

FIGURE 1
Scheme 1

Synthesis of Long Chain Lipid Phosphate of L-BH DU

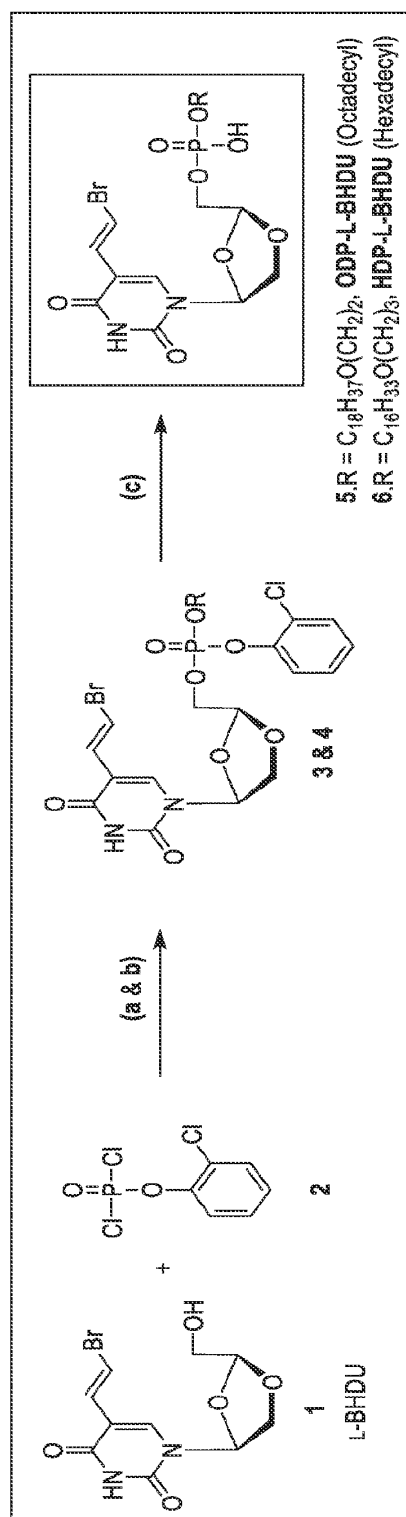


FIGURE 2
Scheme 2

Synthesis of POM-L-BH DU

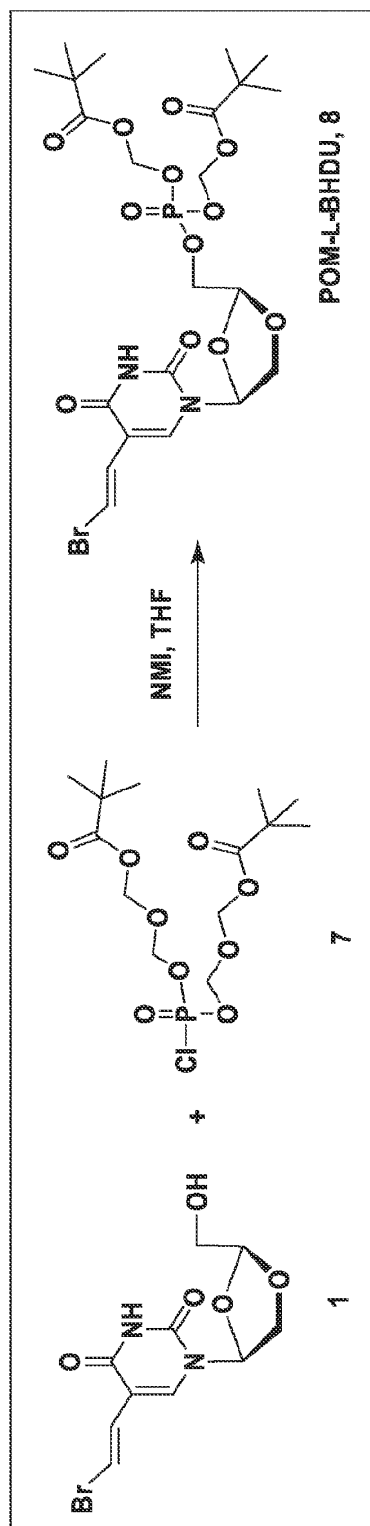


FIGURE 3
Scheme 3

Synthesis of bis POC-L-BDHU prodrug

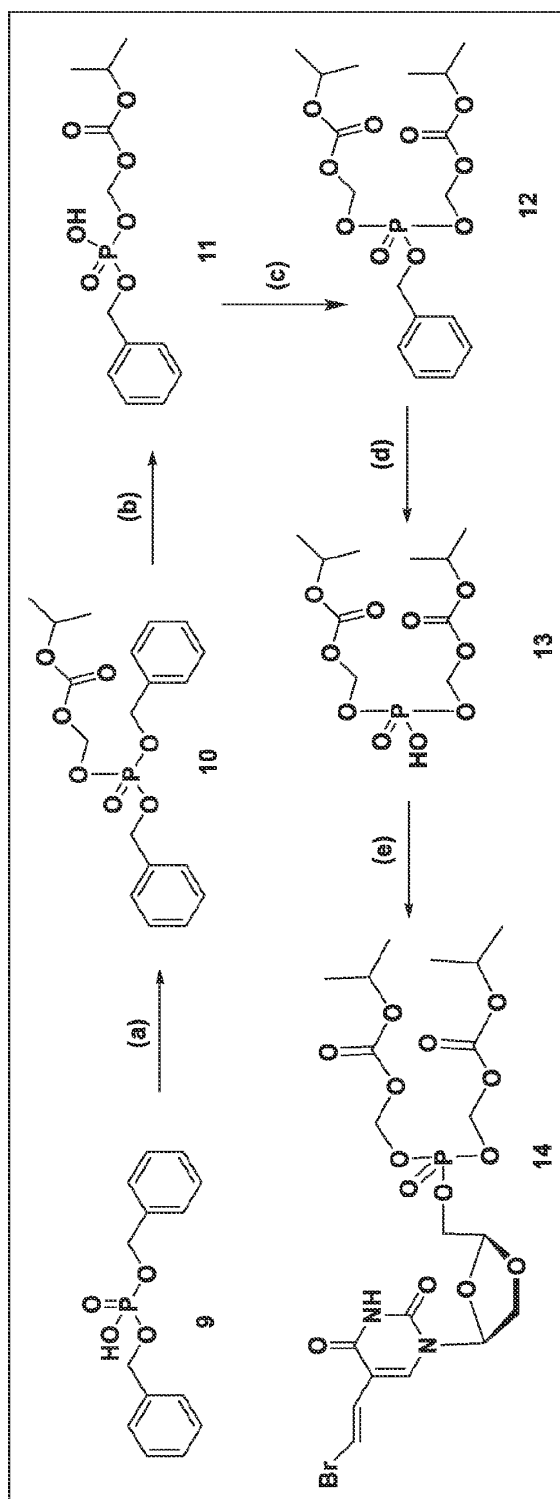


FIGURE 4

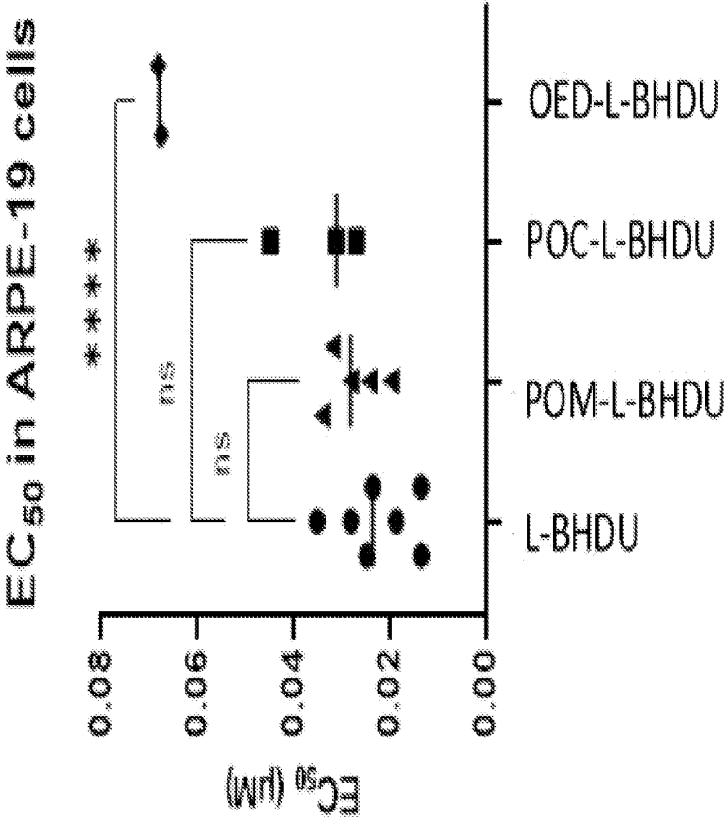


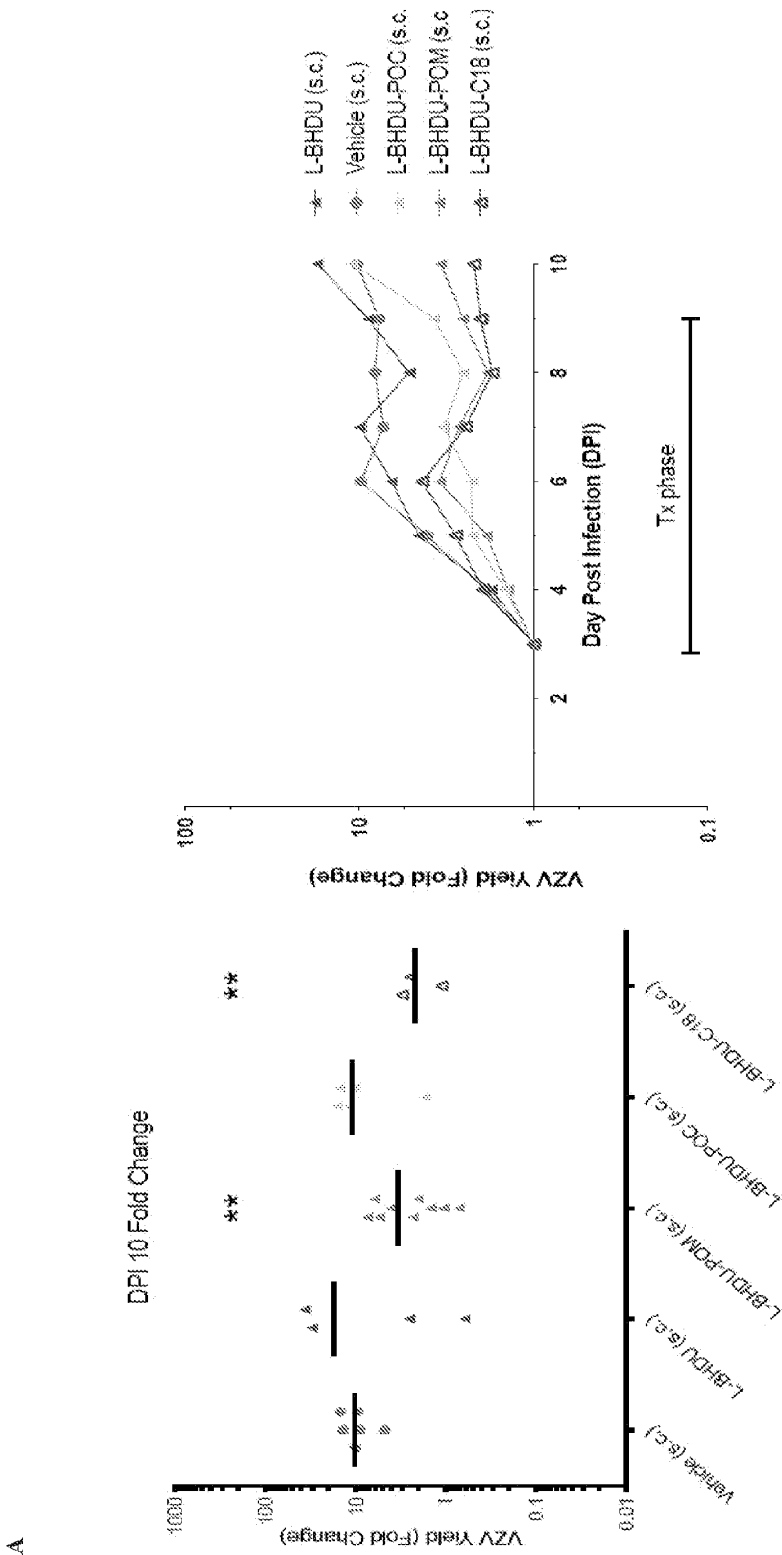
FIGURE 5

Table 1. Anti-VZV activity in ARPE-19 cells

Compounds	EC ₅₀ (μM) ^a (mean±SD)	CC ₅₀ (μM) ^b	SI (CC ₅₀ /EC ₅₀) ^c
L-BHDU	0.022 ± 0.008	>100	>4456
OED-L-BHDU (5)	0.068 ± 0.0005	32.5	479
HDP-L-BHDU (6)	0.090 ± 0.0006	10	111
POM-L-BHDU (8)	0.028 ± 0.006	>100	>3619
POC-L-BDHU (14)	0.034 ± 0.009	>100	>2915

^a 50% inhibitory concentration 48 hpi determined by bioluminescence imaging, mean ± standard deviation from at least 3 experiments.
^b 50% cytotoxic concentration at 72 h determined by neutral red assay from 3 experiments.
^c Selectivity index.

FIGURE 6



B

FIGURE 6 (Cont'd)

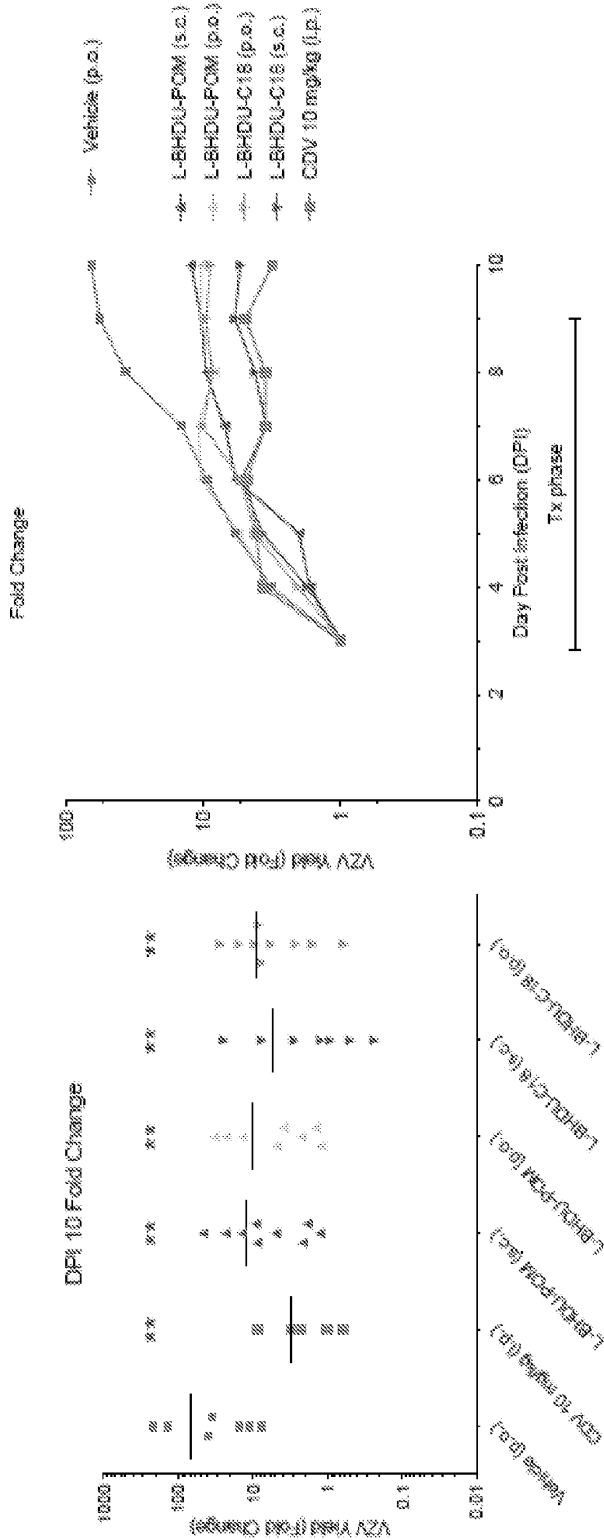


FIGURE 7

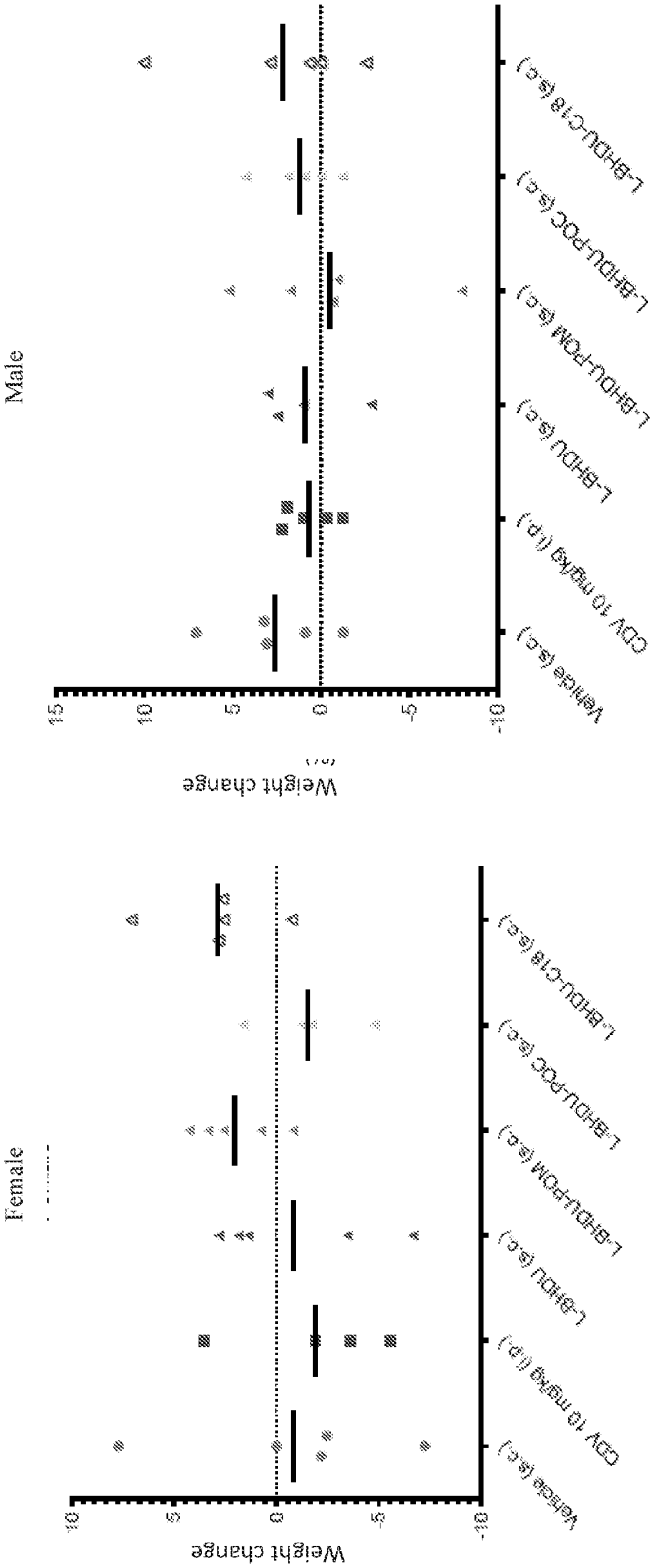


FIGURE 8

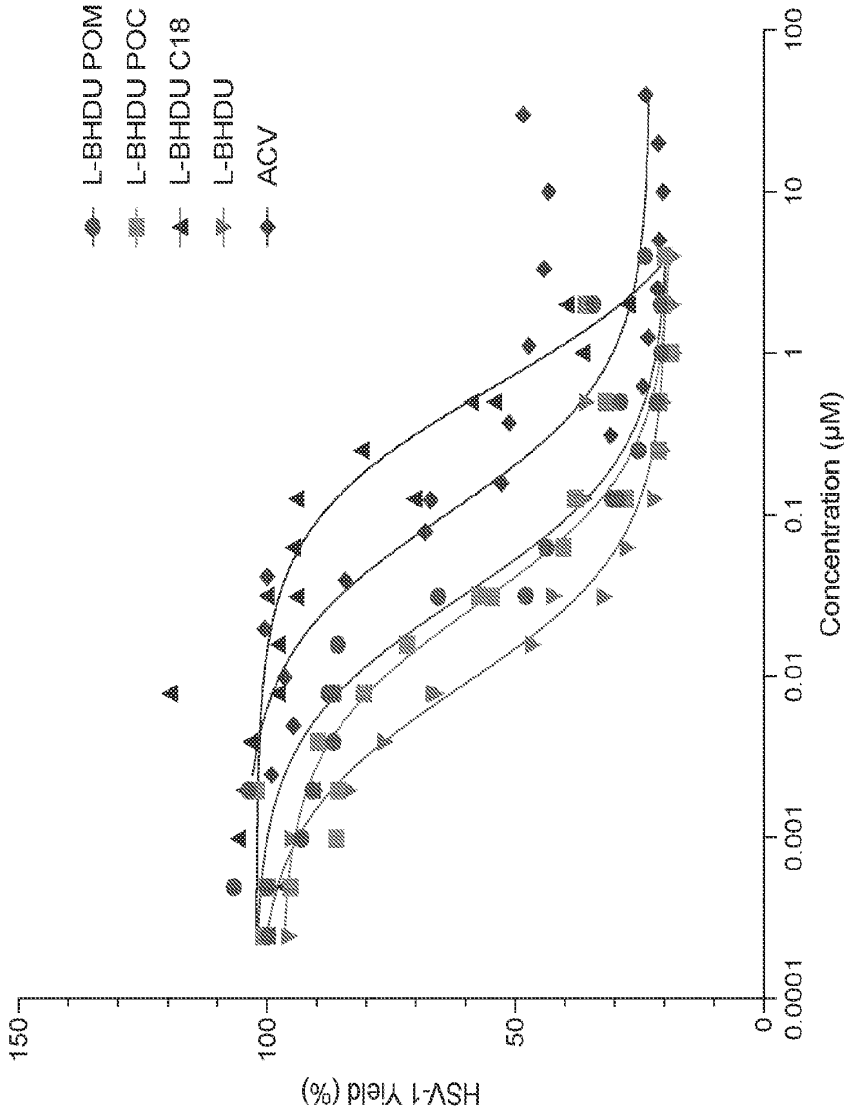


FIGURE 9

Table 2. Anti-*HSV-1* activity of L-BHDU prodrugs in Vero Cells.

Compounds	EC ₅₀ (μM) (mean±SD)	CC ₅₀ (μM)	SI (CC ₅₀ /EC ₅₀)
L-BHDU	0.007	>100	>12,903
OED-L-BHDU	0.7553	20	26
POM-L-BHDU	0.0282	>100	>3,546
POC-L-BDHU	0.0260	>100	>3,846
Acyclovir (ACV)	0.0736	ND	ND

ND : Not Determined.

FIGURE 10

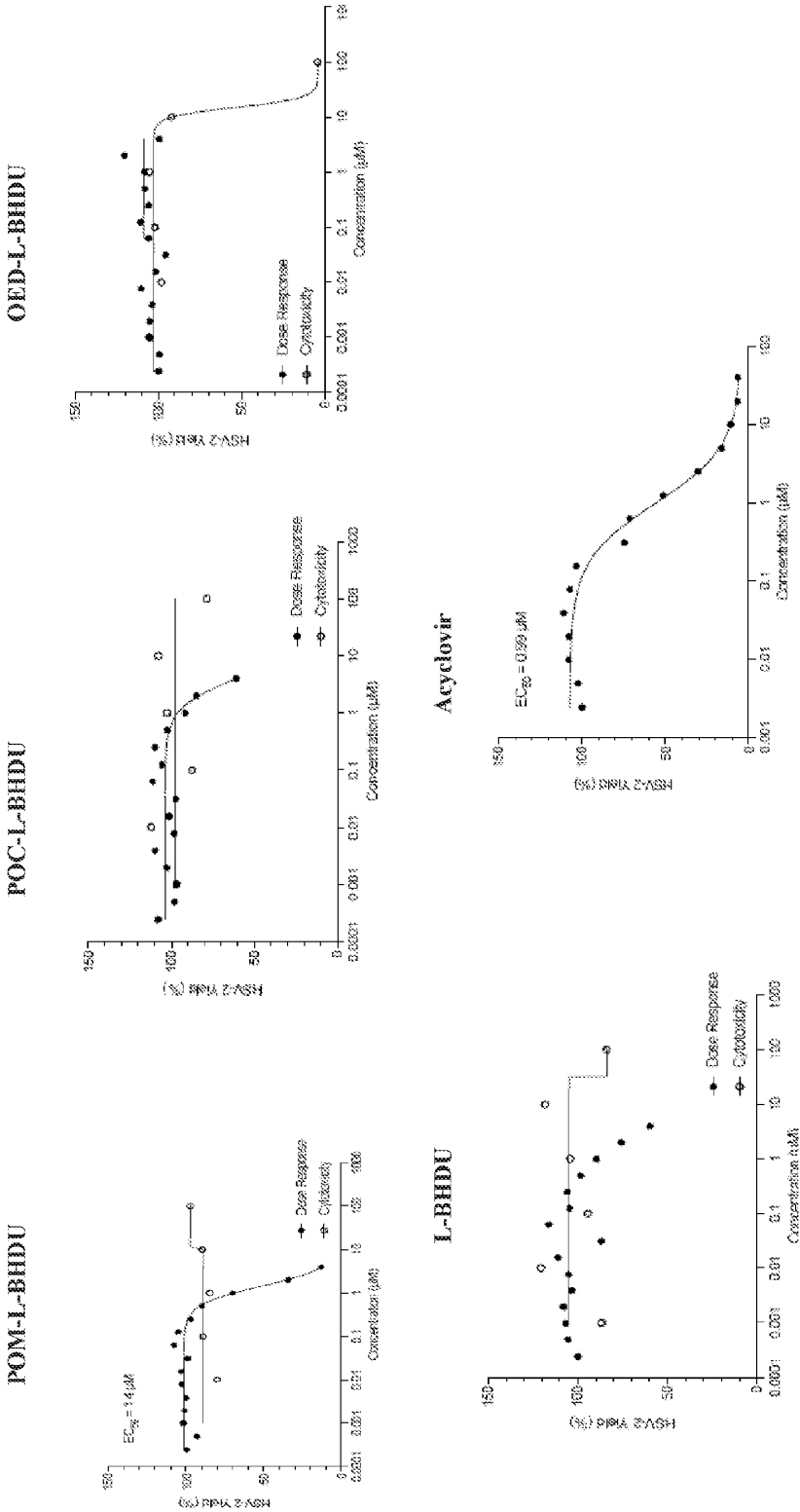


FIGURE 11

Table 3. Anti-HSV-2 activity in Vero Cells.

Compounds	EC ₅₀ (μM) (mean±SD)	CC ₅₀ (μM)	SI (CC ₅₀ /EC ₅₀)
L-BHDU	n/a	>100	--
OED-L-BHDU	n/a	20	--
POM-L-BHDU	1.4	>100	>71
POC-L-BDHU	n/a	>100	--
Acyclovir	0.99	ND	ND

n/a : no activity; ND: Not Determined

FIGURE 12

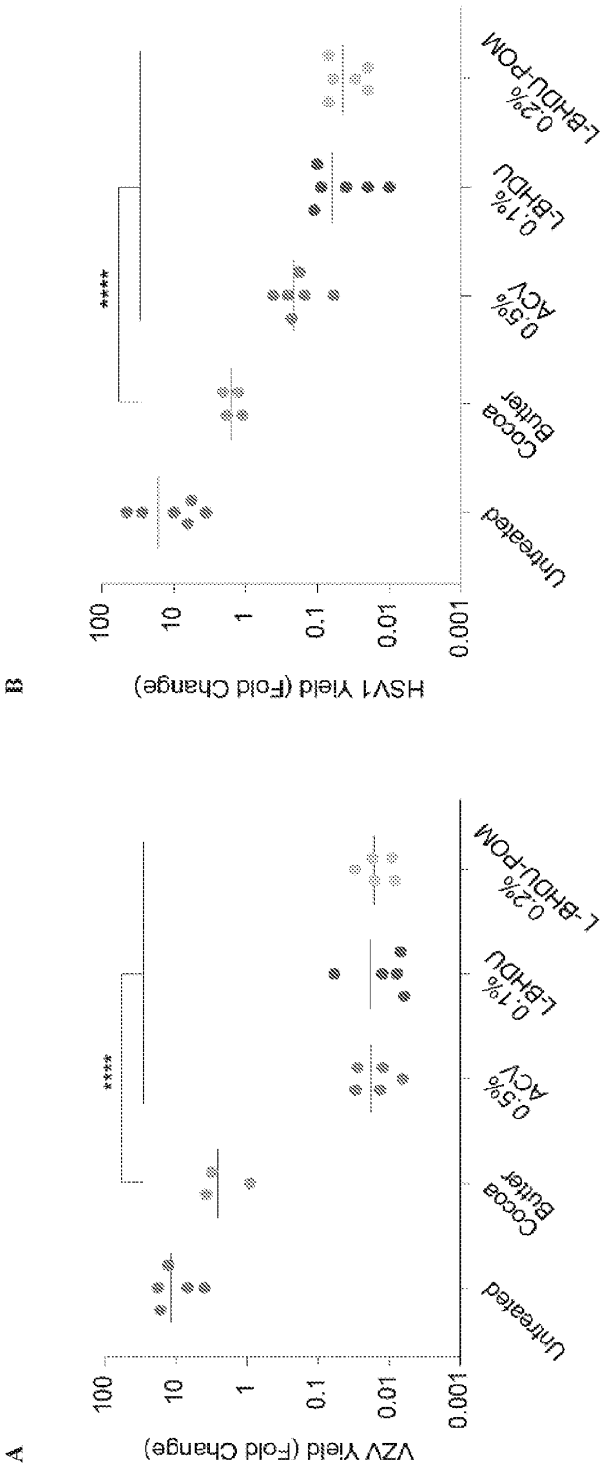


FIGURE 13

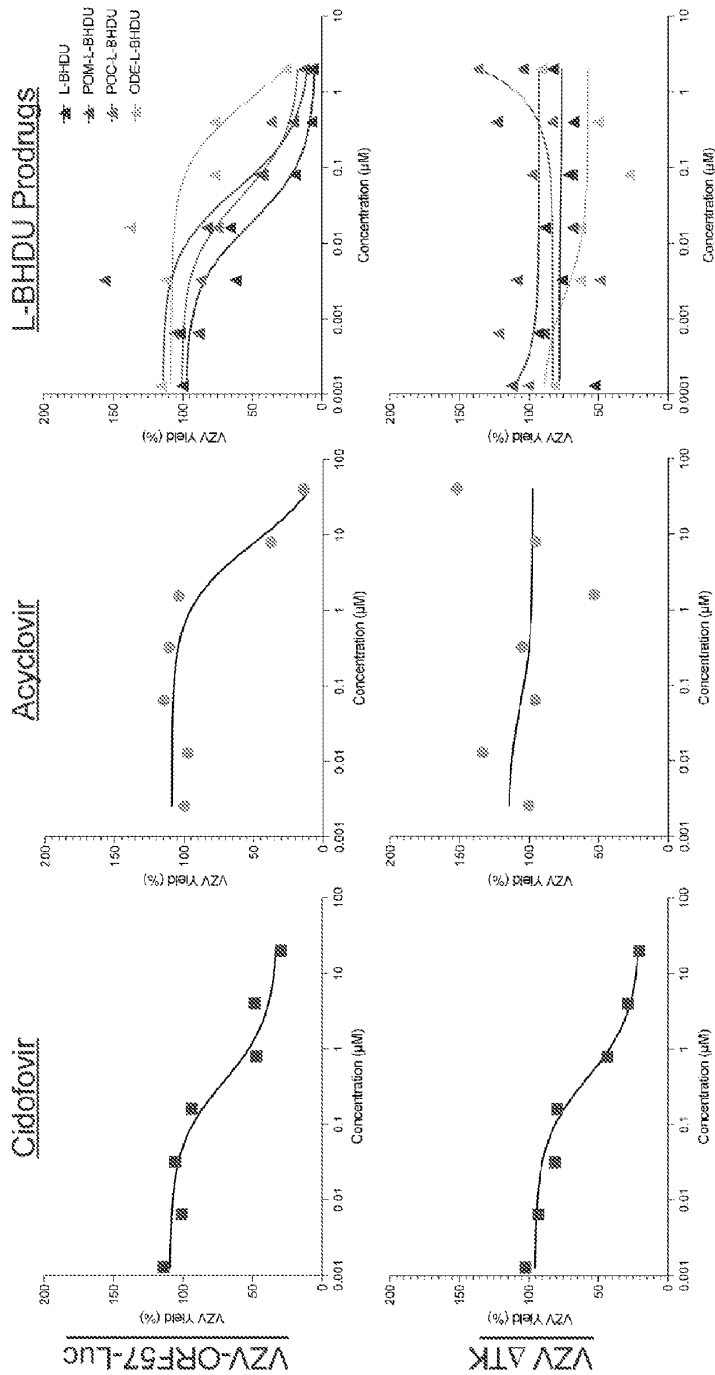


FIGURE 13 (Cont'd)

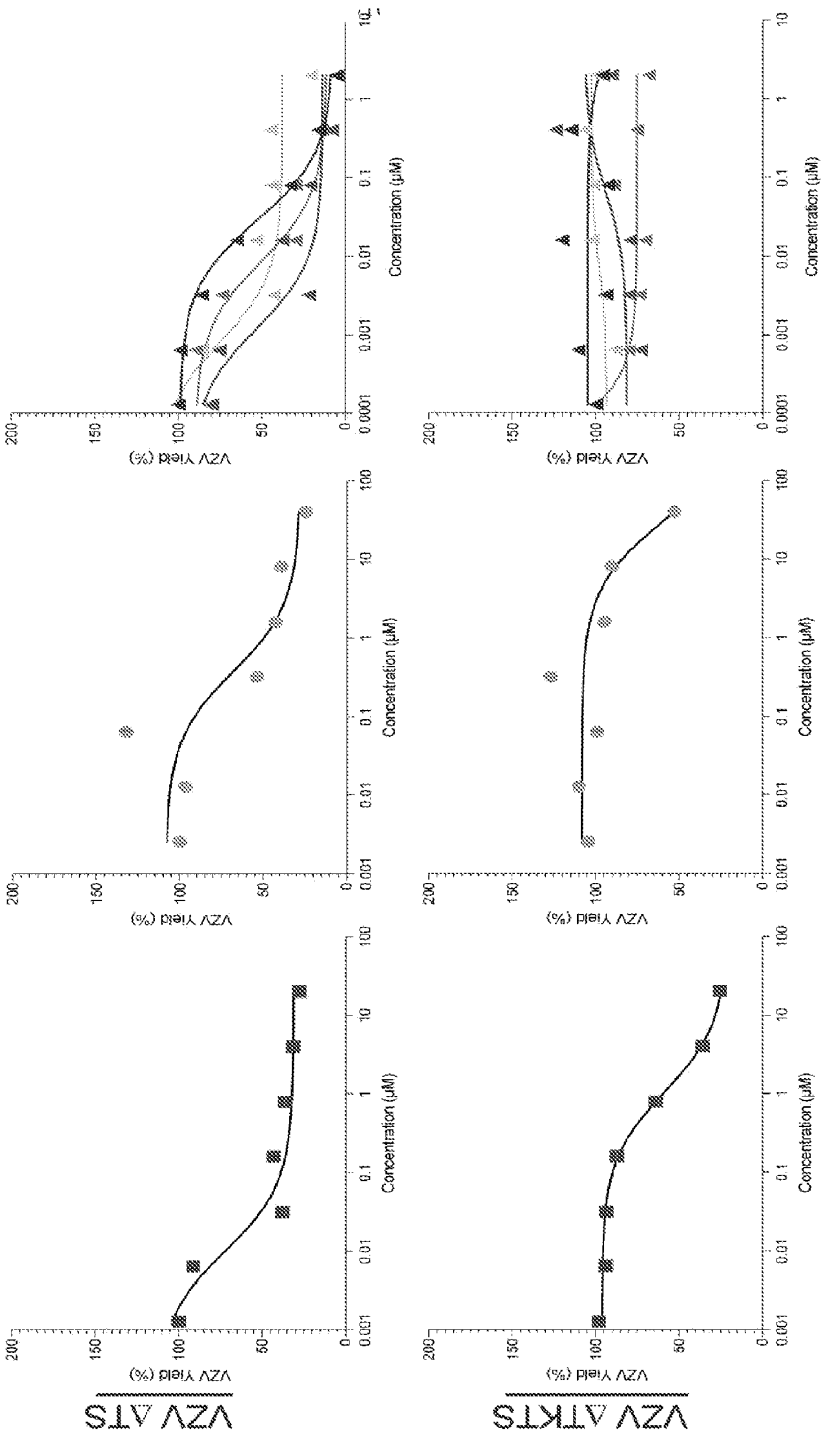


FIGURE 14

Table 4. Antiviral activity of L-BHDU and several prodrugs against cell-associated wild-type and mutant VZV viruses in ARPE-19 cells.

Viral Strains	EC ₅₀ (μM)					
	CDV	ACV	L-BHDU	POM-L-BHDU	POC-L-BHDU	ODE-L-BHDU
VZV-ORF57-Luc	0.37	7.75	0.18	0.051	0.040	0.82
VZV-ORF57-ΔTK	0.42	>20	>2.0	>2.0	>2.0	>2.0
VZV-ORF57-ΔTS	0.01	0.37	0.028	0.0012	0.0084	0.0008
VZV-ORF57-ΔTKTS	1.05	>20	>2.0	>2.0	>2.0	>2.0