626					0.697	0.474	0.515	0.524	0.613	0.680
I							drug 6444 colorimetric background					
							0.121	0.082	0.081	0.078	0.078	0.077

low=cell toxicity oocyte=cell control vo=virus control BOLD = highest drug conc values shown are optical densities

VIRUS CELLS

SHIPMENT NUMBER
STR
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

JE
VERO
63
NAKAYAMA

Satisfactory; Active; Retest
TOXICITY RESULT

PROJECT # 5975-1
SPONSOR USAMRIID
TEST DATE 03/22/90
DATE READ 03/29/90

DRUG 6444	25%	50%	95%
TC (ug/mL)	547.00	861.00	> 1000.00
IC (ug/mL)	280.00	-----	-----
ANTIVIRAL INDEX (AI)	2.10	-----	-----

DRUG 6444		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	3.2	-0.087	100%	1.517	100%	0.005
C	10	-0.145	100%	1.452	100%	0.006
D	32	-0.144	100%	1.351	94%	0.006
E	100	0.017	98%	1.497	100%	0.009
F	320	0.268	70%	1.340	93%	0.010
high G	1000	-0.156	100%	0.567	39%	0.049

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6444 vs. JE (03/22/90)

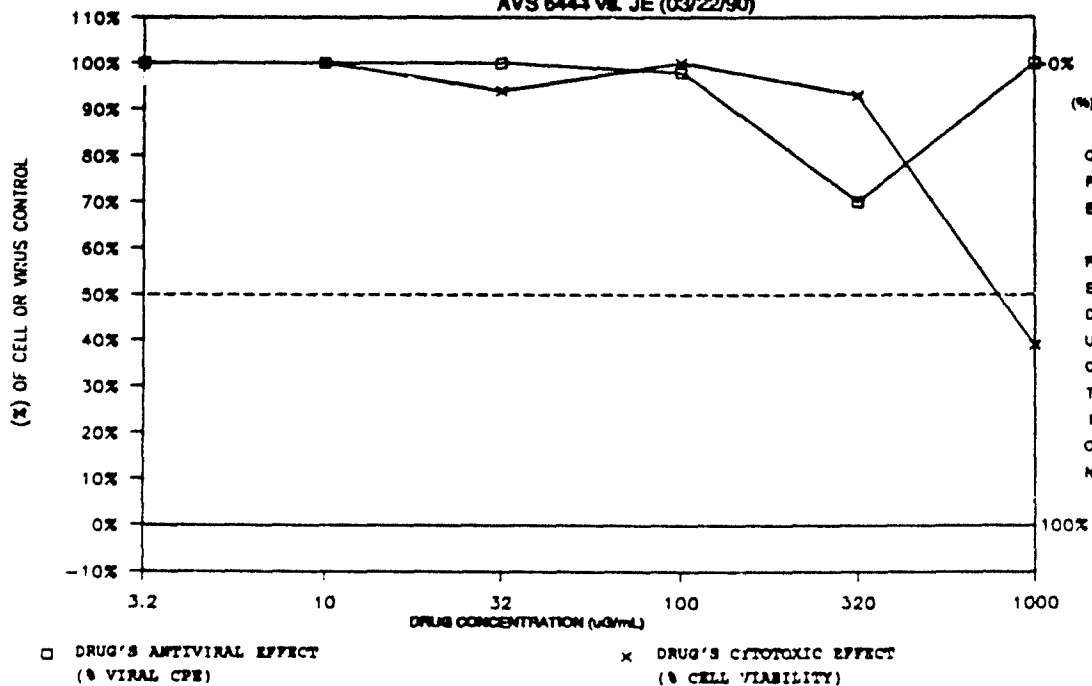


PLATE URI
DRUG 6444

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6444
TAI: 3.44 SI: ———

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plastic background					
A	0.054	0.055	0.054	0.051	0.051	0.053	0.002	0.002	0.001	0.001	0.001	0.001
B		co/ve					tox	drug 6444 experimental		co/ve		tox
C		1.408					1.654	0.253	0.349	0.342	1.305	1.302
D		1.631					1.553	0.377	0.414	0.423	1.539	1.238
E		1.634					1.452	0.477	0.492	0.519	1.485	1.209
F		0.388					1.415	0.593	0.743	0.580	0.418	1.296
G		0.391					1.118	0.988	0.750	0.778	0.386	1.001
H		0.316					0.384	0.422	0.430	0.447	0.402	0.380
I	drug 6444 colorimetric background						0.055	0.057	0.056	0.055	0.051	0.049
	test-cell toxicity	co-cell control	vo-virus control	BOLD = highest drug conc				values shown are optical densities				

VIRUS
CELLS
SHIPMENT NUMBER
SITE
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

PT
VERO Satisfactory; Active; Retest
ADAMES
TOXICITY RERUN
0.053
0.331
1.447
1.117

PROJECT # 5975-1
SPONSOR USAMRIID
TEST DATE 03/22/90
DATE READ 03/30/90

DRUG 6444	25%	50%	95%
TC (uG/mL)	257.00	601.00	> 1000.00
IC (uG/mL)	115.00	-----	-----
ANTIVIRAL INDEX (AI)	2.24	-----	-----

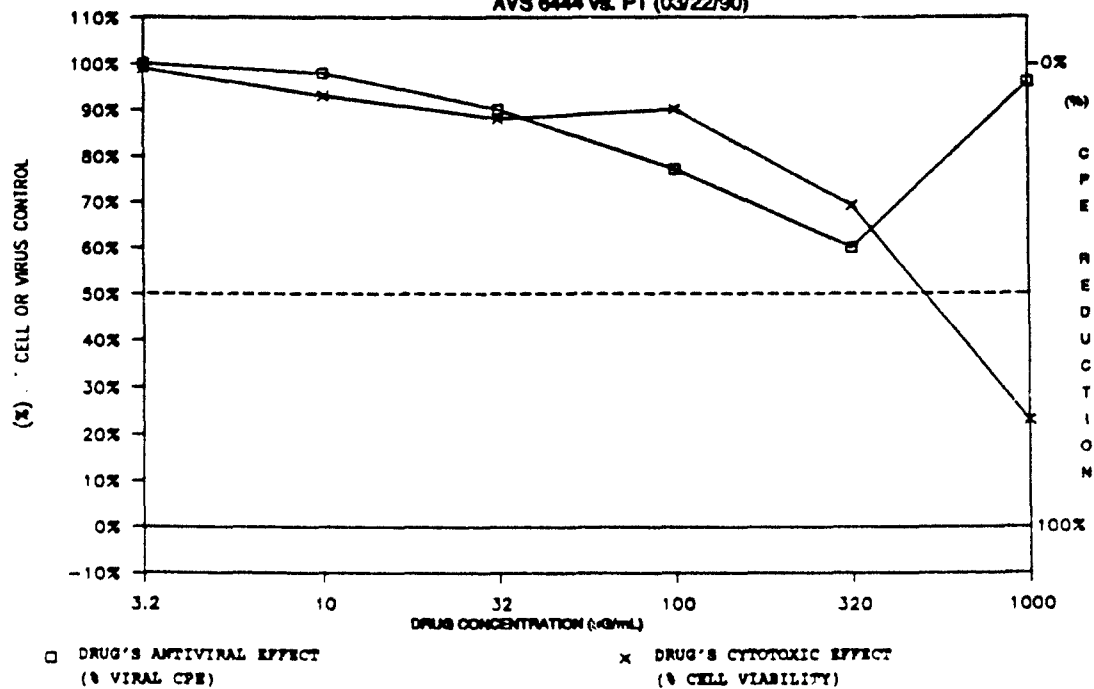
DRUG 6444		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	3.2	-0.065	100%	1.429	99%	-0.004
C	10	0.023	98%	1.349	93%	-0.002
D	32	0.110	90%	1.276	88%	0.002
E	100	0.252	77%	1.300	90%	0.003
F	320	0.451	60%	1.003	69%	0.004
high G	1000	0.047	96%	0.327	23%	0.002

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6444 vs. PT (03/22/90)



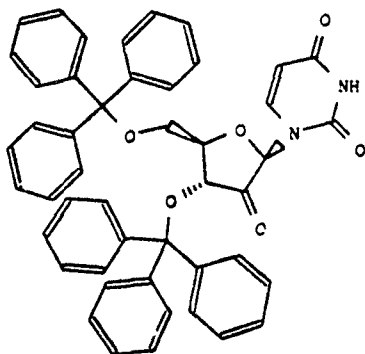
USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL



SUBMITTER

01141.01

CTR NO

KN-VII-21

AVS NO

AVS-006445

DATE RECD

12-28-89

AMT RECEIVED [mg]

74.00

MOL WT (au)

726.837

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

COMPOUND NAME

2'-DEOXY-3',5'-DI-O-TRITYL-2'-OXOURIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VM RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VR	VR*	LD50	CELL	MTC	CI	TI*	LAB	PR	DATE
NIV		NOT ACT	MT2		15.5	0		50 MTT	90-03-20	
JE		NOT ACT	VERO		49	0		50 MTT	90-03-22	
JE		NOT ACT	VERO		23.2	0		50 MTT	90-03-01	
PT		22.6	VERO		49	2.92		50 MTT	90-03-01	
PT		NOT ACT	VERO		8.87	0		50 MTT	90-03-22	
SP		NOT ACT	VERO		30.4	0		50 MTT	90-03-22	
SP		NOT ACT	VERO		43.3	0		50 MTT	90-03-01	
VEE		NOT ACT	VERO		32	0		50 MTT	90-03-02	
VEE		NOT ACT	VERO		44	0		50 MTT	90-03-23	
VV		NOT ACT	VERO		4.6	0		50 MTT	90-03-22	
YF		18.9	VERO		48	3.45		50 MTT	90-03-01	
YF		9.06	VERO		29.6	5.83		50 MTT	90-03-22	

VIR HOST VM VR* DOSE MTC VEH RTE D TOX SP L PR DATE

PLATE UQA
DRUG 6445

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6445
TAI: >18.33 SI: 3.27

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plasma background					
A	0.063	0.063	0.062	0.060	0.056	0.061	0.001	0.001	0.001	0.001	0.001	0.001
B	1.349	1.409	drug 6445 experimental				1.504				1.418	
C	1.442	1.368	0.740	0.805	0.674	1.607					1.392	
D	1.368	1.448	0.998	0.971	0.924	1.488					1.550	
E	1.067	0.526	0.934	0.600	0.848	1.022					0.433	
F	0.062	0.481	0.051	0.050	0.054	0.051					0.380	
G	0.066	0.494	0.066	0.061	0.059	0.065					0.400	
H	drug 6445 colorimetric background											
	0.075	0.071	0.065	0.062	0.064	0.062						
	100% virus control		50% virus control		25% virus control		values shown are optical densities					

VIRUS
CELLS
SHIPMENT NUMBER
SITE
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

YF
VERO Satisfactory: Active: Retest
63 TOXICITY RERUN
AS INI
0.061
0.392
1.370
0.979

PROJECT # 5975-1
SPONSOR USAMRIID
TEST DATE 03/22/90
DATE READ 03/30/90

DRUG 6445	25%	50%	95%
TC (ug/mL)	29.60	52.80	95.30
IC (ug/mL)	2.35	9.06	-----
ANTIVIRAL INDEX (AI)	12.63	5.83	0.00

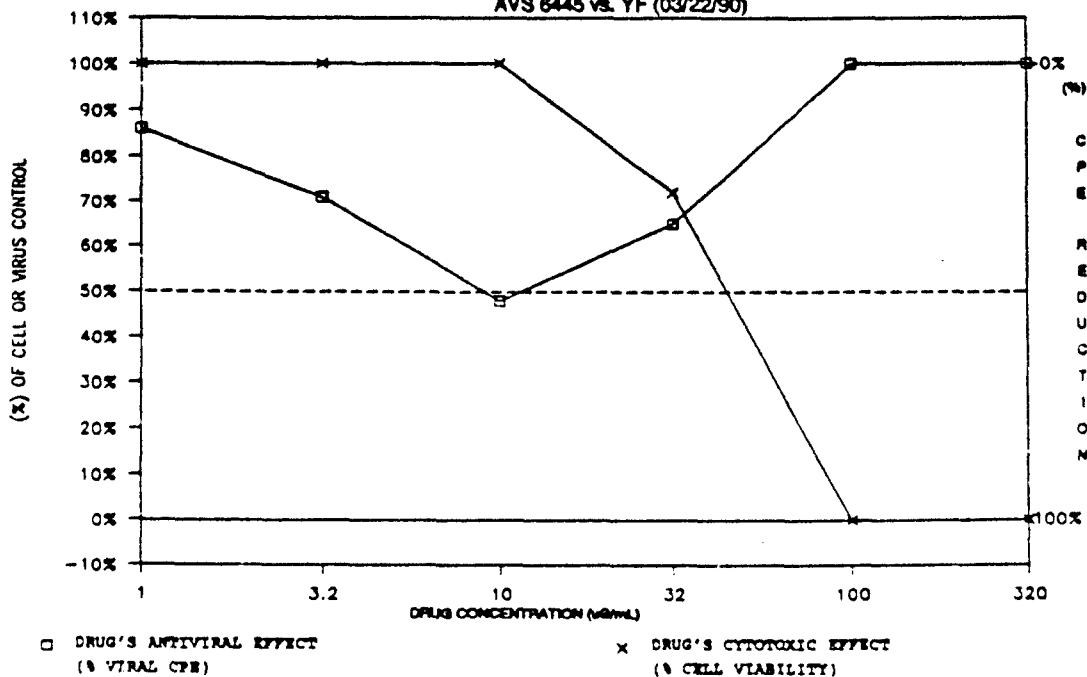
DRUG 6445		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	0.137	86%	1.465	100%	0.001
C	3.2	0.284	71%	1.461	100%	0.003
D	10	0.511	48%	1.368	100%	0.001
E	32	0.338	65%	0.980	72%	0.004
F	100	-0.411	100%	-0.014	0%	0.010
high G	320	-0.404	100%	-0.009	0%	0.014

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6445 vs. YF (03/22/90)



USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL

SUBMITTER
01141.01CTR NO
KN-II-53AVS NO
AVS-006449DATE RECD
12-28-89AMT RECEIVED [mg]
75.00MOL WT (au)
284.271

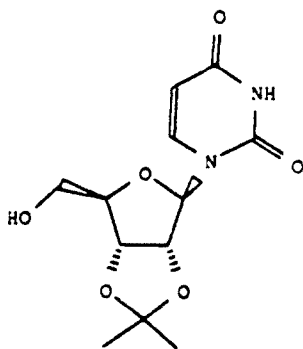
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-O-ISOPROPYLIDINEURIDINE



COMPOUND NAME

2',3'-O-ISOPROPYLIDINEURIDINE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VM RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

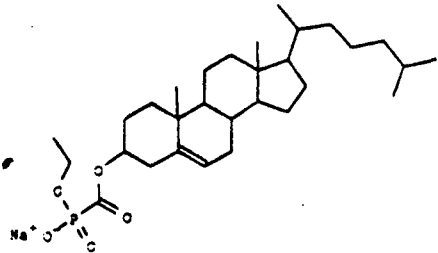
R	VR	VR+	LD50	CELL	MTC	TI	TI+	LAB PR	DATE
V			NOT ACT	MT2	> 100	0		50 MTT	90-03-20
			NOT ACT	VERO	466	0		50 MTT	90-03-22
			NOT ACT	VERO	> 320	0		50 MTT	90-03-01
			264	VERO	> 320	> 1.21		50 MTT	90-03-01
			NOT ACT	VERO	363	0		50 MTT	90-03-22
			NOT ACT	VERO	472	0		50 MTT	90-03-22
			NOT ACT	VERO	> 320	0		50 MTT	90-03-01
E			NOT ACT	VERO	251	0		50 MTT	90-03-02
E			NOT ACT	VERO	320	0		50 MTT	90-03-23
			NOT ACT	VERO	195	0		50 MTT	
			NOT ACT	VERO	517	0		50 MTT	90-03-22
			NOT ACT	VERO	> 320	0		50 MTT	90-03-01

VIR HOST VR VR+ DOSE MTC VER RTE 2 TOX SP L PR DATE

USAMRIID

Antiviral Drug Screening Program

25/10/91

STRUCTURE 	SUBMITTER 01141.01	CTR NO MS-I-47	AVS NO AVS-C06456
	DATE RECD 12-28-89	AMT RECEIVED [mg] 79.20	MOL WT (au) 544.694
	HANDLING/STORAGE		
	SOLUBILITY		
	STABILITY		
ALT NAME SODIUM ETHYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE			

COMPOUND NAME

SODIUM ETHYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

[illegible]

PLATE UDN
DRUG 6456

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6456
TAI: 3.19 SI: ———

	1	2	3	4	5	6	7	8	9	10	11	12
A	reagent background					plates background						
	0.059	0.057	0.063	0.055	0.063	0.054	0.001	0.001	0.002	0.002	0.001	0.002
B	0.936	0.768	0.225	0.228	0.213	0.841					0.941	
C	0.893	0.819	0.172	0.162	0.145	0.951					1.024	
D	0.989	0.750	0.144	0.136	0.135	1.052					0.789	
E	0.964	0.281	0.432	0.408	0.423	0.955					0.268	
F	0.174	0.271	0.053	0.051	0.052	0.077					0.265	
G	0.050	0.280	0.046	0.044	0.044	0.043					0.283	
drug 6456 colorimetric background												
H	0.050	0.053	0.055	0.057	0.052	0.055						

low=cell toxicity cell control vc=virus control BOLD = highest drug conc values shown are optical densities

VIRUS CELLS

SHIPMENT NUMBER

STRN

REAGENT

VIRUS CONTROL

CELL CONTROL

DIFFERENTIAL

SF

VERO

Satisfactory/ Active/ Retest

63

SICILIAN

0.059

0.216

0.790

0.574

PROJECT #

5975-1

SPONSOR

USAMRIID

TEST DATE

03/06/90

DATE READ

03/14/90

DRUG 6456	25%	50%	95%
TC (u0/mL)	30.70	69.40	198.00
IC (u0/mL)	30.60	-----	-----
ANTIVIRAL INDEX (AI)	1.66	-----	-----

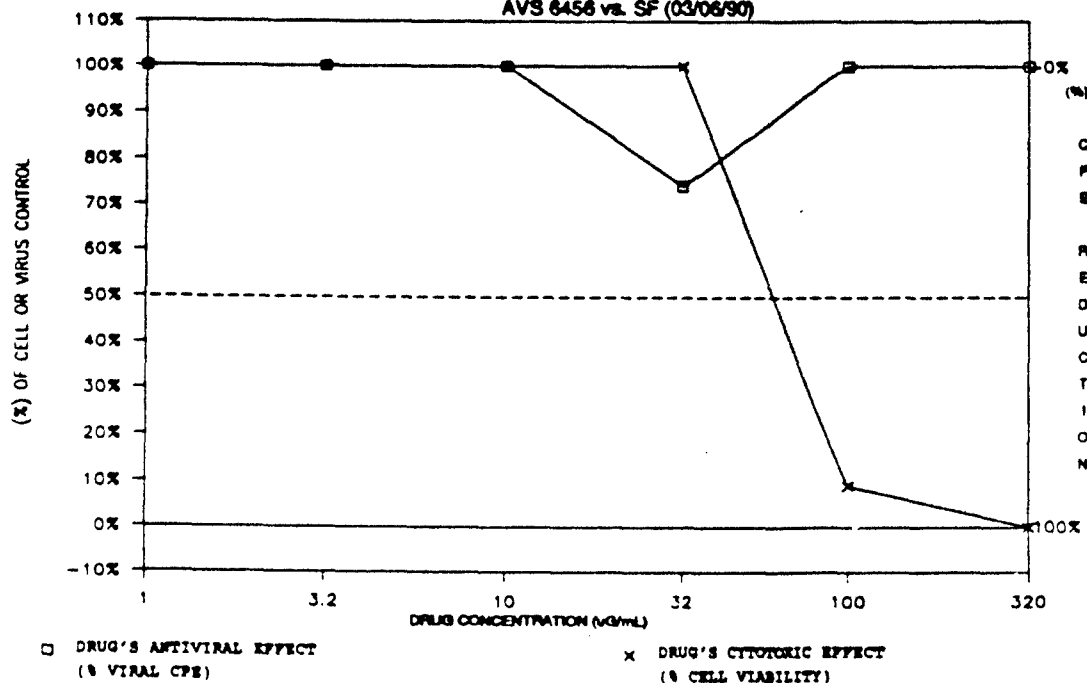
DRUG 6456		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (u0/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	-0.049	100%	0.834	100%	-0.004
C	3.2	-0.108	100%	0.871	100%	-0.007
D	10	-0.135	100%	0.903	100%	-0.001
E	32	0.150	74%	0.905	100%	-0.004
F	100	-0.217	100%	0.073	9%	-0.006
high G	320	-0.222	100%	-0.004	0%	-0.008

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6456 vs. SF (03/06/90)

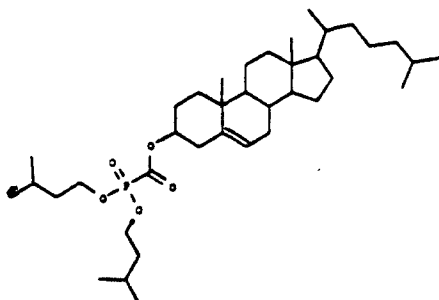


USAMRIID

Antiviral Drug Screening Program

03/18/90

STRUCTURE

SUBMITTER
01141.01CTR NO
KN-I-105AVS NO
AVS-006458DATE RECD
12-28-89AMT RECEIVED [mg]
70.40MOL WT (au)
634.929

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

DI-ISOBUTYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

COMPOUND NAME

DI-ISOBUTYL(CHOLESTERYLOXYCARBONYL)-PHOSPHONATE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY-PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VN RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VN	VR	ID50	CELL	MTG	TI	TI*	LAB	PRT	DATE
HIV		NOT ACT	MT2	> 100	0			SO	MTT	
JE		NOT ACT	VERO	> 320	0			SO	MTT	90-03-06
JE		NOT ACT	VERO	> 1000	0			SO	MTT	90-03-22
PT		NOT ACT	VERO	> 320	0			SO	MTT	90-03-06
PT		NOT ACT	VERO	> 1000	0			SO	MTT	90-03-22
SF		NOT ACT	VERO	> 320	0			SO	MTT	90-03-06
SF		NOT ACT	VERO	> 1000	0			SO	MTT	90-03-22
VEE		NOT ACT	VERO	155	0			SO	MTT	90-03-09
VEE		NOT ACT	VERO	> 1000	0			SO	MTT	90-03-23
VV		NOT ACT	VERO	> 320	0			SO	MTT	
YF		234	VERO	> 1000	> 4.27			SO	MTT	
YF		NOT ACT	VERO	> 320	0			SO	MTT	90-03-06

VIR HOST VN VR* DOSE MTC VEN RTE D TOX SP L PR DATE

PLATE UC0
DRUG 6458

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6458
TAI: >0.50 SI: -----

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.062	0.059	0.057	0.058	0.057	0.058	0.002	0.001	8.001	0.002	0.001	0.001
B	low	curve	drug 6458 experimental				low					curve
C	1.334	1.245	0.411	0.439	0.415	1.113					1.215	
D	1.259	1.243	0.405	0.394	0.392	1.110					1.185	
E	1.298	1.283	0.365	0.422	0.412	1.110					1.211	
F	1.203	0.413	0.454	0.375	0.431	1.054					0.442	
G	1.226	0.403	0.443	0.430	0.497	1.030					0.455	
H	1.024	0.393	0.689	0.669	0.689	0.862					0.446	
	drug 6458 colorimetric background											
I	0.058	0.061	0.061	0.060	0.060	0.061						
125=cell toxicity			40=cell control			10=virus control			BOLD = highest drug conc			
values shown are optical densities												

VIRUS CELLS	PT	PROJECT #	5975-1
SHIPMENT NUMBER	VERO	SPONSOR	USAMRIID
STR	63	TEST DATE	03/06/90
REAGENT	ADAMES	DATE READ	02/16/90
VIRUS CONTROL	0.059	DRUG 6458	
CELL CONTROL	0.367	25%	50%
DIFFERENTIAL	1.172	TC (ug/mL)	> 320.00
	0.805	IC (ug/mL)	239.00
		ANTIVIRAL INDEX (AI)	> 1.34

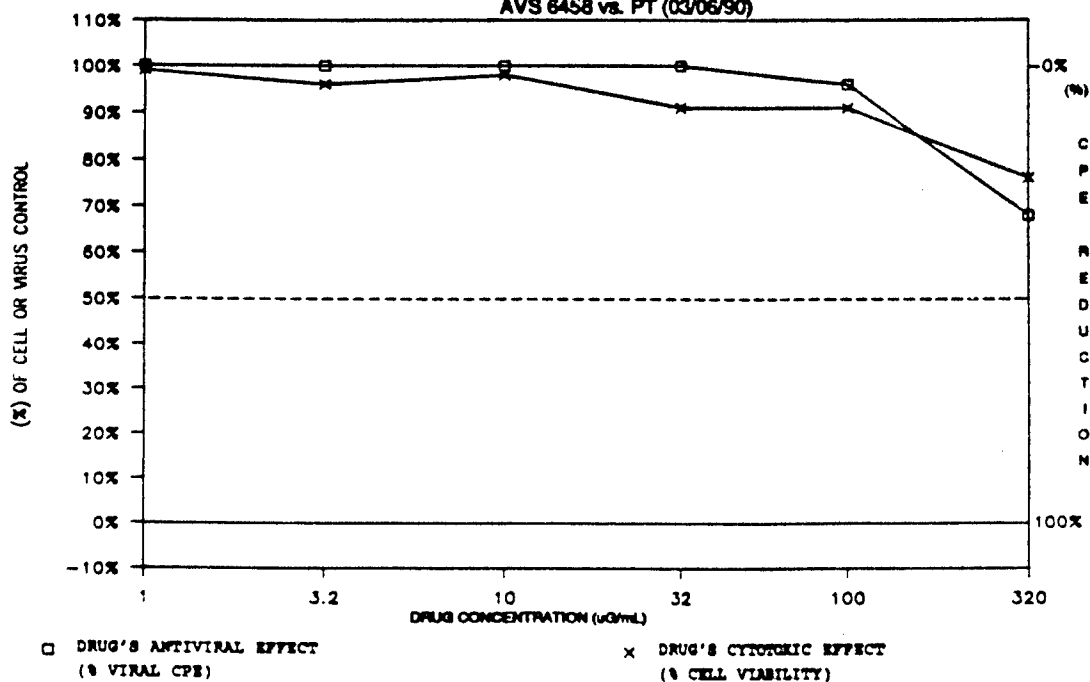
DRUG 6458		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW OR PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	1	-0.006	100%	1.163	99%	0.002
C	3.2	-0.029	100%	1.125	96%	0.001
D	10	-0.027	100%	1.145	98%	0.001
E	32	-0.001	100%	1.068	91%	0.002
F	100	0.029	96%	1.068	91%	0.002
high G	320	0.257	66%	0.885	76%	0.000

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6458 vs. PT (03/06/90)



USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL

SUBMITTER
01141.01CTR NO
KN-II-71AVS NO
AVS-006462DATE RECD
12-28-89AMT RECEIVED [mg]
72.40MOL WT (au)
325.729

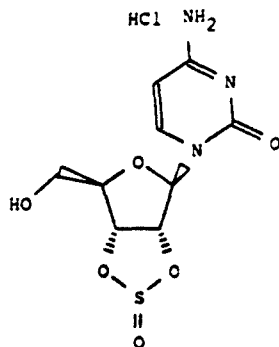
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-O-SULFINYLCTIDINE HYDROCHLORIDE



COMPOUND NAME

2',3'-O-SULFINYLCTIDINE HYDROCHLORIDE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VH RTE LOSO MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VR	VR+	LOS	CELL	MTC	CI	TI	LAB	PRT	DATE
HIV		NOT ACT	MT2		.06	0		SO	MTT	
HIV		NOT ACT	MT2		< .32	0		SO	MTT	
JE		NOT ACT	VERO		22.4	0		SO	MTT	90-03-06
PT		NOT ACT	VERO		38.6	0		SO	MTT	90-03-06
SF		NOT ACT	VERO		21	0		SO	MTT	90-03-06
VEE		NOT ACT	VERO		9.73	0		SO	MTT	90-03-09
VV		1.72	VERO		16.7	14.12		SO	MTT	
VV		3.28	VERO		25.7	18.66		SO	MTT	
YF		NOT ACT	VERO		44.4	0		SO	MTT	90-03-06

VIR	HST	VR	VR+	DOSE	MTC	VEH	RTE	D	TOX	SP	L	PR	DATE
-----	-----	----	-----	------	-----	-----	-----	---	-----	----	---	----	------

PLATE 055
DRUG 6462

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6462
TAI: >32.30 SI: 7.85

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.104	0.114	0.112	0.111	0.111	0.112	0.000	0.000	0.000	0.000	0.000	0.000
B		o/vs					ts	drug 6462 experimental		o/vs		ts
C		1.542					1.492	0.362	0.278	0.427	1.506	1.619
D		1.596					1.491	0.820	0.842	0.963	1.508	1.676
E		1.651					1.650	1.412	1.560	1.551	1.524	1.770
F		0.160					1.040	0.929	0.938	0.852	0.247	1.058
G		0.248					0.573	0.511	0.523	0.524	0.174	0.542
H		0.213					0.320	0.312	0.315	0.305	0.238	0.349
							drug 6462 colorimetric background					
							0.153	0.123	0.110	0.108	0.110	0.117

low=cell toxicity o/vs=cell control vs=virus control BOLD = highest drug conc values shown are optical densities

VIRUS CELLS

SHIPMENT NUMBER
STRS
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

VV VERO

Satisfactory: Active: Retest
RETEST AT 100 UG/ML
LEDCA
0.111
0.103
1.444
1.341

PROJECT # 5973-4
SPONSOR USAMRIID
TEST DATE 03/29/90
DATE READ 04/04/90

DRUG 6462	25%	50%	95%
TC (ug/mL)	25.70	61.10	> 320.00
IC (ug/mL)	1.56	1.28	9.54
ANTIVIRAL INDEX (AI)	16.46	18.66	> 33.56

DRUG 6462		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	1	0.136	90%	1.439	100%	0.006
C	3.2	0.663	51%	1.474	100%	-0.001
D	10	1.297	3%	1.602	100%	-0.003
E	32	0.694	48%	0.939	65%	-0.001
F	100	0.294	78%	0.435	30%	0.012
high G	320	0.055	96%	0.182	13%	0.042

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6462 vs. VV (03/29/90)

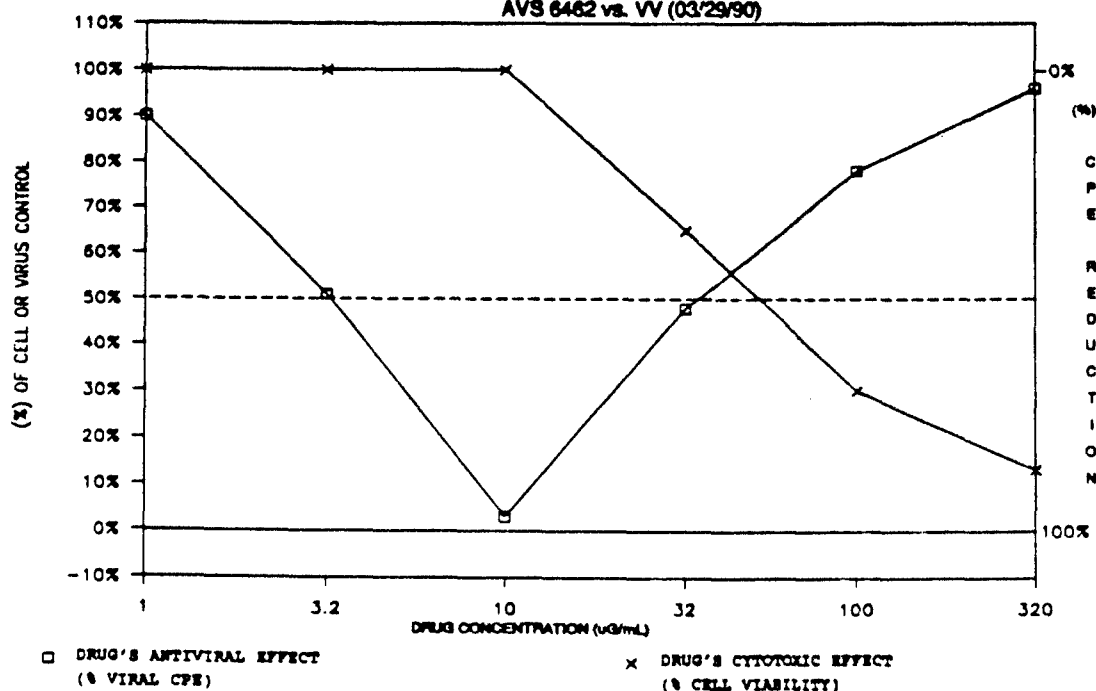


PLATE 002
DRUG 6462

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6462
TAI: 30.00 SI: 9.69

	1	2	3	4	5	6	7	8	9	10	11	12
A	reagent background						plate background					
	0.125	0.117	0.119	0.120	0.124	0.130	0.000	0.000	0.000	0.000	0.000	0.000
B	1.284	1.387	drug 6462 experimental								1.322	
C	1.197	1.494	0.453	0.332	0.473	1.315					1.435	
D	1.183	1.466	1.131	1.258	1.282	1.466					1.513	
E	1.311	0.176	1.234	1.216	1.347	1.456					0.278	
F	0.415	0.176	0.359	0.399	0.430	0.446					0.187	
G	0.280	0.197	0.263	0.256	0.255	0.294					0.173	
H	drug 6462 colorimetric background											
	0.124	0.106	0.110	0.108	0.103	0.152						

tested assay observed control virus control BOLD = highest drug conc values shown are optical densities

VIRUS
CELLS
SHIPMENT NUMBER
STRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

VV
VERO Satisfactory
63 CONFIRMS ORIGINAL ACTIVITY
LEDCA
0.123
0.075
1.314
1.238

PROJECT # 5975-4
SPONSOR USAMRIID
TEST DATE 04/19/90
DATE READ 04/25/90

DRUG 6462	25%	50%	95%
TC (uG/mL)	16.70	24.40	> 100.00
IC (uG/mL)	1.10	1.72	-----
ANTIVIRAL INDEX (AI)	15.27	14.12	-----

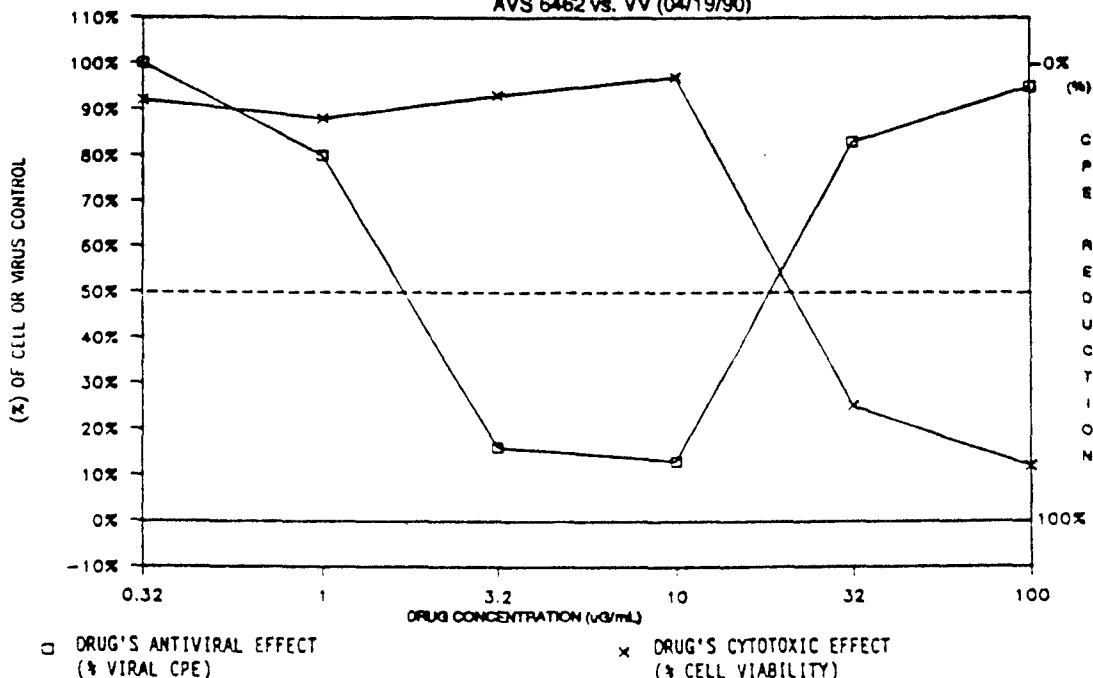
DRUG 6462		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	0.32	0.084	100%	1.211	92%	0.029
C	1	0.242	80%	1.154	88%	0.020
D	3.2	1.041	16%	1.217	93%	0.015
E	10	1.081	13%	1.274	97%	0.013
F	32	0.215	83%	0.325	25%	0.017
high G	100	0.059	95%	0.164	12%	0.001

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6462 vs. VV (04/19/90)



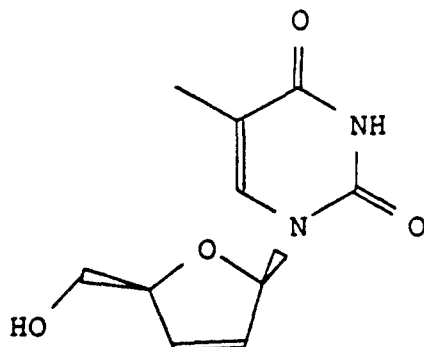
USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL



SUBMITTER

01141.01

CTR NO

KN-II-55

AVS NO

AVS-006466

DATE RECD

12-28-89

AMT RECEIVED [mg]

MOL WT (au)

224.218

HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',3'-DIDEOXYTHYMIDINENE

COMPOUND NAME

2',3'-DIDEOXYTHYMIDINENE

SCREEN INSTRUCTION

PRIORITY=PT>VEE>YF>KHF>PIC>JE>SF>VV>AD2>VSV

IN VIVO TOXICITY [mg/kg]

HOST VN RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

VIR	VR	VR*	LD50	CELL	MTC	TI	TI*	LAB	PRT	DATE
HIV			4.99	MT2	48.8	13.29		50	MTT	
HIVC			.32	CEM	51.5	> 222.13		50	MTT	
JE		NOT ACT		VERO	84.3	0		50	MTT	90-03-06
PT		NOT ACT		VERO	111	0		50	MTT	90-03-06
SF		NOT ACT		VERO	93.8	0		50	MTT	90-03-06
VEE		NOT ACT		VERO	232	0		50	MTT	90-03-09
YF		NOT ACT		VERO	100	0		50	MTT	90-03-06

IN VIVO SCREEN [Dose = mg/kg]

VIR HOST VR VR* DOSE MTC VEH RTE D TOX SP L PR DATE

PLATE 1HK
DRUG 6466

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6466
TAI: 35.67 SI: 9.78

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background						plate background					
A	0.128	0.131	0.131	0.130	0.130	0.131	0.037	0.034	0.035	0.035	0.034	0.034
	low	curve	drug 6466 experimental				low				curve	
B	1.400	1.627	0.356	0.363	0.376	1.639					1.651	
C	1.362	1.625	0.418	0.386	0.384	1.622					1.588	
D	1.367	1.637	0.627	0.570	0.580	1.712					1.666	
E	1.430	0.369	1.821	1.729	1.850	1.785					0.358	
F	1.481	0.364	1.581	1.414	1.737	1.753					0.343	
G	0.160	0.368	0.127	0.130	0.142	0.156					0.338	
	drug 6466 colorimetric background											
H	0.133	0.129	0.131	0.135	0.131	0.132						
	low-cell toxicity	cell control	virus control		BOLD = highest drug done				values shown are optical densities			

VIRUS
CELLS
SHIPMENT NUMBER
STIRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

HIV3B
MT2 Satisfactory; Active; Retest
63
2.5
0.130
0.227
1.506
1.279

PROJECT # 6520-2
SPONSOR USAMRIID
TEST DATE 04/04/90
DATE READ 04/12/90

DRUG 6466	25%	50%	95%
TC (ug/mL)	48.80	66.40	97.90
IC (ug/mL)	3.53	4.99	9.33
ANTIVIRAL INDEX (AI)	13.84	13.29	10.49

DRUG 6466		ANTIVIRAL TEST VALUES			CYTOTOXICITY TEST VALUES		
NOW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% RED. IN VIRAL CPE		MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.006	0%		1.387	92%	0.002
C	1	0.038	3%		1.361	90%	0.001
D	3.2	0.231	18%		1.404	93%	0.005
E	10	1.442	100%		1.476	98%	0.001
F	32	1.222	96%		1.488	99%	-0.001
high G	100	-0.227	0%		0.025	2%	0.003

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6466 vs. HIV3B (04/14/90)

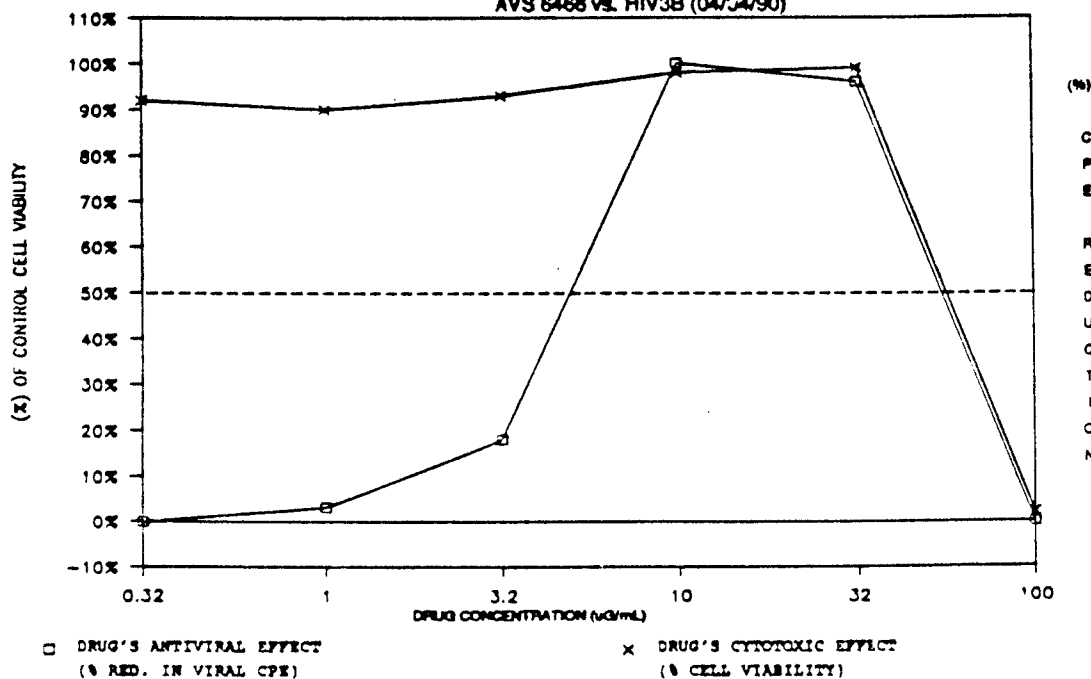


PLATE 1KA
DRUG 6466

IN VITRO ANTIVIRAL RESULTS MTT ASSAY

DRUG: AVS 6466
TAI: >85.47 SI: >161.06

	1	2	3	4	5	6	7	8	9	10	11	12	
	reagent background						plates background						
A	0.118	0.109	0.116	0.115	0.112	0.114	0.034	0.034	0.034	0.034	0.034	0.033	
B		serve					1.190	1.183	1.176	1.067	1.233	1.133	
C		1.089					1.137	1.101	1.193	1.236	1.212	1.245	
D		0.917					1.061	1.207	1.204	1.234	1.205	1.323	
E		0.478					1.197	1.195	1.334	1.246	0.512	1.477	
F		0.469					1.629	1.371	1.380	1.360	0.576	1.578	
G		0.506					0.302	0.174	0.174	0.164	0.566	0.248	
H							drug 6466 colorimetric background						
							0.144	0.137	0.135	0.126	0.121	0.132	
100=cell history 05=cell control 10=virus control BOLD = highest drug done values shown are optical densities													

VIRUS
CELLS

HIVCRF
CEM

PROJECT # 6520-2

SPONSOR USAMRIID

SHIPMENT NUMBER

64

Satisfactory; Active; Retest

TEST DATE 04/26/90

STR

RP2

DATE READ 05/03/90

REAGENT

0.114

VIRUS CONTROL

0.404

CELL CONTROL

1.004

DIFFERENTIAL

0.600

DRUG 6466	25%	50%	95%
IC (ug/mL)	51.50	71.10	> 100.00
IC (ug/mL)	< 0.32	< 0.32	< 0.32
ANTIVIRAL INDEX (AI)	> 161.06	> 272.13	> 312.50

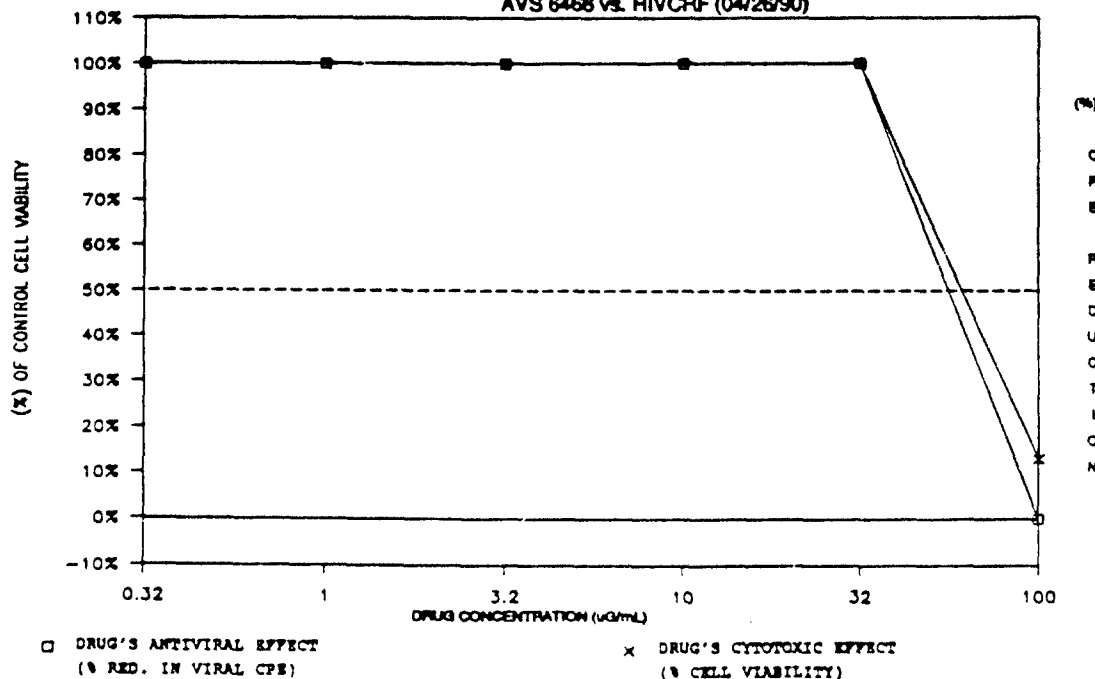
DRUG 6466		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		
ROW ON PLATE	CONC. (ug/mL)	MEAN O.D.	% RED. IN CPE	MEAN O.D.	% CELL VIABILITY	COLORIMETRIC CONTROL
low B	0.32	0.606	100%	1.030	100%	0.018
C	1	0.652	100%	1.070	100%	0.007
D	3.2	0.685	100%	1.066	100%	0.012
E	10	0.720	100%	1.202	100%	0.021
F	32	0.830	100%	1.467	100%	0.023
high G	100	0.377	0%	0.131	13%	0.030

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6466 vs. HIVCRF (04/26/90)



USAMRIID

Antiviral Drug Screening Program

05/18/90

STRUCTURE

CHIRAL

SUBMITTER
01141.01CTR NO
KN-II-95AVS NO
AVS-006467DATE RECD
12-28-89AMT RECEIVED [mg]
72.60MOL WT (au)
261.667

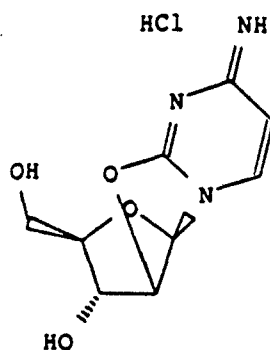
HANDLING/STORAGE

SOLUBILITY

STABILITY

ALT NAME

2',O2-ANHYDROCYTIDINE HYDROCHLORIDE



COMPOUND NAME

2',O2-ANHYDROCYTIDINE HYDROCHLORIDE

SCREEN INSTRUCTION

IN VIVO TOXICITY [mg/kg]

PRIORITY=PT>VEE>VF>KHF>PIC>JE>SF>VV>AD2>VSV

HOST VH RTE LD50 MTC LAB PR DATE

IN VITRO SCREEN [ug/ml]

IN VIVO SCREEN [Dose = mg/kg]

VIR	VR	VR*	LD50	CELL	MTC	TI	TI*	LAB PR	DATE
HIV		NOT ACT	MT2		.04	0		SO MTT	
HIV		NOT ACT	MT2		< .32	0		SO MTT	
JE		NOT ACT	VERO		.71	0		SO MTT	90-03-22
JE		NOT ACT	VERO		1.8	0		SO MTT	90-03-06
PT		NOT ACT	VERO		.48	0		SO MTT	90-03-22
PT		NOT ACT	VERO		4.99	0		SO MTT	90-03-06
SF		NOT ACT	VERO		.58	0		SO MTT	90-03-22
SF		NOT ACT	VERO		2.4	0		SO MTT	90-03-06
VEE		NOT ACT	VERO		.1	0		SO MTT	90-03-09
VEE		NOT ACT	VERO		.5	0		SO MTT	90-03-23
VV		.18	VERO		.82	10.53		SO MTT	
YP		NOT ACT	VERO		.52	0		SO MTT	90-03-22
YP		NOT ACT	VERO		1.96	0		SO MTT	90-03-06

VIR HST VR VR* DOSE MTC VEH RTE D TOX SP L PR DATE

PLATE 004
DRUG 6467

IN VITRO ANTIVIRAL RESULTS
MTT ASSAY

DRUG: AVS 6467
TAI: 23.24 SI: 4.65

	1	2	3	4	5	6	7	8	9	10	11	12
	reagent background					plastic background						
A	0.105	0.097	0.123	0.114	0.109	0.119	0.000	0.000	0.000	0.000	0.000	0.000
B		calve					low	drug 6467 experimental			calve	low
C		1.314					1.488	0.153	0.166	0.134	1.321	1.330
D		1.339					1.510	0.179	0.148	0.205	1.470	1.424
E		1.312					1.553	0.258	0.206	0.325	1.410	1.427
F		0.182					1.415	1.153	1.398	1.302	0.160	1.541
G		0.180					1.058	0.847	0.883	0.733	0.173	0.825
H		0.174					0.450	0.426	0.446	0.427	0.142	0.400
							drug 6467 colorimetric background					
							0.107	0.110	0.105	0.108	0.114	0.117

low=cell toxicity cell=cell control vs=virus control BOLD = highest drug conc values shown are optical densities

VIRUS
CELLS
SHIPMENT NUMBER
STRN
REAGENT
VIRUS CONTROL
CELL CONTROL
DIFFERENTIAL

VV
VERO
63
LEDCA
0.111
0.057
1.250
1.193

Satisfactory; Active; Retest
RETEST AT 3.2 UG/ML

PROJECT #
SPONSOR
TEST DATE
DATE READ

5975-4
USAMRIID
04/19/90
04/25/90

DRUG 6467	25%	50%	95%
TC (uG/mL)	0.82	1.86	3.20
IC (uG/mL)	0.13	0.18	---
ANTIVIRAL INDEX (AI)	6.52	10.53	---

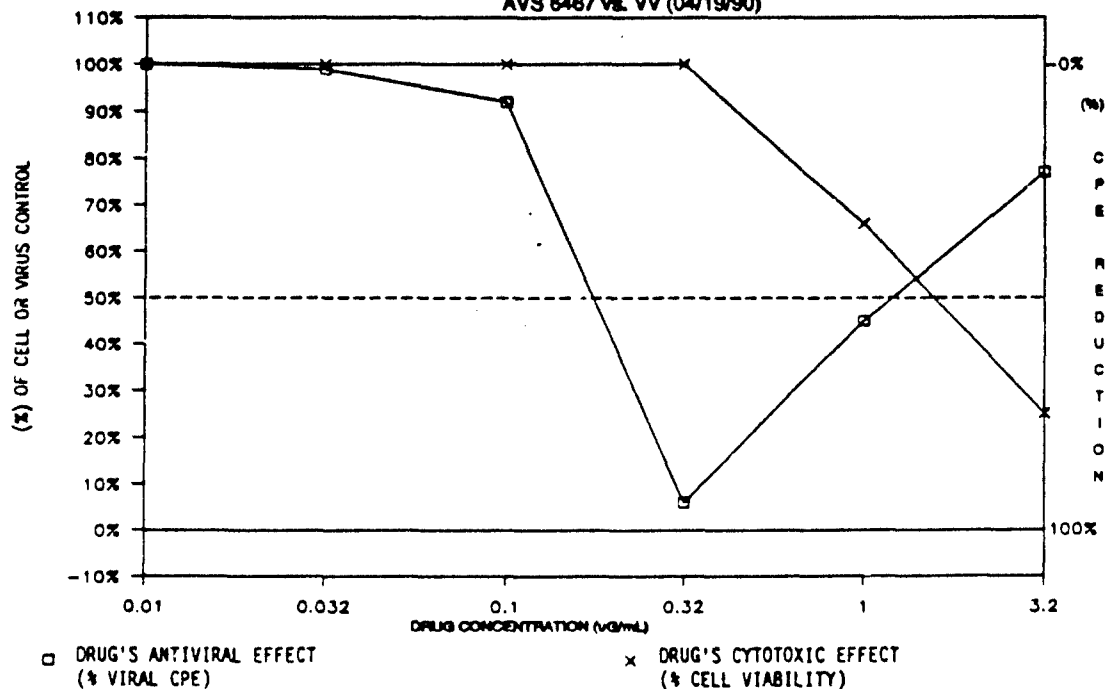
DRUG 6467		ANTIVIRAL TEST VALUES		CYTOTOXICITY TEST VALUES		COLORIMETRIC CONTROL
ROW ON PLATE	CONC. (uG/mL)	MEAN O.D.	% VIRAL CPE	MEAN O.D.	% CELL VIABILITY	
low B	0.01	-0.023	100%	1.272	100%	0.006
C	0.032	0.006	99%	1.353	100%	0.003
D	0.1	0.098	92%	1.382	100%	-0.003
E	0.32	1.122	6%	1.373	100%	-0.006
F	1	0.654	45%	0.831	66%	-0.001
high G	3.2	0.269	77%	0.318	25%	-0.004

* highest drug concentration tested

values shown are final adjusted numbers

SUMMARY GRAPH

AVS 6467 vs. VV (04/19/90)



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