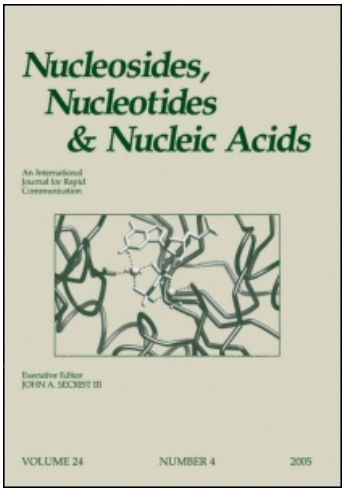

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Cyclopentenyl Cytosine (CPE-C). A Carbocyclic Nucleoside with Antitumor and Antiviral Properties

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CYCLOPENTENYL CYTOSINE (CPE-C). A CARBOCYCLIC NUCLEOSIDE WITH ANTITUMOR AND ANTIVIRAL PROPERTIES

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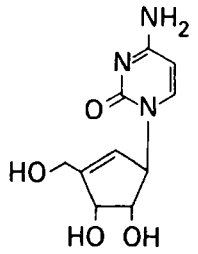
ABSTRACT: CPE-C is a potent antitumor and antiviral agent. It is active against a variety of preclinical murine and human xenograft tumor models in vivo as well as DNA and RNA viruses in vitro.

CPE-C is the synthetic cytidine analogue of the Japanese carbocyclic fermentation product, neplanocin A[1,2]. It is not a substrate for cytidine deaminase and after conversion to its 5'-triphosphate, CPE-C strongly inhibits CTP synthetase. This compound possesses significant preclinical antitumor and antiviral activity.



Cyclopentenyl cytosine
(CPE-C)

CPE-C is active in mouse tumor models as well as human tumor xenografts grown in athymic mice (TABLE 1). However, even greater

TABLE 1

ANTITUMOR ACTIVITY COMPARISON BETWEEN CPE-C AND 3-DEAZAURIDINE[a]

Tumor	CPE-C		3-Deazauridine	
	Dose (mg/kg)	% T/C	Dose (mg/kg)	% T/C
LOX melanoma xenograft	2.25	180	300	104
MX-1 mammary xenograft	2.25	0[b]	300	36[c]
L1210 leukemia	1.5	271 (2/9)[d]	100	180
L1210/ara-C leukemia	2.25	>750 (6/10)	50	266
	1.5	>750 (5/9)	25	462 (3/9)
	1.0	>750 (6/10)	12.5	>750 (9/10)

[a]QD 1-9 treatment schedule. MX-1 subrenal implant, others intraperitoneal.
[b]100% inhibition of solid tumor growth relative to control.
[c]64% tumor inhibition.
[d]Number of 60 day survivors per test group.

TABLE 2

CPE-C ANTIVIRAL ACTIVITY

DNA Viruses

Virus	CPE-C		ARA-A	
	ID_{50} (μg/ml)	VR[a]	ID_{50} (μg/ml)	VR
HSV-1 (TK^+)[b]	0.3	3.8	13.6	1.8
HSV-1 (TK^-)[c]	0.6	3.8	2.1	3.3
HSV-2	2.7	2.3	50.0	1.3
Vaccinia	0.1	4.6	9.8	3.1

[a]Ehrlich virus rating (Shannon and Arnett, So.R.I.).
[b]HSV-1 strain E-377 induces thymidine kinase in Vero host cells.
[c]HSV-1 strain HF does not induce thymidine kinase.

TABLE 3

CPE-C ANTIVIRAL ACTIVITY

RNA Viruses[a]

Virus	CPE-C		Positive Control		
	ID_{50} (μg/ml)	VR[b]	Compound	ID_{50} (μg/ml)	VR
Vesicular Stomatitis	0.3	3.0	3-DA[c]	2.0	3.0
Yellow Fever	5.1	0.9	Selenazole	1.8	2.4
Japanese Encephalitis	0.1	2.4	Ribavirin	3.0	2.4
Punta Toro	1.0	1.5	Ribavirin	20.1	1.8
Influenza A_2 (Hong Kong)	18.2	2.4	Ribavirin	18.7	3.6

[a]Data from the U.S. Army (USAMRIID) antiviral testing program except for influenza (So.R.I.)
[b]USAMRIID virus rating values were converted to Ehrlich VR values.
[c]3-Deazaaristeromycin

activity is observed against the ara-C resistant L1210 tumor. Since this tumor also is reported to show collateral sensitivity to 3-deazauridine (3-DU), a direct comparison between 3-DU and CPE-C was undertaken (TABLE 1). In general, CPE-C is more active and about 100 times more potent than 3-DU.

The carbocyclic nucleoside also has broad spectrum antiviral activity. CPE-C is more active and more potent than ara-A against several DNA viruses (TABLE 2). However, DHPG has greater activity than CPE-C against DHPG-sensitive viruses including cytomegalovirus and varicella-zoster. CPE-C also inhibits several RNA viruses (TABLE 3) but not HIV-1. This compound is being developed toward clinical trial by the National Cancer Institute as an anticancer drug.

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