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## **Nucleosides, Nucleotides and Nucleic Acids**

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

John S. Driscoll<sup>a</sup>; Victor E. Marquez<sup>a</sup>; Jacqueline Plowman<sup>a</sup>

<sup>a</sup> Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH, Bethesda, Maryland

**To cite this Article** Driscoll, John S. , Marquez, Victor E. and Plowman, Jacqueline(1989) 'Cyclopentenyl Cytosine (CPE-C). A Carbocyclic Nucleoside with Antitumor and Antiviral Properties', *Nucleosides, Nucleotides and Nucleic Acids*, 8: 5, 1131 — 1133

**To link to this Article:** DOI: 10.1080/07328318908054309

**URL:** <http://dx.doi.org/10.1080/07328318908054309>

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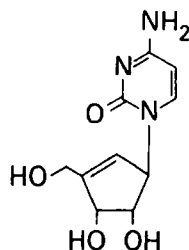
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CYCLOPENTENYL CYTOSINE (CPE-C). A CARBOCYCLIC NUCLEOSIDE  
WITH ANTITUMOR AND ANTIVIRAL PROPERTIES

John S. Driscoll\*, Victor E. Marquez and Jacqueline Plowman  
Developmental Therapeutics Program, Division of Cancer Treatment,  
National Cancer Institute, NIH, Bethesda, Maryland 20892

**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<sup>1,2</sup>. 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<sup>a</sup>

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 <sup>b</sup>	300	36 <sup>c</sup>
L1210 leukemia	1.5	271 (2/9) <sup>d</sup>	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)

<sup>a</sup>QD 1-9 treatment schedule. MX-1 subrenal implant, others intraperitoneal.

<sup>b</sup>100% inhibition of solid tumor growth relative to control.

<sup>c</sup>64% tumor inhibition.

<sup>d</sup>Number of 60 day survivors per test group.

TABLE 2  
CPE-C ANTIVIRAL ACTIVITY

Virus	CPE-C		ARA-A	
	ID <sub>50</sub> (μg/ml)	VR <sup>a</sup>	ID <sub>50</sub> (μg/ml)	VR
HSV-1 (TK <sup>+</sup> ) <sup>b</sup>	0.3	3.8	13.6	1.8
HSV-1 (TK <sup>-</sup> ) <sup>c</sup>	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

<sup>a</sup>Ehrlich virus rating (Shannon and Arnett, So.R.I.).

<sup>b</sup>HSV-1 strain E-377 induces thymidine kinase in Viro host cells.

<sup>c</sup>HSV-1 strain HF does not induce thymidine kinase.

TABLE 3

## CPE-C ANTIVIRAL ACTIVITY

RNA Viruses<sup>a</sup>

Virus	CPE-C		Positive Control		
	ID <sub>50</sub> ( $\mu$ g/ml)	VR <sup>b</sup>	Compound	ID <sub>50</sub> ( $\mu$ g/ml)	VR
Vesicular Stomatitis	0.3	3.0	3-DA <sup>c</sup>	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 <sub>2</sub> (Hong Kong)	18.2	2.4	Ribavirin	18.7	3.6

<sup>a</sup>Data from the U.S. Army (USAMRIID) antiviral testing program except for Influenza (So R.I.).

<sup>b</sup>USAMRIID virus rating values were converted to Ehrlich VR values.

<sup>c</sup>3-Deazaazasteromycin

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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