*Cyclo*Sal-BVDUMP Pronucleotides: How to Convert an Antiviral-Inactive Nucleoside Analogue into a Bioactive Compound against EBV

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Novel *cyclo*Sal-BVDUMP triesters **2**−**4** 5-[(*E*)-2-bromovinyl]-2′-deoxyuridine (BVDU, **1**) have been studied with regard to their potential anti-EBV activity. In addition to the 3′-unmodified *cyclo*Sal-BVDUMP triesters **2a**−**f**, the 3′-hydroxyl function has been esterified with different aliphatic carboxylic acids (**3a**−**g**) and α-amino acids having natural and nonnatural Cα-configuration (**4a**−**m**). In addition to the synthesis of these compounds, different physicochemical properties of the new derivatives will be reported, i.e., lipophilicity and hydrolysis behavior. It could be proven that the monophosphate BVDUMP and not 3′,5′-cyclic BVDUMP was delivered from most of the compounds by chemical hydrolysis in phosphate buffers at pH 6.8 and 7.3 as well as P3HR-1 cell extracts. Finally, the new compounds were tested for their anti-EBV activity. As a result, the prototype compounds and particularly triesters **2c**,**d** exhibited pronounced anti-EBV activity making these compounds promising candidates for further development. However, the 3′-ester derivatives were devoid of any antiviral activity while the 3′-aminoacyl derivatives showed an antiviral activity dependent upon the amino acid and the Cα-configuration

Introduction

Diseases caused by herpes viruses play an important role in infections of humans. Acyclovir was the prototype of the first generation of selective antiviral agents[1] and has been the gold standard for the therapy and suppression of herpes simplex virus (HSV) infections for more then 20 years.[2] It is phosphorylated selectively by HSV- and VZV-encoded thymidine kinase (TK) in virus-infected cells to the mono- and diphosphate, respectively, and finally by cellular enzymes to the di- and triphosphate, which inhibits viral DNA polymerase and/or causes chain elongation arrest. Today, the second (brivudin, famciclovir, valaciclovir) and third (cidofovir[3]) generations of antiherpes virus drugs are in use.

An emerging area of concern are Epstein−Barr virus (EBV)-caused viral infections and their role they play particularly in posttransplant lymphoproliferative disorders. EBV is the causative agent of infectious and chronic mononucleosis.[4] Moreover, it is associated with the development of several human malignancies[5] (e.g., gastric carcinomas[6]) as well as oral hairy leucoplakia.[7] Tumors classically linked with EBV are Burkitt's lymphoma[8] and nasopharyngeal carcinoma.[9] More recently, associations of EBV and B-cell lymphomas in immunosuppressed patients (including AIDS patients),[10] certain rare T-cell lymphomas,[11] lymphoproliferative syndromes,[12] and cases of Hodgkin's lymphomas[13] have been reported. Recently, a successful clinical therapy of EBV-associated lymphoproliferative deseases with cidofovir has been reported.[14]

The second generation drug Brivudin (5-[(*E*)-2-bromovinyl]-2′-deoxyuridine, BVDU **1**)[15] is a potent and highly selective nucleoside analogue-type inhibitor[16] of the replication of several herpes viruses especially VZV and HSV-1.[17] The mode of action as inhibitor depends primarily on intracellular conversion of the nucleoside analogue into the triphosphate form. Brivudin triphosphate (BVDUTP) can act either as an inhibitor of the cellular DNA polymerase or as an alternate substrate that would lead to the formation of nonsense DNA and would render the DNA more prone to degradation when incorporated in DNA.[18] As for other known antiherpes drugs, some limitations are known for the use of BVDU. There is a lack of activity during virus latency because viral TK is not expressed, drug resistance of the virus has been observed, and BVDU is enzymatically degraded to the nucleobase 5-[(*E*)-2-bromovinyl]uracil within 2−3 h in the bloodstream.[17] Additionally, due to altered or deficient enzymes necessary for the phosphorylation to the nucleoside monophosphate and diphosphate, this metabolism is often inefficient and thus the therapeutic activity can be limited. To overcome some of these limitations, the use of pronucleotides that release the nucleotide from a lipophilic precursor after cell entry may be of use.[19] We developed the so−called *cyclo*Sal-pronucleotide system.[20] The basic idea of the *cyclo*Sal-approach was a release of the nucleotide by a selective, chemically induced hydrolysis. This concept has been successfully applied to the intracellular delivery of a number of anti-HIV active nucleotides[21] as well as to acyclovir (ACV).[22]

Here we report on the synthesis, hydrolytic properties, and biological activities of a series of 3′-unmodified **2a**−**f** as well as 3′-*O*-esterified *cyclo*Sal-BVDUMPs **3** and **4**. As 3′-modifications, different lipophilic carboxylic acids (**3a**−**g**) as well as α-amino acids (**4a**−**k**) have been

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Scheme 1. Synthetic Pathways to *Cyclo*Sal-Triesters **2**−**4**[a]
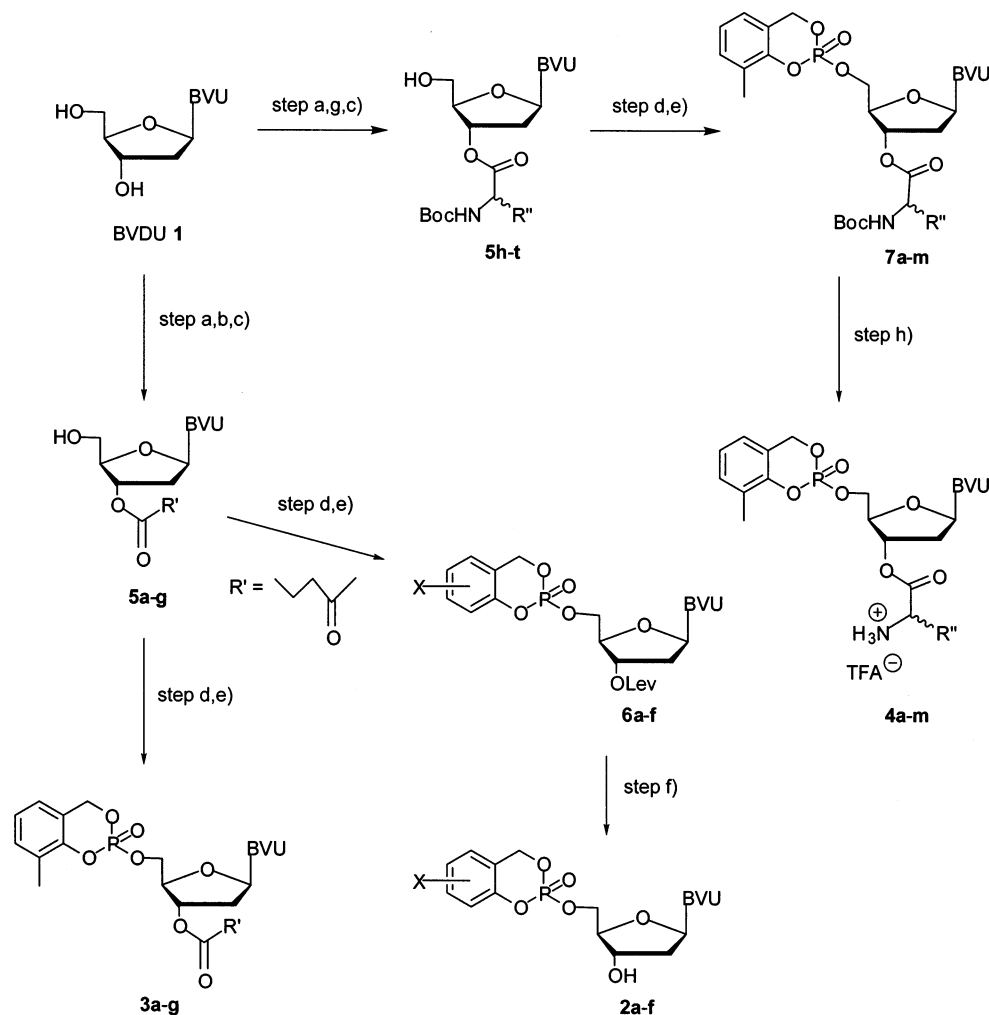
[a] Reaction conditions: (a) TBDMSCl, pyridine, rt, 14 h; (b) carboxylic acids, DMAP, DCC, CH$_2$Cl$_2$, rt, 30 min; (c) TBAF, THF, rt, 4 h; (d) chlorophosphane, DIPEA, CH$_3$CN, −20 °C, 30 min; (e) TBHP, CH$_3$CN, −20 °C to rt, 1 h; (f) H$_2$NNH$_2$·H$_2$O, pyridine, CH$_3$COOH, rt, 5 min; (g) *N*-Boc-amino acids, DMAP, DCC, CH$_2$Cl$_2$, rt, 30 min; (h) TFA, CH$_3$CN, rt, 1 h.

introduced. Although EBV produces its own viral thymidine kinase, BVDU **1** is antivirally inactive against EBV for unknown reasons. One reason may be that EBV-TK cannot convert BVDU into the monophosphate and thus does not initiate the required phosphorylation. So, our aim was to determine whether the *cyclo*Sal-concept is able to broaden the application of BVDU **1** against Epstein−Barr-virus (EBV)-caused infections through the intracellular delivery of BVDUMP.[5] Two reports on pronucleotides of BVDU **1** have been published before but both were unsuccessful.[23] In contrast, the data presented in this report show pronounced anti-EBV activity for some of the *cyclo*Sal-BVDUMP triesters.[24]

Results and Discussion

Chemistry. The prototype *cyclo*Sal-triesters **2a**−**f** were available by our previously reported P(III)-route using chlorophosphites prepared from appropriate salicyl alcohols and oxidation by *t*-BuOOH in DMF/THF 1:1 at −40 °C without using protecting groups at the 3′-position.[21b,c,d] Alternatively, triesters **2** were prepared by 5′-*O*-phosphitylation of 3′-*O*-levulinyl (Lev)-BVDU **5g** and subsequent oxidation. Cleavage of the 3′-*O*-Lev group was achieved by treatment with a solution of

hydrazine hydrate/acetic acid in pyridine to give triesters **2** in 31−50% overall yield. The yields of the latter route were comparable to those obtained via the first variant. For the preparation of both series of 3′-esterified *cyclo*Sal-BVDUMP triesters **3** and **4**, the acyl group was first introduced into BVDU **1** to give 3′-acyl-BVDUs **5a**−**t**. So, BVDU **1** was first 5′-*O*-silylated (TBDMS) in pyridine (84% yield) and then esterified using carboxylic acids, *N*-Boc-protected L- or D-amino acids after DCC/DMAP activation. Desilylation (2% TBAF in THF) yielded BVDU derivatives **5a**−**t** (90−97% yield of both steps). The *cyclo*Sal moiety was introduced as mentioned before to give triesters **3a**−**g** and **7a**−**m** respectively. Alternatively, the reaction was also possible by using the corresponding phosphoramidites.[25] However, the yields were again comparable to those of the chlorophosphite reaction, and triesters **3a**−**g** were prepared in 50−60% yield. Finally, the *N*-Boc protecting group in **7a**−**m** was cleaved by 5% TFA treatment in CH$_2$Cl$_2$/MeOH 7:3 to give triesters **4a**−**m** (50−52% yield). The reaction sequence is outlined in Scheme 1.

All title compounds **2**−**4** were isolated as 1:1 diastereomeric mixtures that were inseparable even by means of preparative HPLC. The compounds were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy as well as

Table 1. Hydrolysis ($t_{1/2}$) in Phosphate Buffers and log P Values

			hydrolysis[a] in phosphate buffer, 37 °C		
compd	subst X	subst R	pH 7.3[b]	pH 6.8[c]	log$P$[e]
2a	5-Cl	H	0.23	0.33	1.8
2b	H	H	1.52	1.79	1.5
2c	5-OMe	H	2.32	2.75	1.6
2d	3-Me	H	6.29	7.79	1.9
2e	3,5-diMe	H	8.61	12.5	2.2
2f	3-*t*Bu	H	20.7	33.7	2.9
3a	3-Me	Ac	5.81	7.60	2.2
3b	3-Me	Prop	6.30	7.77	2.3
3c	3-Me	*t*Bu	4.89	9.00	2.4
3d	3-Me	Piv	13.8	14.6	3.0
3e	3-Me	Hex	8.10	10.9	2.6
3f	3-Me	Dec	14.8	16.0	2.8
3g	3-Me	Lev	4.72	7.02	2.3
4a	3-Me	Gly	1.76	1.92	−0.8
4b,c	3-Me	Ala	1.26	1.43	−0.6
4d,e	3-Me	Val	3.09	3.40	−0.1
4f,g	3-Me	Leu	1.40	1.50	0.4
4h,i	3-Me	Ile	3.20	3.70	−0.02
4j,k	3-Me	Phe	1.70	3.50	0.5
4l,m	3-Me	Pro	0.32	0.35	−0.4
1	−	H	−	−	0.33
ACV	−	−	−	−	−1.6

[a] Half-lives ($t_{1/2}$) were determined from the decreasing peak of the starting phosphate triester and are the mean of duplicate experiments; values are given in hours (h). [b] 25 mM phosphate buffer, pH 7.3. [c] 25 mM phosphate buffer, pH 6.8. [d] log P: log of the partition coefficient determined in *n*-octanol/water.

mass spectrometry (FAB and ESI) and UV spectroscopy. As expected, the phosphate triesters displayed two closely spaced signals in the ^{31}P NMR spectra. The purity was checked by analytical reversed-phase high-performance liquid chromatography (RP-HPLC). After lyophilization, all phosphate triesters **2−4** were obtained as white fluffy solids.

Determination of Partition Coefficients (log P values). The partition coefficients (log P value) of the *cyclo*Sal-BVDUMPs **2−4** as well as those of the parent nucleoside analogue **1** and the reference compound (AZT) were determined in 1-octanol/water by our previously reported HPLC method (Table 1).[21a,21d] The partition coefficients of the prototype *cyclo*Sal-BVDUMPs **2** were up to 370-fold and those of the 3′-*O*-esterified phosphate triesters **3a−g** were up to 470-fold higher as compared to BVDU **1** (log P = 0.33, Table 1). Compared to AZT (log P = 0.025),[21d] which enters mammalian cells by passive, non facilitated diffusion,[26] BVDUMP triester **2a−f** and **3a−g** revealed a pronounced increase in lipophilicity. However, one should take into consideration that in cases of very high log P values the formation of micelles, lipid drops or lipid films could not be excluded. As expected, the lipophilicity was dramatically decreased in the case of the 3′-*O*-aminoacyl-modified *cyclo*Sal-BVDUMP triesters **4** due to the protonated amino group. In general, log P values of the 3′-*O*-aminoacyl-*cyclo*Sal-BVDUMPs **4a−m** were lower (up to 12-fold) than the log P value of BVDU with the consequence that triesters **4** were highly water-soluble.

Kinetic Studies. The *cyclo*Sal-pronucleotide approach has been designed to release the nucleotides and the masking group selectively by a chemically induced tandem or cascade reaction. In contrast to other prodrug concepts based on enzymatically triggered activation,[19] our approach involves the successive coupled cleavage of the phenyl and benzyl esters of the *cyclo*Sal phos-

phate triester. The degradation pathway has been proven by different methodologies and has been applied to the delivery of various nucleosides, e.g. d4T,[21a] dd-(4)A,[21b] F-*ara*/*ribo*-ddA,[21c] CBV/abacavir,[21e] and ACV.[22] The intracellular delivery of the corresponding nucleotides has been demonstrated by the observed biological activity in different cell lines and even in thymidine kinase-deficient CEM cells or virus strains. However, all of the above-mentioned nucleoside analogues did not possess a further nucleophilic group in the vicinity of the 5′-phosphate group. In BVDU, a 3′-hydroxyl group is present in the glycon. Assuming an intramolecular attack at the phosphorus center, this would finally lead to the formation of 3′,5′-cyclic BVDUMP. Such a situation has already been observed in the case of the anti-HSV active penciclovir (PCV): hydrolysis led exclusively to the formation of the cyclic phosphate diester.[27] However, in penciclovir the intramolecular nucleophile is a primary hydroxyl and thus more reactive than the secondary 3′-hydroxyl in BVDU. So, the question arose if the 3′-hydroxyl group is able to compete with the intermolecular ring opening reaction of the *cyclo*Sal-moiety.

The hydrolysis behavior of *cyclo*Sal-BVDUMPs **2−4** was examined in aqueous phosphate buffer at two pH-values, in P3HR-1 cell extract and in human sera. Hydrolysis products were identified by means of HPLC using coinjections with independently synthesized reference compounds, ESI-mass spectrometry, and ^{31}P NMR spectroscopy. The half-lives were determined by integration of the decreasing peaks of the triesters versus time.

The half-lives were determined in phosphate buffers and are summarized in Table 1. First of all, all prototype *cyclo*Sal-BVDUMP triesters **2** selectively hydrolyzed in both buffers to give BVDUMP and the corresponding salicyl alcohol (Scheme 2). It was unambiguously shown by means of analytical HPLC, ESI, and ^{31}P NMR that no 3′,5′-cyclic BVDUMP (cBVDUMP) has been formed. Therefore, the possible concurrent intramolecular process did not take place in contrast to the *cyclo*Sal-PCVMP case mentioned before. This may be attributed (i) to the lower reactivity of the secondary alcohol function and (ii) to the attachment of the hydroxyl group in the ring scaffold. In contrast, the hydroxyl group in PCV is part of a flexible acyclic structure.

Second, as in the case of the *cyclo*Sal-triester of d4T and dd(4)A, a clear correlation between hydrolytic stability and the substituents on the aromatic ring was observed for compounds **2a−f**. In both phosphate buffers, the half-lives increased commensurate with the electron-donating ability of the substituent. In comparison, *cyclo*Sal-BVDUMPs hydrolyzed about 3-fold faster as compared to the identically substituted *cyclo*Sal-d4TMP, e. g., 3-Me-*cyclo*Sal-d4TMP showed a $t_{1/2}$ value of 19h at pH 7.3 while 3-Me-*cyclo*Sal-BVDUMP **2d** showed a $t_{1/2}$ value of 6 h. As expected, the hydrolysis rate was dependent on the pH-value of the buffer (Table 1). Phosphate triesters **2d−f** showed in slightly acidic (pH 6.8) as well as in slightly basic phosphate buffer (pH 7.3) stability properties that should be high enough to allow a sufficient cellular uptake. However, compounds **2a−c** hydrolyzed presumably too fast to be

Scheme 2. Major Hydrolysis Pathways of *Cyclo*Sal-Phosphate Triesters
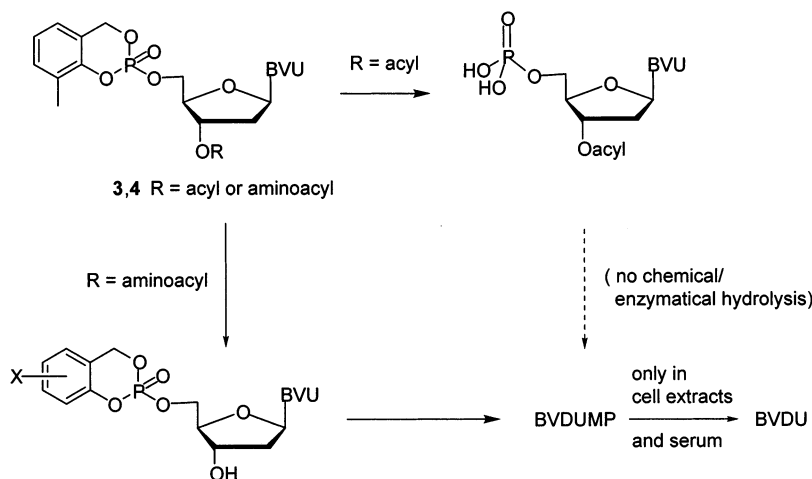
taken up efficiently. This may be deduced from earlier work from our laboratory.

Interestingly, a marked difference in the hydrolysis pathway between the 3′-esterified *cyclo*Sal-triesters **3** and **4** was observed. As expected, hydrolysis of 3′-*O*-acyl modified BVDUMPs **3** led to the cleavage of the *cyclo*Sal-mask releasing 5′-phosphorylated 3′-*O*-acyl-BVDUMP (Scheme 2). No cleavage of the 3′-ester to give the prototype **2d** was observed by means of HPLC. The half-lives of 3′-*O*-acyl-modified BVDUMPs **3** showed a correlation between the hydrolysis behavior and the lipophilicity: the more lipophilic the carboxylic acid the more stable the phosphate triester. This may be due to the interaction of the attacking hydroxide with the highly lipophilic 3′-*O*-acyl residue or to the formation of lipid structures such as micelles that limits the accessibility of the phosphate group. If a further polar carbonyl functionality is introduced as in the 3′-*O*-Lev derivative **3g**, the lipophilicity and the half-life decreased. It is important to note that the 3′-ester group in 3′-*O*-acyl-BVDUMP was stable in all cases to further hydrolysis to give BVDUMP. So, chemical hydrolysis of these compounds led to a dead end.

In contrast, the 3′-α-aminoacyl bearing *cyclo*Sal-BVDUMPs **4** displayed markedly lower half-lives. *Cyclo*Sal-BVDUMPs **4** hydrolyzed in both phosphate buffers in the range of 0.3–3.7 h. Moreover, in contrast to the 3′-*O*-acyl triesters **3**, HPLC analysis proved that in compounds **4** first the aminoacyl residue was cleaved, leading to the prototype 3-methyl-*cyclo*Sal-BVDUMP **2d**. In a further hydrolysis step the *cyclo*Sal-moiety was cleaved to give finally BVDUMP and 3-methyl-saligenin. It should be added that no influence of the Cα-configuration in the aminoacyl group to the hydrolysis rate was observed. The formed prototype triester **2d** hydrolyzed with the same half-life as before. The unexpected lability of the 3′-aminoacyl group may be attributed to a protonation of the amino group (until ~ pH 9) and thus formation of an ammonium group at pH 6.8 or 7.3. This resulting acceptor group destabilizes the ester bond by withdrawing electron density from the ester residue.

Next, triesters **2**–**4** were studied in phosphate buffer containing pig liver esterase (PLE). In contrast to the situation above, it was shown that the 3′-acyl group in triesters **3** was cleaved rapidly to give the prototype

triester **2d** (data not shown).[28] Triester **2d** hydrolyzed with the same rate as in the absence of PLE, indicating that PLE has no effect on the delivery of BVDUMP. 3′-Aminoacyl triesters **4** led again first to the formation of prototype **2d** and then to BVDUMP without any enzymatic contribution.

The hydrolytic behavior of *cyclo*Sal-BVDUMP triesters **2**–**4** was further studied in P3HR-1 cell extracts. This cell type was used for the antiviral evaluation against EBV. Hydrolysis studies in the extracts were done at 37 °C and followed for 8 h only in order to exclude extract degradation with the risk of changing the enzyme content. Incubations were stopped by addition of a solution of acidic methanol, and products were analyzed by means of HPLC.

Again, a clear correlation between hydrolytic stability and the substituents on the aromatic ring was observed for compounds **2**. As an example, the half-live of 3-methyl-*cyclo*Sal-BVDUMP **2d** was determined. The half-life was found to be 8 h and is therefore in the same range as found in phosphate buffer, pH 7.3. Consequently, no indication for an enzymatic contribution was found and so hydrolysis in cell extract is purely chemically driven. As in the phosphate buffer, triesters **2** hydrolyzed to yield BVDUMP. The latter was subsequently dephosphorylated to BVDU **1** by phosphatases/nucleosidases present in the extracts. This dephosphorylation has been proven in a separate assay: BVDUMP was metabolized to BVDU to an extent of 29% within 4 h. Therefore, one may conclude that BVDU will not arise directly from the triester. No formation of 5-[(*E*)-2-bromovinyl]uracil (BVU) was detected in the extracts.

The hydrolysis of the 3′-*O*-acyl modified derivatives **3** exhibited a clear difference with respect to the attached acid. For the 3′-*O*-Ac-, 3′-*O*-Hex-, 3′-*O*-Dec-, and 3′-*O*-Lev derivatives **3a**, **3e**–**g**, respectively, enzymatic deesterification into the prototype triester **2d** was the one hydrolysis product. Triester **2d** was then further cleaved to give BVDUMP. However, also considerable amounts of 3′-acyl-BVDUMP were formed (Table 2). Thus, in contrast to the PLE and phosphate buffer studies, the degradation in cell extracts is not selective. Moreover, derivatives **3b**–**d** hydrolyzed predominantly to give 3′-*O*-acyl-BVDUMP. Interestingly, as in the studies with PLE, 3′-*O*-acyl-BVDUMP was not further metabolized to BVDUMP in the cell extracts.

Table 2. Products after 8 h Incubation Time in P3HR-1 Cell Extract

compd	subst X	subst R	educt	prototype	3′-OR-BVDUMP	BVDUMP	BVDU
2a	5-Cl	H	−	−	−	59	41
2b	H	H	−	−	−	51	49
2c	5-OMe	H	34	−	−	42	24
2d	3-Me	H	51	−	−	31	18
2e	3,5-diMe	H	63	−	−	22	15
2f	3-*t*Bu	H	90	−	−	9	<1
3a	3-Me	Ac	29	29	16	16	10
3b	3-Me	Prop	77	4	14	3	2
3c	3-Me	*i*Bu	45	10	35	7	3
3d	3-Me	Piv	82	2	14	1	<1
3e	3-Me	Hex	77	8	3	7	5
3f	3-Me	Dec	84	6	3	5	2
3g	3-Me	Lev	19	30	11	23	17
4a	3-Me	Gly	−	49	−	32	19
4b,c	3-Me	Ala	−	44	−	31	25
4d,e	3-Me	Val	−	44	−	32	24
4f,g	3-Me	Leu	−	40	−	34	26
4h,i	3-Me	Ile	−	43	−	33	24
4j,k	3-Me	Phe	−	43	−	32	25
4l,m	3-Me	Pro	−	43	−	30	27

The situation was significantly different for the triesters **4**. As in the phosphate buffers, all triesters are loosing rapidly the 3′-*O*-aminoacyl group to yield prototype triester **2d** as major product. From the half-lives and the product distribution it can be deduced that the 3′-*O*-aminoacyl esters were hydrolyzed chemically. No significant difference between the natural L-configured triester and the D-configurated could be detected. In the case of triesters **4**, no trace of 3′-*O*-aminoacyl-BVDUMP was found.

To study the stability of the triester **2**−**4** in human serum, compounds were incubated in 10% human serum in phosphate buffer, pH 6.8. As summarized in Table 1, the half-lives of a few representative examples were found to be in the range as in the pure phosphate buffers. Again, this clearly points to a chemically driven cleavage of the triesters. As in the extracts, the main products of triesters **2** and **4** were again BVDUMP and BVDU, while triesters **3** led mainly to the formation of 3′-*O*-acyl-BVDUMP.

Antiviral Evaluation. The successful thymidine kinase bypass by *cyclo*Sal-d4TMP[21] and *cyclo*Sal-ACVMP phosphate triesters[22] has been shown before. These results demonstrated (i) a pronounced structure−bioactivity correlation with respect to the substituents on the *cyclo*Sal moiety, (ii) the successful membrane penetration of the pronucleotide, (iii) the efficient intracellular delivery of the nucleotide, and (iv) the complete independence from TK.[29] In sharp contrast, the corresponding *cyclo*Sal-AZTMP derivatives lost nearly all the antiviral activity observed in wild-type CEM/O cells[21d,30] when tested in TK-deficient CEM cells.[29] The parent nucleoside BVDU **1**, as well as the *cyclo*Sal phosphate triesters **2**−**4** were evaluated for their ability to inhibit the replication of EBV in human lymphoblastoid P3HR-1 cells. The antiviral activity of the clinically used nucleoside analogue acyclovir (ACV) is given for comparison. The results obtained are displayed in Table 3.

As expected, the parent nucleoside BVDU **1** was devoid of any antiviral activity in the EBV infected P3HR-1 cell system. Most strikingly, the 3′-unmodified *cyclo*Sal-BVDUMPs **2a**−**f** showed pronounced anti-EBV activity in the cell system. Most active compounds

Table 3. Anti-EBV Activity and Selective Indices of *Cyclo*Sal-Triesters **2**−**4**, as well as BVDU **1** and ACV

compd	subst X	subst R	EC$_{50}$ (μM)[a]	CC$_{50}$ (μM)[b]	SI[c]
2a	5-Cl	H	25.8 ± 7.15	80	3.1
2b	H	H	12.3 ± 6.34	92	7.5
2c	5-OMe	H	3.35 ± 3.76	137	41
2d	3-Me	H	4.11 ± 0.81	122	30
2e	3,5-diMe	H	14.4 ± 9.18	143	9.9
2f	3-*t*Bu	H	32.5 ± 8.58	80	2.5
3a	3-Me	Ac	>89.7	109	−
3b	3-Me	Prop	>175	282	−
3c	3-Me	*i*Bu	>171	104	−
3d	3-Me	Piv	>83.4	57	−
3e	3-Me	Hex	>163	>326	−
3f	3-Me	Dec	>149	>299	−
3g	3-Me	Lev	>163	152	−
4a	3-Me	Gly	43.5 ± 30.1	93	2.1
4b	3-Me	L-Ala	35.3 ± 11.6	92	2.6
4c	3-Me	D-Ala	25.3 ± 13.7	38	1.5
4d	3-Me	L-Val	81.8 ± 31.3	47	0.6
4e	3-Me	D-Val	>137	80	−
4f	3-Me	L-Leu	23.0 ± 9.06	45	2.0
4g	3-Me	D-Leu	>135	65	−
4h	3-Me	L-Ile	>135	78	−
4i	3-Me	D-Ile	>135	37	−
4j	3-Me	L-Phe	≥129	35	−
4k	3-Me	D-Phe	46.5 ± 19.3	66	1.4
4l	3-Me	L-Pro	≥138	36	−
4m	3-Me	D-Pro	≥138	38	−
1			>300	225	−
ACV			6.75 ± 2.62	392	58

[a] 50% effective concentration blocking EBV-DNA synthesis. [b] 50% cytotoxic concentration. [c] Selectivity index = CC$_{50}$ (μM)/EC$_{50}$ (μM).

against EBV were 5-methoxy-*cyclo*Sal-BVDUMP **2c** (>90-fold more active as compared to BVDU **1**) and 3-methyl-*cyclo*Sal-BVDUMP **2d** (>73-fold more active). Both compounds are at least as active as the reference compound ACV. Interestingly, as in our previously reported results on *cyclo*Sal-d4TMP triesters, we noticed a clear correlation between antiviral activity, the hydrolysis rates and the substituents in the *cyclo*Sal moiety.[20a]

In contrast to triesters **2**, all 3′-ester derivatives **3** proved to be antivirally inactive. At least for compounds **3a** and **3g** this failure in antiviral activity is somewhat surprising because in the cell extract studies both compounds released the antivirally active triester **2d** in some amounts as well as BVDUMP. However, the

formed BVDUMP amounts from both triesters **3a**,**g** were found to be markedly lower as compared to the prototype triesters **2c**,**d**. In addition, both led also to the formation of 3′-*O*-acyl-BVDUMP in (nearly) comparable amounts. Compounds bearing branched or highly lipophilic ester groups led dominantly to the corresponding 3′-*O*-acyl-BVDUMP derivatives or proved to be hydrolytically too stable in order to release BVDUMP in a reasonable amount (Table 2, <7% BVDUMP in 8 h).

Quite intriguing was the behavior of the α-aminoacyl bearing triesters **4**. Although all compounds completely lost their aminoacyl residue in the cell extracts to yield the prototype triester **2d**, only four triesters showed some antiviral effect in the assay. The most active compound was 3-methyl-*cyclo*Sal-(3′-Leu)BVDUMP **4f** having the natural L-configuration. However, this compound was found to be 5-fold less active than the prototype **2d** (Table 3). In contrast, the corresponding D-Leu triester **4g** was completely inactive. To some extend this is also valid for the 3′-Ala triesters **4b** and **4c**: here both L- or the D-configured triesters showed some antiviral potential. Moreover, the glycine and the D-Phe derivatives **4a** and **4k** showed some anti-EBV activity although 10-fold lower as compared to triester **2d**. It is interesting to note that the L-Phe triester **4j** was devoid of any antiviral potency. The reason for this unexpected effect of the stereochemistry remains unknown and cannot be correlated with the results of the chemical hydrolysis and the cell extract studies. The same stands for the reasons for the entire inactivity of both diastereomers of the amino acids Val, Ile, and Pro. Assuming that the results obtained from the cell extract studies reflect at least somehow the intracellular medium, one explanation may be a strong impact of the attached amino acid on the cellular uptake (active instead of passive?) of triesters **4**. Further studies have to be done in order to shed light on this unexpected outcome of the antiviral tests. Moreover, it is interesting to note that the aminoacyl derivatives **4** showed 2- to 3-fold lower CC_{50} values as compared to the prototype triesters **2** for some unknown reasons.

Although it is known that EBV has a thymidine kinase, the above data show that just the delivery of BVDUMP is sufficient to convert BVDU into an anti-EBV active drug. Consequently, EBV-TK is obviously not able to phosphorylate BVDU. It cannot be deduced from the data, if further metabolism of BVDUMP into its triphosphate is absolutely necessary for the biological activity. Possibly, BVDUMP itself is responsible for the biological effect. Moreover, the complete inactivity of the 3′-ester derivatives in contrast to the prototype triesters **2** demonstrates again that a free 3′-hydroxyl group is essential for the expression of the antiviral activity. This conclusion is further confirmed by the complete inactivity of 3-methyl-*cyclo*Sal-(3′-*O*-methyl)BVDUMP (data not shown).[28] As expected, this triester released the 3′-*O*-methyl ether of BVDUMP in the chemical hydrolysis with a half-life of 6.5 h. However, the ether linkage proved to be entirely stable.

Conclusion

In summary, from the hydrolytic and antiviral data disclosed here, the use of prototype *cyclo*Sal-BVDUMPs **2** provide an efficient method to deliver the nucleoside monophosphate BVDUMP intracellularly. The delivery mechanism is the same as reported before, e. g., for *cyclo*Sal-d4TMP,[21a] and thus proving that an intramolecular concurrent reaction of the secondary alcohol did not take place. Moreover, as a consequence, the anti-EBV inactive BVDU **1** was converted into a bioactive compound. The anti-EBV potency was found to be comparable or even higher than that of ACV. The point that the delivery of BVDUMP is sufficient to convert BVDU into a bioactive compound showed that the mechanism of action of the *cyclo*Sal compounds is based again on a successful bypass of a cellular or of a EBV TK. The antiviral evaluation proved that esterification of the 3′-hydroxy group by simple carboxylic acids abolished all biological activity for unknown reasons. Although delivery of BVDUMP from 3′-aminoacyl *cyclo*Sal-BVDUMPs **4** was clearly shown in chemical hydrolysis and cell extract studies, only a few proved to be antivirally active. The most active compound was the L-leucine derivative **4f**. The advantage of the α-amino acid bearing compounds was their higher solubility in aqueous media. Finally, to the best of our knowledge, the work reported here represents the first example of the application of a pronucleotide approach to a nucleoside analogue possessing a 3′-hydroxyl group with the result of a considerable improvement of antiviral activity.

Experimental Section

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions (argon atmosphere). Solvents: Anhydrous methylene chloride (CH_2Cl_2), anhydrous tetrahydrofurane (THF), and anhydrous acetonitrile (CH_3CN) were obtained in a Sure/Seal bottle from Fluka and stored over 4 Å molecular sieves; ethyl acetate, methylene chloride, and methanol employed in chromatography were distilled before use. Ethyldiisopropylamine (DIPEA) was distilled from Na prior to use. The solvents for the HPLC were obtained from Merck (acetonitrile, HPLC grade). Ion pairing buffer solution was prepared by mixing 6.6 mL of tetrabutylammonium hydroxide with 1000 mL of water. The pH-value adjusted to 3.8 by adding concentrated phosphoric acid (buffer I). To 60 mL of buffer I solution was added 1000 mL of water (buffer II). Evaporation of solvents was carried out on a rotary evaporator under reduced pressure or using a high-vacuum pump. Chromatography: Chromatotron (Harrison Research 7924), silica gel 60$_{Pf}$ (Merck, "gipshaltig"); UV detection at 254 nm. TLC: analytical thin-layer chromatography was performed on Merck precoated aluminum plates 60 F_{254} with a 0.2-mm layer of silica gel containing a fluorescence indicator; sugar-containing compounds were visualized with the sugar spray reagent (0.5 mL of 4-methoxybenzaldehyde, 9 mL of ethanol, 0.5 mL of concentrated sulfuric acid, and 0.1 mL of glacial acectic acid) by heating with a fan or a hot plate. HPLC: (Merck-Hitachi) analytical HPLC, LiChroCART 250-3 with LiChrospher 100 RP-18 endcapped (5 μm), gradient I 12–80% CH_3CN (0–20 min), 12% CH_3CN (20–35 min), flow 0.6 mL, UV detection at 250 nm; gradient II 8–100% CH_3CN (0–22 min), 100% CH_3CN (22–27 min), 8% CH_3CN (27–33 min), flow 0.6 mL, UV detection at 250 nm; gradient III same as II, instead of water the ion pairing buffer solution was used. NMR spectra were recorded using (^{1}H NMR) Bruker AC 250 at 250 MHz, Bruker WM 400 at 400 MHz, Bruker AMX 400 at 400 MHz or Bruker DMX 500 at 500 MHz (CDCl$_3$ or DMSO as internal standard); (^{13}C NMR) Bruker WM 400 at 101 MHz, Bruker AMX 400 at 101 MHz or Bruker DMX 500 at 123 MHz (CDCl$_3$ or DMSO as internal standard); (^{31}P NMR) Bruker AMX 400 at 162 MHz or Bruker DMX 500 at 202 MHz (H$_3$-PO$_4$ as external standard). All ^{1}H and ^{13}C NMR chemical shifts

(δ) are quoted in parts per million (ppm) downfield from tetramethylsilane, (CD$_3$)(CD$_2$H)SO being set at δ_H 2.49 as a reference. ^{31}P NMR chemical shifts are quoted in ppm using H$_3$PO$_4$ as external reference. The spectra were recorded at room temperature, and all ^{13}C and ^{31}P NMR were recorded in proton-decoupled mode. UV spectra were taken with a Varian Cary 1E UV/Vis spectrometer. Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR or a ATI Mattson Genesis Series FT-IR spectrometer in KBr pellets. Mass spectra were obtained with a Finnigan electrospray MAT 95 Trap XL (ESI) or a VG Analytical VG/70−250 F spectrometer (FAB, matrix was *m*-nitrobenzyl alcohol). The test compounds were isolated as mixtures of diastereomers arising from the mixed stereochemistry at the phosphate center. The resulting lyophilized triesters did not gave useful microanalytical data most probably due to incomplete combustion of the compound, but were found to be pure by HPLC analysis, high-field multinuclear NMR spectroscopy, and mass spectroscopy.

5′-*O*-tert-Butyldimethylsilyl-(*E*)-5-(2-bromovinyl)-2′-deoxyuridine. To a solution of BVDU (3.00 mmol) in 25 mL of pyridine was added TBDMSCl (3.75 mmol), and the mixture was stirred for 14 h at room temperature. Then 2.0 mL MeOH were added, and the solvent was removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$, washed twice with water, and dried over sodium sulfate, and again the solvent was removed under reduced pressure. The residues were purified by chromatography on silica gel plates on a chromatotron using a gradient of CH$_3$OH in CH$_2$Cl$_2$. yield: 84%;^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H, NH); 7.78 (s, 1H, H6); 7.26 (d, 1H, H8); 6.81 (d, 1H, H7); 6.10 (t, 1H, H1′); 5.30 (d, 1H, OH); 4.19−4.17 (m, 1H, H3′); 3.76−3.74 (m, 3H, H4′, H5′); 2.20−2.09 (m, 2H, H2′); 0.86 (s, 9H, H3-TBDMS); 0.05 (s, 6H, H1-TBDMS); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.86 (C4); 149.41 (C2); 139.43 (C6); 130.09 (C7); 109.91 (C5); 107.11 (C8); 87.38 (C4′); 84.98 (C1′); 70.39 (C3′); 63.34 (C2′); 26.01 (C3-TBDMS); 18.27 (C2-TBDMS); −5.15 (C1-TBDMS); MS (FAB) *m/z* 447.2 (M + H$^+$); UV (CH$_3$CN) λ_{max} 251.0 nm, 295.0 nm; λ_{min} 216.0 nm, 270.0 nm; R_f value 0.53 (CH$_2$Cl$_2$/MeOH, 9:1).

General Procedure for the Preparation of 3′-Esterified BVDUs 5a−t. To a solution of 5′-TBDMS−BVDU (0.33 mmol), (dimethylamino)pyridine (0.66 mmol), and the carboxylic acid (0.37 mmol) in 5 mL of CH$_2$Cl$_2$ was added dicyclohexylcarbodiimide (0.37 mmol) at room temperature. The reaction mixture was stirred for 30 min (TLC analysis) and filtered, and the solvent was removed under reduced pressure. The residues were purified by chromatography on silica gel plates on a chromatotron using a gradient of MeOH in CH$_2$Cl$_2$. Product containing fractions were combined and evaporated. To a solution of the residue in THF was added 0.5 mL of a 1 M tetrabutylammonium fluoride solution in THF. The mixture was stirred for 4 h at room temperature. Then, the solvent was removed under reduced pressure. The residues were purified by chromatography on silica gel plates on a chromatotron using a gradient of MeOH in CH$_2$Cl$_2$ to yield compounds **5a−t**.

(*E*)-5-(2-Bromovinyl)-3′-*O*-acetyl-2′-deoxyuridine 5a: yield: 87%; ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.52 (s, 1H, NH); 7.90 (s, 1H, H6); 7.38 (d, 1H, H8); 6.68 (d, 1H, H7); 6.32 (dd, 1H, H1′); 5.39−5.33 (m, 1H, H3′); 4.15 (dt, 1H, H4′); 3.99−3.97 (m, 2H, H5′); 2.49 (ddd, 1H, H2″); 2.35 (ddd, 1H, H2′); 2.12 (s, 3H, CH$_3$); ^{13}C NMR (63 MHz, CDCl$_3$) 170.69 (C1-Ac); 160.86 (C4); 149.01 (C2); 137.94 (C6); 128.23 (C7); 111.72 (C5); 109.98 (C8); 85.95 (C4′); 85.34 (C1′); 74.54 (C3′); 62.55 (C5′); 38.00 (C2′); 20.97 (C2-Ac); UV (CH$_3$CN) λ_{max} 251.0 nm, 287.0 nm; λ_{min} 214.0 nm; 268.0 nm; R_f value 0.66 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-propionyl-2′-deoxyuridine 5b: yield 97%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H, H6); 7.24 (d, 1H, H8); 6.83 (d, 1H, H7); 6.14 (dd, 1H, H1′); 5.35−5.10 (m, 2H, H3′, OH); 4.00 (s, 1H, H4′); 3.66−3.58 (m, 2H, H5′); 2.35−2.27 (m, 4H, H2′, H2-Prop); 1.02 (t, 3H, H3-Prop); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.52 (C1-Prop); 161.84 (C4); 149.52 (C2); 139.36 (C6); 129.98 (C7); 110.26 (C5);

107.07 (C8); 85.27 (C4′); 84.71 (C1′); 74.63 (C3′); 61.42 (C5′); 37.30 (C2′); 27.03 (C2-Prop); 9.03 (C3-Prop); R_f value 0.59 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-*i*-butyryl-2′-deoxyuridine 5c: yield 98%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (s, 1H, H6); 7.24 (d, 1H, H8); 6.66 (d, 1H, H7); 6.25 (dd, 1H, H1′); 5.24−5.22 (m, 1H, H3′); 4.01 (dt, H4′); 3.80−3.78 (m, 2H, H5′); 2.49 (sept, 1H, H2-Iso); 2.35 (ddd, 1H, H2″); 2.23 (ddd, 1H, H2′); 1.10 (d, 6H, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 177.01 (C1-Iso); 161.81 (C4); 149.49 (C2); 138.07 (C6); 128.34 (C7); 111.53 (C5); 108.94 (C8); 85.69 (C4′); 85.25 (C1′); 74.85 (C3′); 61.73 (C5′); 38.07 (C2′); 33.69 (C2-Iso); 18.52 (C3-Iso); 18.50 (C3-Iso). R_f value 0.51 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-pivaloyl-2′-deoxyuridine 5d: yield 77%; ^{1}H NMR (250 MHz, CDCl$_3$) δ 9.12 (s, 1H, NH-BVU); 7.93 (s, 1H, H6); 7.39; 7.33 (d, 1H, H8); 6.71−6.66 (d, 1H, H7); 6.31 (dd, 1H, H1′); 5.37−5.32 (m, 1H, H3′); 4.08 (dt, H4′); 3.98 (m, 2H, H5′); 2.49 (ddd, 1H, H2″); 2.37 (ddd, 1H, H2′); 1.23 (s, 9H, 3x CH$_3$); ^{13}C NMR (63 MHz, CDCl$_3$) δ 178.44 (C1−Piv); 161.26 (C4); 149.20 (C2); 138.08 (C6); 128.23 (C7); 111.69 (C5); 109.89 (C8); 85.96 (C4′); 85.60 (C1′); 74.32 (C3′); 62.49 (C5′); 38.68 (C2−Piv); 38.00 (C2′); 26.99 (C3−Piv); R_f value 0.68 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-hexanoyl-2′-deoxyuridine 5e: yield 65%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.60 (s, 1H, NH-BVU); 8.06 (s, 1H, H6); 7.24 (d, 1H, H8); 6.83 (d, 1H, H7); 6.14 (t, 1H, H1′); 5.22 (t, 2H, H3′, OH); 3.99 (s, 1H, H4′); 3.68−3.61 (m, 2H, H5′); 2.34−2.26 (m, 4H, H2′, H2-Hex); 1.54 (quin, 2H, H3-Hex); 1.28−1.25 (m, 4H, H4-Hex, H5-Hex); 0.85 (t, 3H, H6-Hex); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.75 (C1-Hex); 161.80 (C4); 149.47 (C2); 139.33 (C6); 129.96 (C7); 110.21 (C5); 107.00 (C8); 85.19 (C4′); 84.64 (C1′); 74.52 (C3′); 61.37 (C5′); 37.24 (C2′); 33.58 (C2-Hex); 30.79 (C4-Hex); 24.19 (C3-Hex); 21.96 (C5-Hex); 13.97 (C6-Hex); R_f value 0.68 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-decanoyl-2′-deoxyuridine 5f: yield 87%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H, NH-BVU); 8.06 (s, 1H, H6); 7.24 (d, 1H, H8); 6.83 (d, 1H, H7); 6.14 (dd, 1H, H1′); 5.25−5.20 (m, 2H, H3′, OH); 3.99 (dt, 1H, H4′); 3.70−3.57 (m, 2H, H5′); 2.37−2.22 (m, 4H, H2′, H2-Dec); 1.55−1.45 (m, 2H, H3-Dec); 1.30−1.20 (m, 12H, H4-Dec−H9-Dec); 0.85 (t, 3H, H10-Dec); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.78 (C1-Dec); 161.83 (C4); 149.50 (C2); 139.35 (C6); 129.98 (C7); 110.24 (C5); 107.03 (C8); 85.23 (C4′); 84.67 (C1′); 74.54 (C3′); 61.39 (C5′); 37.26 (C2′); 33.64 (C2-Dec); 31.47 (C3-Dec); 29.04; 28.85; 28.61 (C4-Dec−C8-Dec); 22.31 (C9-Dec); 14.15 (C10-Dec); R_f value 0.69 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-levulinyl-2′-deoxyuridine 5g: yield 88%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06 (s, 1H, H6); 7.24 (d, 1H, H8); 6.83 (d, 1H, H7); 6.13 (dd, 1H, H1′); 5.22 (s, 1H, OH); 5.19 (dt, 1H, H3′); 3.98 (dt, 1H, H4′); 3.61 (m, 2H, H5′); 2.72 (t, 2H, H2-Lev); 2.48 (m, 2H, H3-Lev); 2.31 (ddd, 1H, H2″); 2.25 (ddd, 1H, H2′); 2.09 (s, 3H, H5-Lev); ^{13}C NMR (101 MHz, DMSO-d_6) δ 207.08 (C4-Lev); 172.17 (C1-Lev); 161.81 (C4); 149.49 (C2); 139.35 (C6); 129.95 (C7); 110.21 (C5); 106.99 (C8); 85.09 (C4′); 84.65 (C1′); 74.75 (C3′); 61.36 (C5′); 37.62 (C3-Lev); 37.11 (C2′); 29.70 (C5-Lev); 27.92 (C2-Lev); R_f value 0.44 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-glycinyl)-2′-deoxyuridine 5h: yield 63%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H, H6); 7.24 (d, 2H, H8, NH-Gly); 6.83 (d, 1H, H7); 6.16 (t, 1H, H1′); 5.35−5.10 (m, 2H, H3′, OH); 4.00 (s, 1H, H4′); 3.75−3.55 (m, 4H, H5′, H2-Gly); 2.36−2.23 (m, 2H, H2′); 1.38 (s, 9H, H3-Boc); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.21 (C1-Gly); 161.82 (C4); 156.09 (C1-Boc); 149.48 (C2); 139.32 (C6); 129.97 (C7); 110.25 (C5); 107.03 (C8); 85.12 (C4′); 84.62 (C1′); 78.54 (C2-Boc); 75.21 (C3′); 61.36 (C5′); 42.38 (C2-Gly); 37.16 (C2′); 28.33 (C3-Boc); R_f value 0.48 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-L-alaninyl)-2′-deoxyuridine 5i: yield 69%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H, NH-BVU); 8.06 (s, 1H, H6); 7.37 (d, 1H, NH-Ala); 7.24 (d, 1H, H8); 6.83 (d, 1H, H7); 6.17 (t, 1H, H1′); 5.30−5.20 (m, 2H, H3′, OH); 4.02−3.95 (m, 2H, H4′, H2-Ala); 3.67−3.59 (m, 2H, H5′); 2.36−2.07 (m, 2H, H2′); 1.37 (s, 9H, H3-Boc); 1.24

(d, 3H, H3-Ala); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.89 (C1-Ala); 161.80 (C4); 155.53 (C1-Boc); 149.46 (C2); 139.32 (C6); 129.95 (C7); 110.24 (C5); 107.00 (C8); 85.18 (C4′); 84.54 (C1′); 78.46 (C2-Boc); 75.12 (C3′); 61.38 (C5′); 49.44 (C2-Ala); 37.06 (C2′); 28.31 (C3-Boc); 16.70 (C3-Ala); R_f value 0.55 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-D-alaninester)-2′-deoxyuridine 5j: yield 60%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H, NH-BVU); 8.06 (s, 1H, H6); 7.37 (d, 1H, NH-Ala); 7.24 (d, 1H, H8); 6.83 (d, 1H, H7); 6.17 (t, 1H, H1′); 5.26−5.21 (m, 2H, H3′, OH); 4.02−3.96 (m, 2H, H4′, H2-Ala); 3.68−3.59 (m, 2H, H5′); 2.36−2.20 (m, 2H, H2′); 1.37 (s, 9H, H3-Boc); 1.24 (d, 3H, H3-Ala); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.89 (C1-Ala); 161.80 (C4); 155.53 (C1-Boc); 149.46 (C2); 139.32 (C6); 129.95 (C7); 110.24 (C5); 107.00 (C8); 85.18 (C4′); 84.54 (C1′); 78.46 (C2-Boc); 75.12 (C3′); 61.38 (C5′); 49.44 (C2-Ala); 37.06 (C2′); 28.31 (C3-Boc); 16.70 (C3-Ala); R_f value 0.57 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-L-valinyl)-2′-deoxyuridine 5k: yield 97%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1H, NH-BVU); 7.94 (s, 1H, H6); 7.33 (d, 1H, H8); 6.66 (d, 1H, H7); 6.28 (dd, 1H, H1′); 5.43 (dt, 2H, H3′); 5.11 (d, 1H, OH); 4.19 (dd, 1H, H2-Val); 4.11 (dt, 1H, H4′); 3.94 (ddd, H5′); 3.93 (ddd, 1H, H5′′); 2.52 (ddd, 1H, H2′); 2.42 (ddd, 1H, H2′′); 2.18−2.10 (m, 2H, H3-Val); 1.45 (s, 9H, H3-Boc); 0.99 (d, 3H, H4-Val); 0.91 (d, 3H, H4′-Val); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.21 (C1-Val); 161.62 (C4); 155.81 (C1-Boc); 149.34 (C2); 138.26 (C6); 128.25 (C7); 111.59 (C5); 109.72 (C8); 86.07 (C1′); 85.43 (C4′); 80.23 (C2-Boc); 75.29 (C3′); 62.23 (C5′); 58.39 (C2-Val); 37.89 (C2′); 30.83 (C3-Val); 28.25 (C3-Boc); 19.09; 17.62 (C4-Val). R_f value 0.56 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-D-valinyl)-2′-deoxyuridine 5l: yield 97%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (s, 1H, NH-BVU); 7.92 (s, 1H, H6); 7.35 (d, 1H, H8); 6.69 (d, 1H, H7); 6.28 (dd, 1H, H1′); 5.43−5.40 (m, 2H, H3′); 5.07−5.00 (m, 1H, OH); 4.21−4.16 (m, 2H, H4′, H2-Val); 4.01−3.93 (m, 2H, H5′); 2.48 (ddd, 1H, H2′); 2.41 (ddd, 1H, H2′′); 2.18−2.10 (m, 2H, H3-Val); 1.46 (s, 9H, H3-Boc); 1.00 (d, 3H, H4-Val); 0.93 (d, 3H, H4′-Val); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.40 (C1-Val); 161.36 (C4); 155.79 (C1-Boc); 149.21 (C2); 138.02 (C6); 128.28 (C7); 111.63 (C5); 109.81 (C8); 85.97 (C1′); 85.29 (C4′); 80.21 (C2-Boc); 74.98 (C3′); 62.17 (C5′); 58.69 (C2-Val); 38.04 (C2′); 30.94 (C3-Val); 28.28 (C3-Boc); 19.09; 17.64 (C4-Val); R_f value 0.64 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-L-leucinyl)-2′-deoxyuridine 5m: yield 94%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (s, 1H, NH-BVU); 7.94 (s, 1H, H6); 7.34 (d, 1H, H8); 6.83 (d, 1H, H7); 6.30 (dd, 1H, H1′); 5.45−5.40 (m, 2H, H3′); 4.98 (s, 1H, OH); 4.43 (dt, 1H, H2-Leu); 4.15−4.05 (m, 1H, H4′); 3.98−3.87 (m, 2H, H5′); 2.55−2.35 (m, 2H, H2′); 1.80−1.66 (m, 1H, H4-Leu); 1.65−1.49 (m, 2H, H3-Leu); 1.45 (s, 9H, H3-Boc); 0.96 (d, 6H, H5-Leu); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.29 (C1-Leu); 161.38 (C4); 155.57 (C1-Boc); 149.28 (C2); 138.25 (C6); 128.26 (C7); 111.65 (C5); 109.78 (C8); 86.09 (C1′); 85.42 (C4′); 80.29 (C2-Boc); 75.29 (C3′); 62.32 (C5′); 52.30 (C2-Leu); 40.98 (C3-Leu); 37.86 (C2′); 28.27 (C3-Boc); 24.84 (C4-Leu); 22.84; 21.67 (C5-Leu). R_f value 0.42 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-D-leucinyl)-2′-deoxyuridine 5n: yield 99%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (s, 1H, NH-BVU); 7.94 (s, 1H, H6); 7.35 (d, 1H, H8); 6.68 (d, 1H, H7); 6.29 (dd, 1H, H1′); 5.45−5.40 (m, 2H, H3′); 4.98 (d, 1H, OH); 4.27 (m, 1H, H2-Leu); 4.19−4.13 (m, 1H, H4′); 4.00−3.92 (m, 2H, H5′); 2.49 (ddd, 1H, H2′); 2.39 (ddd, 1H, H2′′); 1.76−1.68 (m, 1H, H4-Leu); 1.64−1.50 (m, 2H, H3-Leu); 1.44 (s, 9H, H3-Boc); 0.97 (d, 6H, H4-Leu); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.50 (C1-Leu); 161.40 (C4); 155.55 (C1-Boc); 149.22 (C2); 138.14 (C6); 128.27 (C7); 111.61 (C5); 109.81 (C8); 85.97 (C1′); 85.32 (C4′); 80.27 (C2-Boc); 74.97 (C3′); 62.20 (C5′); 52.25 (C2-Leu); 41.07 (C3-Leu); 37.99 (C2′); 28.28 (C3-Boc); 24.86 (C4-Leu); 22.83; 21.73 (C5-Leu); R_f value 0.42 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-L-isoleucinyl)-2′-deoxyuridine 5o: yield 99%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.30 (s, 1H, NH-BVU); 7.92 (s, 1H, H6); 7.35 (d, 1H, H8); 6.67 (d, 1H, H7); 6.28 (dd, 1H, H1′); 5.42 (m, 2H, H3′); 5.06 (d, 1H, NH-Ile); 4.23 (dd, 1H, H2-Ile); 4.12 (m, 1H, H4′); 3.95 (m, 2H, H5′); 2.45 (m, 2H, H2′); 1.88 (m, 1H, H3-Ile); 1.45 (s, 9H, H3-Boc); 1.17 (m, 1H, H5-Ile); 0.95 (m, 6H, H4-Ile, H6-Ile); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.199 (C1-Ile); 161.36 (C4); 155.68 (C1-Boc); 149.20 (C2); 138.19 (C6); 128.25 (C7); 111.63 (C5); 109.84 (C8); 86.15 (C1′); 85.34 (C4′); 80.24 (C2-Boc); 75.18 (C3′); 62.30 (C5′); 58.06 (C2-Ile); 37.89 (C2′); 37.53 (C3-Ile); 28.28 (C3-Boc); 25.16 (C5-Ile); 15.69 (C6-Ile); 11.57 (C4-Ile). R_f value 0.60 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-D-isoleucinyl)-2′-deoxyuridine 5p: yield 99%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.30 (s, 1H, NH-BVU); 7.94 (s, 1H, H6); 7.35 (d, 1H, H8); 6.67 (d, 1H, H7); 6.28 (dd, 1H, H1′); 5.42 (m, 2H, H3′); 5.08 (d, 1H, NH-Ile); 4.25 (dd, 1H, H2-Ile); 4.17 (m, 1H, H4′); 3.97 (m, 2H, H5′); 2.48 (m, 2H, H2′); 1.88 (m, 1H, H3-Ile); 1.45 (s, 9H, H3-Boc); 1.17 (m, 1H, H5-Ile); 0.95 (m, 6H, H4-Ile, H6-Ile); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.40 (C1-Ile); 161.44 (C4); 155.70 (C1-Boc); 149.21 (C2); 138.13 (C6); 128.27 (C7); 111.57 (C5); 109.80 (C8); 85.93 (C1′); 85.26 (C4′); 80.21 (C2-Boc); 74.95 (C3′); 62.16 (C5′); 58.01 (C2-Ile); 38.03 (C2′); 37.63 (C3-Ile); 28.28 (C3-Boc); 25.10 (C5-Ile); 15.65 (C6-Ile); 11.56 (C4-Ile); R_f value 0.60 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-L-phenylalaninyl)-2′-deoxyuridine 5q: yield 54%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H, H6); 7.42 (d, 1H, NH-Phe); 7.25 (m, 6H, H8, H-aryl-Phe); 6.83 (d, 1H, H7); 6.12 (t, 1H, H1′); 5.35−5.10 (m, 2H, H3′, OH); 4.19−4.12 (m, 1H, H2-Phe); 3.80−3.75 (m, 1H, H4′); 3.58 (ddd, 1H, H5′); 3.59 (ddd, 1H, H5′); 2.32−2.21 (m, 2H, H2′); 1.34 (s, 9H, H3-Boc); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.21 (C1-Phe); 161.79 (C4); 155.65 (C1-Boc); 149.44 (C2); 139.31 (C6); 137.52 (C4-Phe); 129.95 (C7); 129.31 (C5-Phe); 128.41 (C4-Phe); 126.70 (C6-Phe); 110.23 (C5); 106.99 (C8); 85.01 (C4′); 84.52 (C1′); 78.64 (C2-Boc); 75.23 (C3′); 61.35 (C5′); 55.68 (C2-Phe); 37.15 (C2′, C3-Phe); 28.26 (C3-Boc); R_f value 0.66 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-D-phenylalaninyl)-2′-deoxyuridine 5r: yield 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H, NH-BVU); 7.79 (s, 1H, H6); 7.27 (m, 6H, H8, H-aryl-Phe); 6.83 (d, 1H, H7); 6.06 (t, 1H, H1′); 5.25−5.15 (m, 2H, H3′); 5.05−4.92 (m, 1H, OH); 4.43 (dt, 1H, H2-Phe); 3.98−3.95 (m, 1H, H4′); 3.86−3.74 (m, 2H, H5′); 2.25−2.08 (m, 2H, H2′); 1.32 (s, 9H, H3-Boc); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.92 (C1-Phe); 161.38 (C4); 155.15 (C1-Boc); 149.19 (C2); 138.21 (C6); 135.60 (C4-Phe); 129.18 (C7); 128.73 (C5$_{Ph3}$); 128.26 (C4-Phe); 127.30 (C6-Phe); 111.59 (C5); 109.80 (C8); 86.04 (C1′); 85.19 (C4′); 80.39 (C2-Boc); 75.22 (C3′); 62.15 (C5′); 54.63 (C2-Phe); 38.24 (C2′); 37.73 (C3-Phe); 28.23 (C3-Boc); R_f value 0.76 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-L-prolinyl)-2′-deoxyuridine 5s: yield 94%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.00 (s, 1H, NH-BVU); 7.92 (s, 1H, H6); 7.35 (d, 1H, H8); 6.69 (d, 1H, H7); 6.30 (m, 1H, H1′); 5.42 (m, 1H, H3′); 4.32 (dd, 1H, H2-Pro); 4.25 (m, 1H, H4′); 3.95 (m, 2H, H5′); 3.50 (m, 2H, H5-Pro); 2.45 (m, 2H, H2′); 1.94 (m, 4H, H3-Pro, H4-Pro); 1.46 (s, 9H, H3-Boc); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.77 (C1-Pro); 161.36 (C4); 154.53 (C1-Boc); 149.21 (C2); 138.25 (C6); 128.26 (C7); 111.63 (C5); 109.75 (C8); 85.91 (C1′); 85.50 (C4′); 80.31 (C2-Boc); 75.27 (C3′); 62.40 (C5′); 58.93 (C2-Pro); 37.93 (C2′); 30.88 (C3-Pro); 29.89 (C5-Pro); 28.36 (C3-Boc); 24.50 (C4-Pro); R_f value 0.71 (CH$_2$Cl$_2$/MeOH, 9:1).

(*E*)-5-(2-Bromovinyl)-3′-*O*-(*N*-Boc-D-prolinyl)-2′-deoxyuridine, 5t: yield 92%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.00 (s, 1H, NH-BVU); 7.92 (s, 1H, H6); 7.35 (d, 1H, H8); 6.69 (d, 1H, H7); 6.30 (m, 1H, H1′); 5.42 (m, 1H, H3′); 4.30 (dd, 1H, H2-Pro); 4.25 (m, 1H, H4′); 3.95 (m, 2H, H5′); 3.50 (m, 2H, H5-Pro); 2.45 (m, 2H, H2′); 1.91 (m, 4H, H3-Pro, H4-Pro); 1.46 (s, 9H, H3-Boc); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.77 (C1-Pro); 161.36 (C4); 154.53 (C1-Boc); 149.21 (C2); 138.25 (C6); 128.21 (C7); 111.73 (C5); 109.71 (C8); 85.89 (C1′); 85.55 (C4′); 80.31 (C2-Boc); 75.27 (C3′); 62.43 (C5′); 58.93 (C2-Pro); 37.93 (C2′); 30.88 (C3-Pro); 29.89 (C5-Pro); 28.36 (C3-Boc); 24.50 (C4-Pro); R_f value 0.71 (CH$_2$Cl$_2$/MeOH, 9:1).

General Procedure for the Preparation of the *cy-cloSal*-(3′-*O*-Lev)BVDUMPs 6a–f. To a solution of 3′-*O*-levulinyl BVDU **5g** (0.28 mmol) in 10 mL of CH₃CN was added diisopropylethylamine (0.56 mmol, DIPEA), and the mixture was cooled to −20 °C. The chlorophosphanes (0.56 mmol) were added slowly, and the solution was stirred for 20 min to complete the reaction (TLC analysis). For the oxidation, *tert*-butyl hydroperoxide (0.56 mmol) was added to the reaction mixture at −20 °C. After being stirred for 0.5 h, the reaction mixture was warmed to room temperature, and the solvent was removed under reduced pressure. The reaction mixtures were purified twice by chromatotron chromatography on silica gel plates using first a gradient of CH₃OH in ethyl acetate followed by a gradient of CH₃OH in CH₂Cl₂ to yield *cyclo*Sal-3′-*O*-Lev-BVDUMP triesters **6**.

***cyclo*(5-Chlorosaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-levulinyl-2′-deoxyuridinyl)phosphate (5-Cl-*cyclo*Sal-3′-*O*-Lev-BVDUMP) 6a:** yield 54%; ¹H NMR (500 MHz, CDCl₃) δ 9.02 (s, 2H, NH-BVU); 7.72 (s, 2H, H6); 7.45 (d, 1H, H8); 7.43 (d, 1H, H8); 7.33 (s, 1H, H4-aryl); 7.31 (s, 1H, H4-aryl); 7.14 (d, 1H, H6-aryl); 7.13 (d, 1H, H6-aryl); 7.04 (d, 1H, H3-aryl); 7.03 (d, 1H, H3-aryl); 6.75 (d, 1H, H7); 6.71 (d, 1H, H7); 6.31 (dd, 1H, H1′); 6.29 (dd, 1H, H1′); 5.47−5.27 (m, 6H, H-benzyl, H3′); 4.56−4.45 (m, 4H, H5′); 4.23 (m, 2H, H4′); 2.84−2.72 (m, 4H, H2-Lev); 2.63−2.51 (m, 4H, H3-Lev); 2.21 (s, 3H, H5-Lev); 2.20 (s, 3H, H5-Lev); 2.14−2.05 (m, 4H, H2′); ¹³C NMR (101 MHz, CDCl₃) δ 206.47 (C4-Lev); 172.41 (C1-Lev); 172.38 (C1-Lev); 161.67 (C4); 161.63 (C4); 156.27 (C5-aryl); 156.24 (C5-aryl); 149.18 (C2); 143.50 (C2-aryl); 143.42 (C2-aryl); 137.08 (C4-aryl); 128.09 (C7); 121.47 (C1-aryl); 121.32 (C1-aryl); 119.39 (C3-aryl); 119.30 (C3-aryl); 111.89 (C8); 111.82 (C8); 110.41 (C5aryl); 110.29 (C5); 110.16 (C5); 85.27 (C1′); 85.23 (C1′); 83.10 (C4′); 83.04 (C4′); 74.35 (C3′); 74.22 (C3′); 68.75 (C5′); 68.63 (C5′); 67.96 (d, C-benzyl); 67.79 (d, C-benzyl); 37.79 (C2′); 37.72 (C3-Lev); 37.70 (C2′); 29.69 (C5-Lev); 27.76 (C2-Lev); ³¹P NMR (202 MHz, CDCl₃) δ −7.90; −7.97; *R_f* value 0.53 (CH₂Cl₂/MeOH, 9:1).

***cyclo*Saligenyl-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-levulinyl-2′-deoxyuridinyl)phosphate (*cyclo*Sal-3′-*O*-Lev-BVDUMP) 6b:** yield 39%; ¹H NMR (500 MHz, CDCl₃) δ 8.75 (s, 1H, NH-BVU); 8.74 (s, 1H, NH-BVU); 7.73 (s, 1H, H6); 7.72 (s, 1H, H6); 7.46 (d, 1H, H8); 7.43 (d, 1H, H8); 7.35 (dd, 2H, H4-aryl); 7.19−7.08 (m, 6H, H3-aryl, H5-aryl, H6-aryl); 6.76 (d, 1H, H7); 6.69 (d, 1H, H7); 6.32 (dd, 1H, H1′); 6.30 (dd, 1H, H1′); 5.49 (dd, 1H, H_A-benzyl); 5.45 (dd, 1H, H_B-benzyl); 5.36 (dd, 1H, H_A-benzyl); 5.34 (dd, 1H, H_B-benzyl); 5.29 (m, 2H, H3′); 4.55−4.46 (m, 4H, H5′); 4.25−4.22 (m, 2H, H4′); 2.84−2.72 (m, 4H, H3-Lev); 2.63−2.49 (m, 4H, H2-Lev); 2.21 (s, 3H, H5-Lev); 2.53 (ddd, 2H, H2′′); 2.20 (s, 3H, H5-Lev); 2.08 (ddd, 2H, H2′); ¹³C NMR (101 MHz, CDCl₃) δ 206.32 (C4-Lev); 172.43 (C1-Lev); 172.40 (C1-Lev); 160.96 (C4); 160.94 (C4); 149.96 (d, C2-aryl); 149.93 (d, C2-aryl); 148.96 (C2); 136.84 (C6); 136.83 (C6); 130.27 (C4-aryl); 128.10 (C7); 125.55 (C5-aryl); 124.81 (C6-aryl); 124.77 (C6-aryl); 118.63 (C3-aryl); 118.55 (C3-aryl); 112.02 (C8); 111.98 (C8); 110.44 (C5); 110.30 (C5); 85.26 (C1′), 85.15 (C1′); 83.11 (d, C4′); 83.04 (d, C4′); 74.34 (C3′); 74.24 (C3′); 68.71 (d, C5′); 68.62 (d, C5′); 68.04 (d, C-benzyl); 67.88 (d, C-benzyl); 37.82 (C2′); 37.75 (C3-Lev); 29.72 (C5-Lev); 27.79 (C4-Lev); ³¹P NMR (202 MHz, CDCl₃) δ −7.90; −7.97; *R_f* value 0.51 (CH₂Cl₂/MeOH, 9:1).

***cyclo*(5-Methoxysaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-levulinyl-2′-deoxyuridinyl)phosphate (5-OMe-*cyclo*Sal-3′-*O*-Lev-BVDUMP) 6c:** yield 70%; ¹H NMR (500 MHz, CDCl₃) δ 9.71 (s, 2H, NH-BVU); 7.73 (s, 1H, H6); 7.72 (s, 1H, H6); 7.43 (d, 1H, H8); 7.39 (d, 1H, H8); 7.00 (d, 1H, H4-aryl); 6.99 (d, 1H, H4-aryl); 6.85 (d, 1H, H6-aryl); 6.83 (d, 1H, H6-aryl); 6.75 (d, 1H, H7); 6.69 (d, 1H, H7); 6.62 (d, 1H, H3-aryl); 6.61 (d, 1H, H3-aryl); 6.30 (dd, 1H, H1′); 6.29 (dd, 1H, H1′); 5.46−5.24 (m, 6H, H-benzyl, H3′); 4.52−4.44 (m, 4H, H5′); 4.23−4.20 (m, 2H, H4′); 3.77 (s, 6H, OMe); 2.79−2.75 (m, 4H, H3-Lev); 2.59−2.48 (m, 6H, H2-Lev, H3′); 2.19 (s, 6H, H5-Lev); 2.12−2.02 (m, 4H, H2′); ¹³C NMR (101 MHz, CDCl₃) δ 206.47 (C4-Lev); 172.41 (C1-Lev); 172.38 (C1-Lev); 161.67 (C4); 161.63 (C4); 156.27 (C5-aryl); 156.24 (C5-aryl); 149.18 (C2); 143.50

(d, C2-aryl); 143.42 (d, C2-aryl); 137.08 (C4-aryl); 128.09 (C7); 121.47 (d, C1-aryl); 121.32 (d, C1-aryl); 119.39 (C3-aryl); 119.30 (C3-aryl); 111.89 (C8); 111.82 (C8); 110.41 (C5-aryl); 110.29 (C5); 110.16 (C5); 85.27 (C1′), 85.23 (C1′); 83.10 (d, C4′); 83.04 (d, C4′); 74.35 (C3′); 74.22 (C3′); 68.75 (d, C5′); 68.63 (d, C5′); 67.96 (d, C-benzyl); 67.79 (d, C-benzyl); 55.73 (OMe); 37.79 (C2′); 37.72 (C3-Lev); 37.70 (C2′); 29.69 (C5-Lev); 27.76 (C2-Lev); ³¹P NMR (202 MHz, CDCl₃) δ −7.24; −7.36; *R_f* value 0.61 (CH₂Cl₂/MeOH, 9:1).

***cyclo*(3,5-Dimethylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-levulinyl-2′-desoxyuridinyl)phosphate (3,5-DiMe-*cyclo*Sal-3′-*O*-Lev-BVDUMP) 6e:** yield 49%; ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 2H, NH-BVU); 7.75 (s, 1H, H6); 7.74 (s, 1H, H6); 7.45 (d, 1H, H8); 7.43 (d, 1H, H8); 7.00 (s, 2H, H4-aryl); 6.75 (m, 2H, H6-aryl); 6.72 (d, 1H, H7); 6.71 (d, 1H, H7); 6.32 (dd, 1H, H1′); 6.30 (dd, 1H, H1′); 5.46−5.19 (m, 6H, H-benzyl, H3′); 4.53−4.38 (m, 4H, H5′); 4.23 (dt, 1H, H4′); 4.21 (dt, 1H, H4′); 2.83−2.71 (m, 4H, H2-Lev); 2.61−2.55 (m, 4H, H3-Lev); 2.28 (s, 6H, H5-Lev); 2.23 (s, 6H, CH₃-C5-aryl); 2.19 (s, 6H, CH₃-C3-aryl); 2.22−2.00 (m, 4H, H2′); ¹³C NMR (101 MHz, CDCl₃) δ 206.37 (C4-Lev); 175.71 (C1-Lev); 172.39 (C1-Lev); 172.37 (C1-Lev); 161.41 (C4); 149.10 (C2); 136.98 (C6); 136.96 (C6); 134.03 (C5-aryl); 133.97 (C5-aryl); 132.18 (C4-aryl); 132.14 (C4-aryl); 128.07 (C7); 127.42 (d, C3-aryl); 127.34 (d, C3-aryl); 123.33 (C6-aryl); 120.25 (d, C2-aryl); 120.18 (d, C2-aryl); 111.99 (C8); 111.92 (C8); 110.37 (C5); 110.28 (C5); 85.32 (C4′); 85.20 (C4′); 83.16 (C1′); 83.10 (C1′); 74.47 (C3′); 74.36 (C3′); 68.87 (d, C5′); 68.81 (d, C5′); 67.89 (d, C-benzyl); 67.67 (d, C-benzyl); 37.80 (C2′); 37.74 (C3-Lev); 37.70 (C2′); 29.70 (C5-Lev); 27.78 (C4-Lev); 20.61 (CH₃-C5-aryl); 20.57 (CH₃-C5-aryl); 15.31 (CH₃-C3-aryl); 15.26 (CH₃-C3-aryl); ³¹P NMR (202 MHz, CDCl₃) δ -5.61; −5.91; *R_f* value 0.49 (CH₂-Cl₂/MeOH, 9:1).

***cyclo*(3-*t*Butylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-levulinyl-2′-deoxyuridinyl)phosphate (3-*t*Bu-*cyclo*Sal-3′-*O*-Lev-BVDUMP) 6f:** yield 50%; ¹H NMR (400 MHz, CDCl₃) δ 9.98 (s, 2H, NH-BVU); 7.78 (s, 2H, H6); 7.43 (d, 1H, H8); 7.42 (d, 1H, H8); 7.35 (d, 2H, H4-aryl); 7.10 (dd, 1H, H5-aryl); 7.00 (d, 2H, H6-aryl); 6.72 (d, 1H, H7); 6.72 (d, 1H, H7); 6.31 (dd, 1H, H1′); 6.30 (dd, 1H, H1′); 5.46−5.23 (m, 6H, H-benzyl, H3′); 4.59−4.39 (m, 4H, H5′); 4.22 (m, 2H, H4′); 2.84−2.70 (m, 4H, H2-Lev); 2.61−2.55 (m, 4H, H3-Lev); 2.18 (s, 6H, H5-Lev); 2.22−2.00 (m, 4H, CH₃-*t*Bu); 1.39 (s, 9H, CH₃-*t*Bu); 1.38 (s, 9H, CH₃-*t*Bu); ¹³C NMR (101 MHz, CDCl₃) δ 206.49 (C4-Lev); 206.46 (C4-Lev); 176.36 (C1-aryl); 172.36 (C1-Lev); 161.88 (C4); 161.85 (C4); 149.24 (C2); 139.49 (C); 139.42 (C); 137.17 (C6); 137.11 (C6); 128.02 (C7); 127.89 (C7); 124.46 (C); 124.38 (C); 123.81 (C6-aryl); 123.79 (C6-aryl); 122.10 (d, C2-aryl); 122.01 (d, C2-aryl); 111.93 (C8); 111.89 (C8); 110.35 (C5); 110.24 (C5); 85.34 (C4′); 85.04 (C4′); 83.11 (C1′); 83.01 (C1′); 74.29 (C3′); 74.23 (C3′); 68.80 (d, C5′); 68.73 (d, C5′); 68.19 (d, C-benzyl); 67.88 (d, C-benzyl); 53.39 (C7-aryl); 37.71 (C2′); 37.70 (C3-Lev); 37.63 (C2′); 29.75 (C8-aryl); 27.74 (C2-Lev); 20.69 (C5-Lev); ³¹P NMR (202 MHz, CDCl₃) δ −6.67; −7.21; *R_f* value 0.67 (CH₂Cl₂/MeOH, 9:1).

General Procedure for the Preparation of the *cyclo*Sal-BVDUMPs 2a–f. To a solution of the *cyclo*Sal-3′-*O*-Lev-BVDUMPs **6** (0.28 mmol) in 10 mL of pyridine was added a solution of hydrazine hydrate (13.3 mL, H₂NNH₂*H₂O (24%)/pyridine/CH₃COOH 2:4:3), and the reaction mixture was stirred for 5 min at room temperature. Then the solution was cooled to 0 °C, and 50 mL of ethyl acetate and 50 mL of water were added and mixed well. After separation, the organic phase was washed with 5% sodium hydrogencarbonate solution and dried with magnesium sulfate, and the solvent was removed under reduced pressure. The residues were purified by chromatography on silica gel plates on a chromatotron, using a gradient of CH₃OH in CH₂Cl₂ to yield the title compounds **2a–f**.

***cyclo*(5-Chlorsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxyuridinyl)phosphate (5-Cl-*cyclo*Sal-BVDUMP) 2a:** yield 91%; ¹H NMR (500 MHz, CDCl₃) δ 11.57 (s, 2H, NH-BVU); 7.77 (s, 1H, H6); 7.74 (s, 1H, H6); 7.40−7.37 (m, 4H, H3-aryl, H6-aryl); 7.28 (d, 1H, H8); 7.27 (d, 1H, H8); 7.14 (dd,

2H, H4-aryl); 6.86 (d, 1H, H7); 6.82 (d, 1H, H7); 6.15 (dd, 1H, H1′); 6.13 (dd, 1H, H1′); 5.52−5−38 (m, 4H, H-benzyl); 4.40−4.25 (m, 4H, H5′); 4.23−4.20 (m, 2H, H4′); 3.93−3.91 (m, 2H, H3′); 2.20−2.11 (m, 4H, H2′); ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.21 (C4); 156.19 (C5-aryl); 149.21 (C2); 143.20 (d, C2-aryl); 143.19 (d, C2-aryl); 137.29 (C4-aryl); 137.18 (C4-aryl); 128.31 (C7); 128.24 (C7); 121.20 (d, C1-aryl); 121.19 (d, C1-aryl); 119.20 (d, C3-aryl); 119.10 (d, C3-aryl); 111.31 (C8); 111.26 (C8); 110.33 (C5-aryl); 110.31 (C5-aryl); 109.40 (C5); 109.33 (C5); 85.30 (C1′); 85.20 (C1′); 84.75 (d, C4′); 84.52 (d, C4′); 69.72 (C3′); 69.35 (C3′), 68.74 (d, C5′); 68.64 (d, C5′); 67.37 (d, C-benzyl); 67.03 (d, C-benzyl); 40.31 (C2′); 40.19 (C2′); ^{31}P NMR (202 MHz, CDCl$_3$) δ −8.79; −8.89; MS (FAB) *m/z* 535.0; 537.0 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ$_{max}$ 289.6 nm, 248.0 nm; λ$_{min}$ 268.8 nm, 224.7 nm; R$_f$ value 0.23 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t$_R$ 13.36 min (98%, gradient II).

***cyclo*Saligenyl-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxyuridinyl)phosphate (*cyclo*Sal-BVDUMP) 2b:** yield 88%; ^{1}H NMR (500 MHz, CDCl$_3$/MeOD) δ 7.55 (s, 1H, H6); 7.52 (s, 1H, H6); 7.39 (d, 1H, H8); 7.34 (d, 1H, H8); 7.37−7.33 (m, 2H, H4-aryl); 7.21−7.14 (m, 4H, H3-aryl, H6-aryl); 7.10 (t, 2H, H5-aryl); 6.66 (d, 1H, H7); 6.56 (d, 1H, H7); 6.23 (dd, 4H, H1′) 5.47 (dd, 1H, H$_A$-benzyl); 5.46 (dd, 1H, H$_A$-benzyl); 5.39 (dd, 2H, H$_B$-benzyl); 4.49−4.40 (m, 6H, H5′, H4′); 4.09−4.06 (m, 2H, H3′); 2.43 (ddd, 1H, H2′); 2.40 (ddd, 1H, H2′); 2.14 (ddd, 1H, H2″); 2.09 (ddd, 1H, H2″); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.42 (C4); 149.11 (C2); 149.07 (C2); 146.24 (C2-aryl); 146.18 (C2-aryl); 137.42 (C6); 137.27 (C6); 134.19 (C5-aryl); 134.12 (C5-aryl); 132.27 (C4-aryl); 132.22 (C4-aryl); 128.26 (C7); 128.09 (C7); 127.42 (d, C3-aryl); 127.34 (d, C3-aryl); 123.52 (C6-aryl); 123.39 (C6-aryl); 120.35 (d, C2-aryl); 120.07 (d, C2-aryl); 111.45 (C8); 111.43 (C8); 110.09 (C5); 110.05 (C5); 85.55 (C1′); 85.28 (C1′); 84.98 (d, C4′); 84.65 (d, C4′); 70.54 (C3′); 69.59 (C3′); 69.17 (d, C5′); 68.88 (d, C5′); 66.64 (d, C-benzyl); 66.65 (d, C-benzyl); 40.62 (C2′); 40.34 (C2′); ^{31}P NMR (202 MHz, CDCl$_3$) δ −2.95; MS (FAB) *m/z* 501.0; 502.9 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ$_{max}$ 289.6 nm, 248.0 nm; λ$_{min}$ 268.8 nm, 224.7 nm; IR (KBr) ν 3471, 3453, 3424, 3311, 3195, 3104, 3070, 2958, 2923, 1714, 1594, 1488, 1459, 1411, 1365, 1292, 1247, 1224, 1191, 1157, 1106, 1058, 1020, 946, 844, 759, 435; R$_f$ value 0.28 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t$_R$ 12.19 min (98%, gradient II)

***cyclo*(5-Methoxysaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxyuridinyl)phosphate (5-OMe-*cyclo*Sal-BVDUMP) 2c:** yield 71%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.11 (s, 2H, NH-BVU); 7.58 (s, 1H, H6); 7.56 (s, 1H, H6); 7.40 (d, 1H, H8); 7.36 (d, 1H, H8); 7.02 (d, 1H, H4-aryl); 7.00 (d, 1H, H4-aryl); 6.85 (m, 2H, H3-aryl); 6.65 (d, 1H, H7); 6.64 (d, 1H, H6-aryl); 6.63 (d, 1H, H6-aryl); 6.54 (d, 1H, H7); 6.25 (m, 2H, H1′); 5.46−5.24 (m, 4H, H-benzyl); 4.57−4.39 (m, 6H, H3′, H5′); 4.13−4.09 (m, 2H, H4′); 3.79 (s, 3H, OMe); 3.78 (s, 3H, OMe); 2.53−2.45 (m, 2H, H2′); 2.23−2.12 (m, 2H, H2′); ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.21 (C4); 156.19 (C5-aryl); 149.21 (C2); 143.20 (d, C2-aryl); 143.19 (d, C2-aryl); 137.29 (C4-aryl); 137.18 (C4-aryl); 128.31 (C7); 128.24 (C7); 121.20 (d, C1-aryl); 121.19 (d, C1-aryl); 119.20 (d, C3-aryl); 119.10 (d, C3-aryl); 111.31 (C8); 111.26 (C8); 110.33 (C5-aryl); 110.31 (C5-aryl); 109.40 (C5); 109.33 (C5); 85.30 (C1′); 85.20 (C1′); 84.75 (d, C4′); 84.52 (d, C4′); 69.72 (C3′); 69.35 (C3′); 68.74 (d, C5′); 68.64 (d, C5′); 67.37 (d, C-benzyl); 67.03 (d, C-benzyl); 55.56 (OMe); 55.53 (OMe); 40.31 (C2′); 40.19 (C2′); ^{31}P NMR (202 MHz, CDCl$_3$) δ −6.40; −6.54; MS (FAB) *m/z* 531.4; 533.4 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ$_{max}$ 289.6 nm, 248.0 nm; λ$_{min}$ 268.8 nm, 224.7 nm; IR (KBr) ν 3423, 3193, 3102, 3068, 2948, 2836, 1708, 1594, 1496, 1465, 1432, 1363, 1284, 1197, 1159, 1085, 1024, 950, 914, 865, 848, 804, 665, 530, 431; R$_f$ value 0.30 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t$_R$ 12.32 min (98%, gradient II)

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-BVDUMP) 2d:** yield 99%; ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 11.56 (s, 2H, NH-BVU); 7.76 (s, 1H, H6); 7.75 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.23 (dd, 1H, H5-aryl); 7.22 (dd, 1H, H5-aryl); 7.07−7.05 (m, 4H, H4-aryl, H6-aryl); 6.86 (d, 1H, H7); 6.84 (d, 1H, H7); 6.15 (d, 1H, H1′); 6.14 (d, 1H, H1′); 5.48−5.36 (m,

6H, H-benzyl, OH); 4.38−4.22 (m, 6H, H5′, H3′); 3.94−3.90 (m, 2H, H4′); 2.20−2.13 (m, 2H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); ^{13}C NMR (101 MHz, DMSO-*d$_6$*) δ 161.81 (C4); 161.79 (C4); 149.39 (C2); 148.12 (d, C2-aryl); 148.07 (d, C2-aryl); 139.48 (C6); 139.41 (C6); 131.10 (C4-aryl); 131.08 (C4-aryl); 129.94 (C7); 127.07 (C3-aryl); 126.99 (C3-aryl); 124.15 (C5-aryl); 123.74 (C6-aryl); 123.71 (C6-aryl); 121.14 (d, C1-aryl); 121.09 (d, C1-aryl); 110.37 (C5); 110.34 (C5); 107.19 (C8); 84.87 (C1′); 84.80 (C1′); 84.67; (d, C4′); 84.63 (d, C4′); 69.89 (C3′); 69.83 (C3′); 68.66 (d, C5′); 68.59 (d, C5′); 67.97 (d, C-benzyl); 67.91 (d, C-benzyl); 15.07 (CH$_3$-C3-aryl); 15.04 (CH$_3$-C3-aryl); ^{31}P NMR (162 MHz, DMSO-*d$_6$*) δ −8.82; −8.90; MS (FAB) *m/z* 515.3 (M); UV (CH$_3$CN) λ$_{max}$ 293.39 nm, 250.10 nm, 196.82 nm; λ$_{min}$ 270.08 nm, 226.79 nm; IR (KBr) ν 3423, 2346, 1701, 1560, 1466, 1364, 1286, 1187, 1086, 1023, 955, 869, 526, 478; R$_f$ value 0.51 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t$_R$ 12.69 min (>97%, gradient II).

***cyclo*(3,5-Dimethylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxyuridinyl)phosphate (3,5-DiMe-*cyclo*Sal-BVDUMP) 2e:** yield 77%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.34 (s, 2H, NH-BVU); 7.59 (s, 1H, H6); 7.57 (s, 1H, H6); 7.38 (d, 1H, H8); 7.36 (d, 1H, H8); 7.00 (m, 2H, H4-aryl); 6.77 (m, 2H, H6-aryl); 6.61 (d, 1H, H7); 6.55 (d, 1H, H7); 6.26 (dd, 1H, H1′); 6.24 (dd, 1H, H1′); 5.45−5.26 (m, 6H, H-benzyl, H3′); 4.58−4.36 (m, 4H, H5′); 4.14 (m, 1H, H4′); 4.09 (m, 1H, H4′); 2.28 (s, 6H, CH$_3$-C5-aryl); 2.27 (s, 6H, CH$_3$-C3-aryl); 2.22−2.00 (m, 4H, H2′); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.42 (C4); 149.11 (C2); 149.07 (C2); 146.24 (C2-aryl); 146.18 (C2-aryl); 137.42 (C6); 137.27 (C6); 134.19 (C5-aryl); 134.12 (C5-aryl); 132.27 (C4-aryl); 132.22 (C4-aryl); 128.26 (C7); 128.09 (C7); 127.42 (d, C3-aryl); 127.34 (d, C3-aryl); 123.52 (C6-aryl); 123.39 (C6-aryl); 120.35 (d, C2-aryl); 120.07 (d, C2-aryl); 111.45 (C8); 111.43 (C8); 110.09 (C5); 110.05 (C5); 85.55 (C1′); 85.28 (C1′); 84.98 (d, C4′); 84.65 (d, C4′); 70.54 (C3′); 69.59 (C3′); 69.17 (d, C5′); 68.88 (d, C5′); 66.64 (d, C-benzyl); 66.65 (d, C-benzyl); 40.62 (C2′); 40.34 (C2′); 20.61 (CH$_3$-C5-aryl); 15.19 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, CDCl$_3$) δ −5.55; −5.98; MS (FAB) *m/z* 529.1; 531.5 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ$_{max}$ 289.6 nm, 248.0 nm; λ$_{min}$ 268.8 nm, 224.7 nm; IR (KBr) ν 3424, 3195, 3102, 3066, 2950, 2923, 2832, 1704, 1594, 1481, 1463, 1363, 1284, 1199, 1149, 1108, 1085, 1025, 995, 950, 856, 802, 665, 532, 430; R$_f$ value 0.49 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t$_R$ 13.65 min (98%, gradient II)

***cyclo*(3-*t*Butylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxyuridinyl)phosphate (3-*t*Bu-*cyclo*Sal-BVDUMP) 2f:** yield 62%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.63 (s, 1H, NH-BVU); 9.59 (s, 1H, NH-BVU); 7.63 (s, 1H, H6); 7.59 (s, 1H, H6); 7.41 (d, 1H, H8); 7.36 (d, 1H, H8); 7.36 (d, 2H, H4-aryl); 7.12 (dd, 1H, H5-aryl); 7.11 (dd, 1H, H5-aryl); 7.06 (d, 1H, H6-aryl); 7.01 (d, 1H, H6-aryl); 6.60 (d, 2H, H7); 6.28 (dd, 1H, H1′); 6.25 (dd, 1H, H1′); 5.47−5.28 (m, 4H, H-benzyl); 4.59−4.52 (m, 4H, H5′); 4.48−4.38 (m, 2H, H4′); 2.54−2.45 (m, 2H, H3′); 2.24−2.09 (m, 4H, H2′); 1.43 (s, 9H, CH$_3$-*t*Bu); 1.40 (s, 9H, CH$_3$-*t*Bu); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.61 (C4); 149.25 (C2); 149.16 (C2); 149.10 (C3-aryl); 149.01 (C3-aryl); 139.54 (d, C2-aryl); 139.44 (d, C2-aryl); 137.48 (C6); 137.38 (C6); 128.24 (C7); 128.13 (C7); 128.04 (C4-aryl); 127.99 (C4-aryl); 124.65 (C5-aryl); 124.51 (C5-aryl); 124.05 (C6-aryl); 123.92 (C6-aryl); 122.24 (d, C1-aryl); 122.16 (d, C1-aryl); 111.58 (C8); 111.43 (C8); 110.14 (C5); 85.42 (C1′); 85.27 (C1′); 84.89 (d, C4′); 84.70 (d, C4′); 70.63 (C3′); 69.52 (C3′); 69.10 (d, C5′); 68.77 (d, C5′); 67.84 (d, C-benzyl); 67.05 (d, C-benzyl); 40.65 (C2′); 40.28 (C2′); 34.80 (C7-aryl); 34.78 (C7-aryl); 29.85 (C8-aryl); 29.80 (C8-aryl); ^{31}P NMR (202 MHz, CDCl$_3$) δ −5.68; −6.08; MS (FAB) *m/z* 557.4 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ$_{max}$ 289.6 nm, 248.0 nm; λ$_{min}$ 268.8 nm, 224.7 nm; IR (KBr) ν 3424, 3262, 3249, 3232, 3216, 3205, 3068, 2996, 2960, 2884, 1708, 1693, 1594, 1463, 1440, 1365, 1284, 1214, 1199, 1180, 1145, 1087, 1018, 997, 944, 802, 784, 742, 665, 530, 428; R$_f$ value 0.49 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t$_R$ 14.77; 14.96 min (98%, gradient II).

General Procedure for the Preparation of the *cyclo*Sal-BVDUMPs 3a−g and 7a−m. To a solution of 3′-esterified BVDU **5** (0.28 mmol) in 10 mL of CH$_3$CN was added diisopropylethylamine (0.56 mmol, DIPEA), and the mixture

was cooled to −20 °C. Then, chlorophosphanes (0.56 mmol) were added slowly, and the solution was stirred for 20 min. For the oxidation of the intermediate cyclic phosphites, *tert*-butyl hydroperoxide (0.56 mmol) was added to the reaction mixture at −20 °C. After being stirred for 0.5 h, the reaction mixture was warmed to room temperature, and the solvent was removed under reduced pressure. The residues were purified twice by chromatography on silica gel plates on a chromatotron, first using a gradient of CH_3OH in ethyl acetate followed by a gradient of CH_3OH in CH_2Cl_2 to yield the title compounds **3a−g** and **7a−m** in 49−73% yield. Triesters **7a−m** were isolated, and the *N*-Boc group was immediately cleaved by TFA to give **4a−m**.

cyclo(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-acetyl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-Ac−BVDUMP) 3a: yield 73%; ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H, H6); 7.83 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.24 (dd, 1H, H5-aryl); 7.23 (dd, 1H, H5-aryl); 7.08−7.05 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.82 (d, 1H, H7); 6.14 (dd, 1H, H1′); 6.13 (dd, 1H, H1′); 5.20−5.15 (m, 2H, H3′); 5.49−5.38 (m, 4H, H-benzyl); 4.43−4.31 (m, 4H, H5′); 4.20−4.15 (m, 2H, H4′); 2.43−2.30 (m, 4H, H2′); 2.19 (s, 3H, CH_3-C3-aryl); 2.18 (s, 3H, CH_3-C3-aryl); 2.04 (s, 3H, CH_3-Ac); 2.03 (s, 3H, CH_3-Ac); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.13 (C1-Ac); 161.74 (C4); 161.72 (C4); 149.34 (C2); 148.01 (C2); 148.05 (d, C2-aryl); 139.29 (C6); 139.24 (C6); 131.09 (C4-aryl); 131.04 (C4-aryl); 129.73 (C7); 127.04 (C3-aryl); 126.96 (C3-aryl); 124.15 (C5-aryl); 123.70 (C6-aryl); 121.12 (d, C1-aryl); 121.03 (d, C1-aryl); 110.47 (C5); 110.43 (C5); 107.30 (C8); 85.05 (C1′); 84.98 (C1′); 82.08 (d, C4′); 82.02 (d, C4′); 73.36 (C3′); 73.31 (C3′); 68.65 (d, C5′); 68.60 (d, C5′); 67.67 (d, C-benzyl); 67.62 (d, C-benzyl); 36.18 (C2′); 36.05 (C2′); 20.88 (C2-Ac); 15.02 (CH_3-C3-aryl); 14.97 (CH_3C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ −8.95; −9.06; MS (ESI$^+$) *m/z* 558.9 (M + H); UV (CH_3CN) λ_{max} 293.39 nm, 250.10 nm, 196.82 nm; λ_{min} 268.42 nm, 226.79 nm; IR (KBr) ν 3430, 2346, 1718, 1708, 1654, 1637, 1560, 1474, 1291, 1023, 574, 484, 455; R_f value 0.37 (CH_2Cl_2/MeOH, 95:5); analytical HPLC t_R 17.85 min (98.63%, gradient I).

cyclo(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-propionyl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-Prop-BVDUMP) 3b: yield 30%; ^1H NMR (500 MHz, CDCl$_3$) δ 8.85 (s, 2H, NH-BVU); 7.75 (s, 1H, H6), 7.74 (s, 1H, H6); 7.47 (d, 1H, H8); 7.45 (d, 1H, H8); 7.22 (d, 2H, H4-aryl); 7.08 (dd, 2H, H5-aryl); 6.98 (d, 2H, H3-aryl); 6.75 (d, 1H, H7); 6.73 (d, 1H, H7); 6.34 (dd, 1H, H1′); 6.32 (dd, 1H, H1′); 5.46 (dt, 2H, H3′); 5.35−5.24 (m, 4H, H-benzyl); 4.57−4.41 (m, 4H, H5′); 4.21 (m, 1H, H4′); 2.52 (dd, 2H, H2′); 2.37 (q, 2H, H2-Prop); 2.36 (q, 2H, H2-Prop); 2.30 (s, 6H, CH_3-C3-aryl); 2.08 (ddd, 2H, H2″); 1.17 (t, 3H, H3-Prop); 1.16 (t, 3H, H3-Prop); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.00 (C1-Prop); 160.62 (C4); 148.78 (C2); 136.72 (C6); 131.65 (C4-aryl); 128.02 (C7, C3-aryl); 124.39 (C5-aryl); 123.08 (C6-aryl); 112.11 (C8); 110.54 (C5); 85.25 (C4′), 84.33 (C1′); 83.27 (C1′); 74.09 (C3′); 74.03 (C3′); 68.72 (C5′); 37.92 (C2′); 27.36 (C2-Prop); 15.33 (CH_3-C3-aryl); 8.84 (C3-Prop); ^{31}P NMR (202 MHz, CDCl$_3$) δ −6.78; −6.92; MS (FAB) *m/z* 571.4 (M); UV (H_2O/CH_3CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 266.6 nm, 224.7 nm; IR (KBr) ν 3417, 3407, 3386, 3361, 3193, 3106, 3070, 2952, 2925, 2854, 1714, 1594, 1465, 1417, 1365, 1294, 1191, 1164, 1110, 1062, 1020, 941, 869, 852, 819, 769, 651, 530, 430; R_f value 0.79 (CH_2Cl_2/MeOH, 9:1); analytical HPLC t_R 13.60 min (>97%, gradient II).

cyclo(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-*i*butyryl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-*i*Bu-BVDUMP) 3c: yield 70%; ^1H NMR (500 MHz, CDCl$_3$) δ 8.72 (s, 2H, NH-BVU); 7.76 (s, 1H, H6), 7.75 (s, 1H, H6); 7.47 (d, 1H, H8); 7.45 (d, 1H, H8); 7.21 (d, 2H, H4-aryl); 7.07 (dd, 2H, H5-aryl); 6.97 (d, 2H, H3-aryl); 6.73 (d, 1H, H7); 6.72 (d, 1H, H7); 6.33 (dd, 1H, H1′); 6.32 (dd, 1H, H1′); 5.45 (dt, 2H, H3′); 5.35−5.23 (m, 4H, H-benzyl); 4.55−4.42 (m, 4H, H5′); 4.20−4.16 (m, 2H, H4′); 2.64 (m, 3H, H2′, H2-*i*Bu); 2.29 (s, 6H, CH_3-C3-aryl); 2.08 (ddd, 2H, H2″); 1.19 (d, 3H, H3-*i*Bu); 1.18 (t, 3H, H3-*i*Bu); ^{13}C NMR (101 MHz, CDCl$_3$) δ 176.74 (C1-*i*Bu); 160.95 (C4); 148.99 (C2); 148.47 (C2-aryl); 148.40

(C2-aryl); 136.80 (C6); 136.76 (C6); 131.63 (C4-aryl); 131.60 (C4-aryl); 128.04 (C7); 127.89 (C3-aryl); 127.80 (C3-aryl); 124.37 (C5-aryl); 124.33 (C5-aryl); 123.07 (C6-aryl); 120.65 (C1-aryl); 120.57 (C1-aryl); 112.11 (C8); 112.06 (C8); 110.50 (C5); 110.42 (C5); 85.33 (C4′), 85.15 (C4′); 83.40 (C1′); 83.33 (C1′); 74.04 (C3′); 73.99 (C3′), 68.81 (C5′); 68.75 (C5′); 67.95 (C-benzyl); 67.76 (C-benzyl); 37.89 (C2′); 37.81 (C2′); 33.68 (C2-*i*Bu); 18.75 (C3-*i*Bu); 15.32 (CH_3-C3-aryl); 15.28 (CH_3-C3-aryl); ^{31}P NMR (202 MHz, CDCl$_3$) δ −6.79; −6.94; MS (FAB) *m/z* 585.0; 587.0 (M + H$^+$); UV (H_2O/CH_3CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 266.6 nm, 224.7 nm; IR (KBr) ν 3440, 3424, 3197, 3104, 3070, 2975, 2933, 2881, 1714, 1631, 1594, 1467, 1367, 1294, 1189, 1155, 1116, 1062, 1018, 943, 819, 771, 659, 532, 431; R_f value 0.86 (CH_2Cl_2/MeOH, 9:1); analytical HPLC t_R 13.99 min (>97%, gradient II)

cyclo(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-pivaloyl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-Piv-BVDUMP) 3d: yield 61%; ^1H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 2H, NH-BVU); 7.84 (s, 1H, H6); 7.83 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.23 (dd, 1H, H5-aryl); 7.22 (dd, 1H, H5-aryl); 7.07−7.05 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.82 (d, 1H, H7); 6.16−6.11 (m, 2H, H1′); 5.49−5.38 (m, 4H, H-benzyl); 5.19−5.14 (m, 2H, H3′); 4.43−4.31 (m, 4H, H5′); 4.15−4.11 (m, 2H, H4′); 2.44−2.27 (m, 4H, H2′); 2.19 (s, 3H, CH_3-C3-aryl); 2.18 (s, 3H, CH_3-C3-aryl); 1.14 (s, 9H, CH_3-Piv); 1.13 (s, 9H, CH_3-Piv); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.13 (C1−Piv); 161.72 (C4); 149.34 (C2); 148.06 (d, C2-aryl); 147.99 (d, C2-aryl); 139.37 (C6); 139.26 (C6); 131.08 (C4-aryl); 131.04 (C4-aryl); 129.72 (C7); 127.02 (C3-aryl); 126.95 (C3-aryl); 124.16 (C5-aryl); 123.70 (C6-aryl); 121.08 (d, C1-aryl); 120.52 (d, C1-aryl); 110.55 (C5); 110.45 (C5); 107.33 (C8); 85.13 (C1′); 85.06 (C1′); 82.19 (d, C4′); 82.12 (d, C4′); 73.50 (C3′); 73.45 (C3′); 68.71 (d, C5′); 68.64 (d, C5′); 67.70 (d, C-benzyl); 67.64 (d, C-benzyl); 38.25 (C2−Piv); 36.29 (C2′); 36.15 (C2′); 26.78 (C3−Piv); 15.03 (CH_3-C3-aryl); 14.97 (CH_3-C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ −8.99; −9.04; MS (FAB) *m/z* 598.0 (M − H$^+$); 621.0 (M − H$^+$+Na$^+$); UV (CH_3-CN) λ_{max} 291.73 nm, 250.10 nm, 195.15 nm; λ_{min} 268.42 nm, 226.79 nm; IR (KBr) ν 3447, 2346, 1718, 1654, 1560, 1458, 1364, 1281, 1191, 1157, 1017, 940, 776; R_f value 0.86 (CH_2Cl_2/MeOH, 9:1); analytical HPLC t_R 20.77 min (>99%, gradient I).

cyclo(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-hexanoyl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-Hex-BVDUMP) 3e: yield 50%; ^1H NMR (500 MHz, CDCl$_3$) δ 8.28 (s, 2H, NH-BVU); 7.76 (s, 1H, H6); 7.75 (s, 1H, H6); 7.47 (d, 1H, H8); 7.45 (d, 1H, H8); 7.22 (d, 2H, H4-aryl); 7.08 (dd, 2H, H5-aryl); 6.98 (d, 2H, H3-aryl); 6.75 (d, 1H, H7); 6.73 (d, 1H, H7); 6.33 (dd, 1H, H1′); 6.32 (dd, 1H, H1′); 5.46 (dt, 2H, H3′); 5.35−5.22 (m, 4H, H-benzyl); 4.55−4.42 (m, 4H, H5′); 4.23−4.17 (m, 2H, H4′); 2.53 (dd, 1H, H2′); 2.49 (dd, 1H, H2′); 2.35 (q, 2H, H2-Hex); 2.34 (q, 2H, H2-Hex); 2.28 (s, 6H, CH_3-C3-aryl); 2.13 (ddd, 1H, H2″); 2.04 (ddd, 1H, H2″); 1.68−1.60 (m, 4H, H3-Hex); 1.38−1.25 (m, 8H, H4-Hex, H5-Hex); 0.97 (t, 6H, H6-Hex); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.43 (C1-Hex); 173.41 (C1-Hex); 160.69 (C4); 148.83 (C2); 136.77 (C6); 136.73 (C6); 131.65 (C4-aryl); 131.63 (C4-aryl); 128.03 (C7, C3-aryl); 124.38 (C5-aryl); 124.34 (C5-aryl); 123.09 (C6-aryl); 112.11 (C8); 112.06 (C8); 110.54 (C5); 110.45 (C5); 85.34 (C4′), 85.17 (C4′); 83.35 (C1′); 83.30 (C1′); 74.03 (C3′); 73.98 (C3′), 68.82 (d, C5′); 68.82 (d, C5′); 67.95 (d, C-benzyl); 67.76 (d, C-benzyl); 37.92 (C2′); 37.84 (C2′); 33.97 (C2-Hex); 31.20 (C4-Hex); 24.41 (C3-Hex); 22.25 (C5-Hex); 15.33 (CH_3-C3-aryl); 15.28 (CH_3-C3-aryl); 13.86 (C6-Hex); ^{31}P NMR (202 MHz, CDCl$_3$) δ −6.80; −6.93; MS (FAB) *m/z* 613.5 (M); UV (H_2O/CH_3CN) λ_{max} 288.1 nm, 248.0 nm; λ_{min} 266.6 nm, 224.7 nm; IR (KBr) ν 3447, 2346, 1718, 1654, 1560, 1458, 1364, 1281, 1191, 1157, 1017, 940, 776; R_f value 0.80 (CH_2Cl_2/MeOH, 9:1); analytical HPLC t_R 16.61 min (>97%, gradient II).

cyclo(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-decanoyl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-Dec-BVDUMP) 3f: yield 56%; ^1H NMR (500 MHz, CDCl$_3$) δ 8.96 (s, 2H, NH-BVU); 7.75 (s, 1H, H6); 7.74 (s, 1H, H6); 7.47 (d, 1H, H8); 7.45 (d, 1H, H8); 7.22 (d, 2H, H4-aryl);

7.08 (dd, 2H, H5-aryl); 6.98 (d, 1H, H6-aryl); 6.73 (d, 1H, H7); 6.72 (d, 1H, H7); 6.34 (dd, 1H, H1′); 6.35 (dd, 1H, H1′); 5.46 (dt, 2H, H3′); 5.35−5.22 (m, 4H, H-benzyl); 4.55−4.40 (m, 4H, H5′); 4.23−4.15 (m, 2H, H4′); 2.54 (dd, 1H, H2′); 2.48 (dd, 1H, H2′); 2.35 (q, 2H, H2-Dec); 2.34 (q, 2H, H2-Dec); 2.28 (s, 6H, CH$_3$-C3-aryl); 2.14 (ddd, 1H, H2″); 2.04 (ddd, 1H, H2′); 1.65−1.58 (m, 4H, H3-Dec); 1.28 (m, 24H, H4-Dec − H9-Dec); 0.88 (t, 6H, H10-Dec); ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.40 (C1-Dec); 173.38 (C1-Dec); 161.03 (C4); 161.02 (C4); 149.07 (C2); 148.55 (d, C2-aryl); 148.45 (d, C2-aryl); 136.79 (C6); 136.75 (C6); 131.62 (C4-aryl); 131.60 (C4-aryl); 128.07 (C7); 127.85 (d, C3-aryl); 127.82 (d, C3-aryl); 124.32 (C5-aryl); 124.30 (C5-aryl); 123.07 (C6-aryl); 112.11 (C5); 112.06 (C5); 110.47 (C8); 110.38 (C8); 85.35 (C4′); 85.18 (C4′); 83.35 (C1′); 83.30 (C1′); 74.03 (C3′); 74.01 (C3′); 67.95 (d, C5′); 67.90 (d, C5′); 37.90 (C2′); 37.82 (C2′); 33.99 (C2-Dec); 31.80 (C4-Dec); 29.34 (C5-Dec); 29.20 (C7-Dec); 29.18 (C6-Dec); 29.05 (C8-Dec); 24.72 (C3-Dec); 22.62 (C9-Dec); 15.26 (CH$_3$-C3-aryl); 15.25 (CH$_3$-C3-aryl); 13.85 (C10-Dec); ^{31}P NMR (202 MHz, CDCl$_3$) δ −6.80; −6.94; MS (FAB) m/z 668.9 (M − H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 288.1 nm, 248.0 nm; λ_{min} 266.6 nm, 224.7 nm; IR (KBr) ν 3417, 3407, 3386, 3361, 3193, 3106, 3070, 2952, 2925, 2854, 1714, 1594, 1465, 1417, 1365, 1294, 1191, 1164, 1110, 1062, 1020, 941, 869, 852, 819, 769, 651, 530, 430; R_f value 0.77 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 21.01 min (>97%, gradient II).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-3′-*O*-levulinyl-2′-deoxyuridinyl)phosphate (3-Me-*cyclo*Sal-3′-*O*-Lev-BVDUMP) 3g:** yield 81%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.93 (s, 2H, NH-BVU); 7.76 (s, 1H, H6); 7.75 (s, 1H, H6); 7.46 (d, 1H, H8); 7.44 (d, 1H, H8); 7.21 (d, 2H, H4-aryl); 7.08 (dd, 2H, H5-aryl); 6.96 (d, 2H, H6-aryl); 6.73 (d, 1H, H7); 6.71 (d, 1H, H7); 6.33 (dd, 1H, H1′); 6.32 (dd, 1H, H1′); 5.46 (dt, 2H, H3′); 5.35−5.22 (m, 4H, H-benzyl); 4.55−4.40 (m, 4H, H5′); 4.25−4.17 (m, 2H, H4′); 2.81−2.75 (m, 4H, H3-Lev); 2.23 (s, 6H, CH$_3$-C3-aryl); 2.21 (s, 3H, H5-Lev); 2.20 (s, 3H, H5-Lev); 2.20−2.00 (m, 4H, H2′); ^{13}C NMR (101 MHz, CDCl$_3$) δ 206.34 (C4-Lev); 172.40 (C1-Lev); 161.03 (C4); 149.03 (C2); 136.81 (C6); 131.62 (C4-aryl); 131.58 (C4-aryl); 128.07 (C7); 127.89 (C3-aryl); 127.78 (C3-aryl); 124.35 (C5-aryl); 124.31 (C5-aryl); 123.06 (C6-aryl); 112.05 (C8); 112.02 (C8); 110.42 (C5); 110.32 (C5); 85.32 (C4′); 85.14 (C4′); 83.13 (C1′); 83.07 (C1′); 74.39 (C3′); 74.31 (C3′); 68.78 (d, C5′); 68.71 (d, C5′); 67.95 (d, C-benzyl); 67.76 (d, C-benzyl); 37.75 (C2′, C3-Lev); 29.71 (C5-Lev); 27.79 (C4-Lev); 15.31 (CH$_3$-C3-aryl); 15.26 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, CDCl$_3$) δ −6.80; −6.94; MS (FAB) m/z 611.03 (M − H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 288.1 nm, 248.0 nm; λ_{min} 266.6 nm, 224.7 nm; IR (KBr) ν 3424, 3199, 3104, 3070, 2969, 2927, 1714, 1594, 1467, 1409, 1365, 1294, 1189, 1159, 1122, 1058, 1018, 943, 819, 773, 657, 433; R_f value 0.63 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.56 min (>97%, gradient II).

General Procedure for the Preparation of the *cyclo*Sal-BVDUMPs 4a−m. To cleave the *N*-Boc-protecting group, triesters **7a−m**, that were prepared according to triesters **3a−g**, were dissolved in 5 mL of CH$_3$CN, mixed with 1 mL of trifluoroacetic acid, and stirred for 1.5 h at room temperature. The reaction mixtures were diluted with 20 mL of water and lyophilized. The residues were purified first by chromatography on silica gel plates on a chromatotron using a 1:9 mixture of CH$_3$OH in CH$_2$Cl$_2$ and second by gel filtration on Sephadex LH-20 (Fluka) using CH$_3$OH as eluent.

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-glycinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-Gly-BVDUMP) 4a:** yield 27%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (s, 2H, NH-BVU); 8.28 (s, 4H, NH$_2$-Gly); 7.84 (s, 1H, H6); 7.83 (s, 1H, H6); 7.30 (d, 1H, H8); 7.29 (d, 1H, H8); 7.22 (m, 2H, H5-aryl); 7.05 (m, 4H, H4-aryl, H6-aryl); 6.84 (d, 1H, H7); 6.82 (d, 1H, H7); 6.19 (dd, 1H, H1′); 6.18 (dd, 1H, H1′); 5.45 (m, 4H, H-benzyl); 5.33 (m, 2H, H3′); 4.40 (m, 4H, H5′); 4.26 (m, 2H, H4′); 3.86 (s, 4H, H2-Gly); 2.40 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.33 (C1-Gly); 161.76 (C4); 161.74 (C4); 149.37 (C2); 148.07 (d, C2-aryl); 148.01 (d, C2-aryl); 139.35 (C6); 139.27 (C6); 131.14 (C4-aryl); 131.11 (C4-aryl);

129.74 (C7); 129.72 (C7); 127.06 (C3-aryl); 126.98 (C3-aryl); 124.24 (C5-aryl); 124.22 (C5-aryl); 123.77 (C6-aryl); 123.74 (C6-aryl); 121.05 (d, C1-aryl); 121.06 (d, C1-aryl); 110.53 (C5); 110.49 (C5); 107.40 (C8); 85.09 (C4′); 85.04 (C1′); 75.02 (C3′); 74.90 (C3′); 68.72 (d, C5′); 68.66 (d, C5′); 67.58 (C-benzyl); 67.38 (C-benzyl); 45.89 (C2-Gly); 35.98 (C2′); 35.83 (C2′); 15.07 (CH$_3$-C3-aryl); 15.00 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, DMSO-d_6) δ −7.76; −7.81; MS (FAB) m/z 572.2; 574.2 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 291.73 nm, 250.10 nm, 195.15 nm; λ_{min} 268.42 nm, 226.79 nm; IR (KBr) ν 3442, 3421, 3158, 3066, 3031, 2964, 2933, 2854, 2829, 1756, 1681, 1596, 1469, 1432, 1292, 1232, 1199, 1130, 1052, 1024, 1006, 944, 829, 800, 721; R_f value 0.60 (CH$_2$Cl$_2$/MeOH, 8:2); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-L-alanyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-L-Ala-BVDUMP) 4b:** yield 25%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 2H, NH-BVU); 8.45 (s, 4H, NH$_2$-Ala); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.30 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25−7.20 (m, 2H, H5-aryl); 7.12−7.05 (m, 4H, H4-aryl, H6-aryl); 6.84 (d, 1H, H7); 6.81 (d, 1H, H7); 6.21 (dd, 1H, H1′); 6.19 (dd, 1H, H1′); 5.52−5.36 (m, 4H, H-benzyl); 5.34−5.28 (m, 2H, H3′); 4.48−4.33 (m, 4H, H5′); 4.29−4.23 (m, 2H, H4′); 4.14 (q, 1H, H2-Ala); 4.13 (q, 1H, H2-Ala); 2.52−2.17 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.38 (d, 3H, H3-Ala); 1.37 (d, 3H, H3-Ala); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.43 (C1-Ala); 161.73 (C4); 161.71 (C4); 149.35 (C2); 149.34 (C2); 139.27 (C6); 139.18 (C6); 131.12 (C4-aryl); 131.09 (C4-aryl); 129.70 (C7); 129.68 (C7); 126.99 (d, C3-aryl); 127.98 (d, C3-aryl); 124.22 (C5-aryl); 124.21 (C5-aryl); 123.74 (C6-aryl); 123.72 (C6-aryl); 121.09 (d, C1-aryl); 121.06 (d, C1-aryl); 110.51 (C5); 110.46 (C5); 107.37 (C8); 85.15 (C4′); 85.01 (C1′); 75.29 (C3′); 75.20 (C3′); 68.70 (d, C5′); 68.65 (d, C5′); 48.14 (C2-Ala); 36.14 (C2′); 35.98 (C2′); 15.68 (C3-Ala); 15.04 (CH$_3$-C3-aryl); 14.96 (CH$_3$-C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ −7.75; −7.80; MS (FAB) m/z 586.5; 588.6 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3424, 3178, 3075, 3029, 3018, 2956, 2854, 2827, 1752, 1681, 1596, 1465, 1436, 1367, 1290, 1236, 1199, 1132, 1052, 1024, 1002, 956, 946, 831, 800, 775, 721, 659, 532; R_f value 0.15 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-D-alanyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-D-Ala-BVDUMP) 4c:** yield 25%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 2H, NH-BVU); 8.55 (s, 4H, NH$_2$-Ala); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.30 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25−7.20 (m, 2H, H5-aryl); 7.08−7.05 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.81 (d, 1H, H7); 6.22−6.17 (m, 2H, H1′); 5.51−5.36 (m, 4H, H-benzyl); 5.30−5.26 (m, 2H, H3′); 4.45−4.33 (m, 4H, H5′); 4.28−4.25 (m, 2H, H4′); 4.10−4.05 (m, 2H, H2-Ala); 2.52−2.32 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.40 (d, 3H, H3-Ala); 1.39 (d, 3H, H3-Ala); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.43 (C1-Ala); 161.71 (C4); 149.34 (C2); 149.33 (C2); 139.36 (C6); 139.28 (C6); 131.10 (C4-aryl); 131.05 (C4-aryl); 129.70 (C7); 129.69 (C7); 126.98 (d, C3-aryl); 127.97 (d, C3-aryl); 124.19 (C5-aryl); 124.17 (C5-aryl); 124.12 (C6-aryl); 123.72 (C6-aryl); 121.09 (d, C1-aryl); 121.06 (d, C1-aryl); 110.49 (C5); 110.46 (C5); 107.34 (C8); 85.12 (C4′); 85.05 (C1′); 74.95 (C3′); 74.86 (C3′); 68.70 (d, C5′); 68.63 (d, C5′); 48.07 (C2-Ala); 35.95 (C2′); 35.80 (C2′); 15.95 (C3-Ala); 15.04 (CH$_3$-C3-aryl); 14.97 (CH$_3$-C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ −7.78; −7.84 (s); MS (FAB) m/z 586.5; 588.6 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3424, 3178, 3075, 3029, 3018, 2956, 2854, 2827, 1752, 1681, 1596, 1465, 1436, 1367, 1290, 1236, 1199, 1132, 1052, 1024, 1002, 956, 946, 831, 800, 775, 721, 659, 532; R_f value 0.51 (CH$_2$Cl$_2$/MeOH, 7:3); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-L-valinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-L-Val-BVDUMP) 4d:** yield 32%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 2H, NH-BVU); 8.28 (s, 4H, NH$_2$-Val); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d,

1H, H8); 7.25–7.21 (m, 2H, H5-aryl); 7.08–7.06 (m, 4H, H4-aryl, H6-aryl); 6.84 (d, 1H, H7); 6.83 (d, 1H, H7); 6.20 (dd, 1H, H1′); 6.18 (dd, 1H, H1′); 5.52–5.38 (m, 4H, H-benzyl); 5.36–5.33 (m, 2H, H3′); 4.45–4.33 (m, 4H, H5′); 4.27–4.24 (m, 2H, H4′); 3.93 (d, 2H, H2-Val); 2.45–2.35 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 2.17–2.10 (m, 2H, H3-Val); 0.96 (d, 2H, H4-Val); 0.93 (d, 2H, H4-Val); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.49 (C1-Val); 161.74 (C4); 149.37 (C2); 139.32 (C6); 139.23 (C6); 131.14 (C4-aryl); 131.11 (C4-aryl); 129.74 (C7); 127.03 (C3-aryl); 126.95 (C3-aryl); 124.24 (C5-aryl); 123.74 (C6-aryl); 121.11 (d, C1-aryl); 121.02 (d, C1-aryl); 110.53 (C5); 110.47 (C5); 107.41 (C8); 85.13 (C4′); 85.09 (C1′); 75.28 (C3′); 75.22 (C3′); 68.75 (d, C5′); 68.68 (d, C5′); 67.53 (d, C-benzyl); 67.31 (d, C-benzyl); 36.25 (C2′); 36.07 (C2′); 29.61 (C3-Val); 29.54 (C3-Val); 18.35 (C4-Val); 17.80 (C4-Val); 15.06 (CH$_3$-C3-aryl); 14.99 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, DMSO-d_6) δ −7.77; −7.83; MS (FAB) m/z 614.6; 616.6 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3432, 3424, 3168, 3068, 2971, 2854, 2829, 1749, 1687, 1631, 1596, 1467, 1432, 1369, 1288, 1199, 1132, 1051, 1024, 1004, 944, 829, 800, 721, 657, 532; R_f value 0.37 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

cyclo(**3-Methylsaligenyl**)**-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-D-valinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-D-Val-BVDUMP) 4e:** yield 29%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.67 (s, 2H, NH-BVU); 8.36 (s, 4H, NH$_2$-Val); 7.87 (s, 1H, H6); 7.86 (s, 1H, H6); 7.31 (d, 1H, H8); 7.30 (d, 1H, H8); 7.26–7.23 (m, 2H, H5-aryl); 7.10–7.08 (m, 4H, H4-aryl, H6-aryl); 6.85 (d, 1H, H7); 6.84 (d, 1H, H7); 6.22 (dd, 1H, H1′); 6.21 (dd, 1H, H1′); 5.53–5.40 (m, 4H, H-benzyl); 5.39–5.34 (m, 2H, H3′); 4.49–4.36 (m, 4H, H5′); 4.29–4.26 (m, 2H, H4′); 3.95 (d, 1H, H2-Val); 3.94 (d, 1H, H2-Val); 2.45–2.35 (m, 4H, H2′); 2.22 (s, 3H, CH$_3$-C3-aryl); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.19–2.16 (m, 2H, H3-Val); 0.99 (d, 2H, H4-Val); 0.97 (d, 2H, H4-Val); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.43 (C1-Val); 161.73 (C4); 149.38 (C2); 139.33 (C6); 139.25 (C6); 131.14 (C4-aryl); 131.10 (C4-aryl); 129.74 (C7); 127.04 (C3-aryl); 126.96 (C3-aryl); 124.24 (C5aryl); 123.74 (C6-aryl); 121.11 (C1-aryl); 121.01 (C1-aryl); 110.53 (C5); 110.49 (C5); 107.41 (C8); 85.04 (C4′); 84.99 (C1′); 75.22 (C3′); 75.12 (C3′); 68.75 (d, C5′); 68.65 (d, C5′); 67.51 (d, C-benzyl); 67.28 (d, C-benzyl); 35.92 (C2′); 35.76 (C2′); 29.56 (C3-Val); 18.34 (C4-Val); 17.78 (C4-Val); 15.07 (CH$_3$-C3-aryl); 15.00 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, DMSO-d_6) δ −7.78; −7.85; MS (FAB) m/z 614.6; 616.6 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3432, 3424, 3168, 3068, 2971, 2854, 2829, 1749, 1687, 1631, 1596, 1467, 1432, 1369, 1288, 1199, 1132, 1051, 1024, 1004, 944, 829, 800, 721, 657, 532; R_f value 0.37 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

cyclo(**3-Methylsaligenyl**)**-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-L-leucinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-L-Leu-BVDUMP) 4f:** yield 35%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (s, 4H, NH$_2$-Leu); 7.84 (s, 1H, H6); 7.83 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25–7.20 (m, 2H, H5-aryl); 7.08–7.05 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.82 (d, 1H, H7); 6.19 (dd, 1H, H1′); 6.18 (dd, 1H, H1′); 5.51–5.36 (m, 4H, H-benzyl); 5.33–5.29 (m, 2H, H3′); 4.45–4.33 (m, 4H, H5′); 4.27–4.24 (m, 2H, H4′); 3.98 (t, 2H, H2-Leu); 2.45–2.35 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.74–1.53 (m, 6H, H3-Leu, H4-Leu); 0.91–0.87 (m, 12H, H5-Leu); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.93 (C1-Leu); 161.75 (C4); 149.39 (C2); 139.32 (C6); 139.23 (C6); 131.14 (C4-aryl); 129.74 (C7); 127.65 (d, C3-aryl); 127.25 (d, C3-aryl); 124.25 (C5-aryl); 124.23 (C5-aryl); 123.78 (C6-aryl); 123.75 (C6-aryl); 121.12 (C1-aryl); 110.47 (C5); 107.41 (C8); 85.15 (C4′); 85.12 (C1′); 75.29 (C3′); 75.20 (C3′); 68.79 (C5′); 68.47 (C-benzyl); 50.89 (C2-Leu); 36.23 (C2′); 35.95 (C2′); 31.38 (C3-Leu); 24.01 (C4-Leu); 22.25 (C5-Leu); 22.15 (C5-Leu); 15.08 (CH$_3$-C3-aryl); 14.99 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, DMSO-d_6) δ −7.77; −7.81; MS (FAB) m/z 628.3; 630.3 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3436, 3424, 3320, 3168, 3160, 3070, 2964,

2877, 1687, 1596, 1471, 1434, 1369, 1290, 1201, 1135, 1052, 1024, 1006, 944, 833, 798, 721; R_f value 0.27 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

cyclo(**3-Methylsaligenyl**)**-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-D-leucinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-D-Leu-BVDUMP) 4g:** yield 39%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (s, 4H, NH$_2$-Leu); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25–7.20 (m, 2H, H5-aryl); 7.08–7.06 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.82 (d, 1H, H7); 6.22–6.17 (m, 2H, H1′); 5.52–5.36 (m, 4H, H-benzyl); 5.33–5.29 (m, 2H, H3′); 4.48–4.32 (m, 4H, H5′); 4.26–4.24 (m, 2H, H4′); 4.00 (t, 2H, H2-Leu); 2.45–2.35 (m, 4H, H2′); 2.19 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.74–1.53 (m, 6H, H3-Leu, H4-Leu); 0.91–0.87 (m, 12H, H5-Leu); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.47 (C1-Leu); 161.75 (C4); 161.73 (C4); 149.37 (C2); 139.32 (C6); 139.24 (C6); 131.14 (C4-aryl); 131.09 (C4-aryl); 129.69 (C7); 127.04 (C3-aryl); 126.96 (C3-aryl); 124.23 (C5-aryl); 124.21 (C5-aryl); 123.78 (C6-aryl); 121.04 (C1-aryl); 121.02 (C1-aryl); 110.53 (C5); 110.49 (C5); 107.41 (C8); 85.05 (C4′); 84.99 (C1′); 75.29 (C3′); 75.16 (C3′); 68.75 (d, C5′); 68.63 (d, C5′); 67.53 (C-benzyl); 67.36 (C-benzyl); 50.79 (C2-Leu); 36.70 (C2′); 35.70 (C2′); 30.87 (C3-Leu); 24.00 (C4-Leu); 22.21 (C5-Leu); 22.19 (C5-Leu); 15.07 (CH$_3$-C3-aryl); 14.99 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, DMSO-d_6) δ −7.78; −7.84; MS (FAB) m/z 628.3; 630.3 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3436, 3424, 3320, 3168, 3160, 3070, 2964, 2877, 1687, 1596, 1471, 1434, 1369, 1290, 1201, 1135, 1052, 1024, 1006, 944, 833, 798, 721; R_f value 0.27 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

cyclo(**3-Methylsaligenyl**)**-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-L-isoleucinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-L-Ile-BVDUMP) 4h:** yield 25%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (s, 2H, NH-BVU); 8.01 (s, 4H, NH$_2$-Ile); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25–7.22 (m, 2H, H5-aryl); 7.08–7.06 (m, 4H, H4-aryl, H6-aryl); 6.84 (d, 1H, H7); 6.83 (d, 1H, H7); 6.19 (dd, 1H, H1′); 6.18 (dd, 1H, H1′); 5.51–5.36 (m, 4H, H-benzyl); 5.35–5.30 (m, 2H, H3′); 4.44–4.33 (m, 4H, H5′); 4.27–4.24 (m, 2H, H4′); 3.94 (d, 2H, H2-Ile); 2.45–2.35 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.87–1.82 (m, 2H, H3-Ile); 1.48–1.40 (m, 2H, H4$_A$-Ile); 1.29–1.20 (m, 2H, H4$_B$-Ile); 0.90–0.86 (m, 12H, H5-Ile, H6-Ile); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.72 (C1-Ile); 161.72 (C4); 149.33 (C2); 139.30 (C6); 139.20 (C6); 131.10 (C4-aryl); 129.70 (C7); 127.02 (C3-aryl); 126.96 (C3-aryl); 124.23 (C5-aryl); 124.22 (C5-aryl); 123.74 (C6-aryl); 123.72 (C6-aryl); 121.10 (d, C1-aryl); 121.02 (d, C1-aryl); 110.53 (C5); 110.47 (C5); 107.39 (C8); 85.13 (C4′); 85.09 (C1′); 75.18 (C3′); 75.11 (C3′); 68.75 (d, C5′); 68.71 (d, C5′); 67.51 (d, C-benzyl); 67.30 (d, C-benzyl); 56.52 (C2-Ile); 36.35 (C2′); 36.24 (C2′); 25.34 (C4-Ile); 22.25 (C5-Leu); 22.15 (C5-Leu); 15.08 (CH$_3$-C3-aryl); 14.99 (CH$_3$-C3-aryl); 14.48 (C4-Ile); 11.61 (C5-Ile); ^{31}P NMR (162 MHz, DMSO-d_6) δ −7.77; −7.84; MS (FAB) m/z 628.5; 630.5 (M + H$^+$); UV (H$_2$O/CH$_3$-CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3436, 3261, 3249, 3180, 3068, 2967, 2931, 2884, 2854, 1685, 1639, 1596, 1467, 1284, 1201, 1132, 1056, 1024, 944, 800, 721, 657, 532; R_f value 0.32 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

cyclo(**3-Methylsaligenyl**)**-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-D-isoleucinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-D-Ile-BVDUMP) 4i:** yield 25%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (s, 2H, NH-BVU); 8.03 (s, 4H, NH$_2$-Ile); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25–7.21 (m, 2H, H5-aryl); 7.08–7.06 (m, 4H, H4-aryl, H6-aryl); 6.84 (d, 1H, H7); 6.83 (d, 1H, H7); 6.19 (dd, 1H, H1′); 6.18 (dd, 1H, H1′); 5.52–5.38 (m, 4H, H-benzyl); 5.35–5.30 (m, 2H, H3′); 4.47–4.33 (m, 4H, H5′); 4.27–4.24 (m, 2H, H4′); 3.97–3.93 (m, 2H, H2-Ile); 2.45–2.35 (m, 4H, H2′); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.86–1.84 (m, 2H, H3-Ile); 1.50–1.40 (m, 2H, H4$_A$-Ile); 1.29–1.20 (m, 2H, H4$_B$-Ile); 0.91–0.86 (m, 12H, H5-Ile, H6-Ile); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.72 (C1-Ile); 161.72 (C4); 149.33 (C2); 139.30 (C6); 139.20 (C6); 131.10 (C4-aryl); 129.70 (C7); 127.02

(C3-aryl); 126.96 (C3-aryl); 124.23 (C5-aryl); 124.22 (C5-aryl); 123.74 (C6-aryl); 123.72 (C6-aryl); 121.10 (d, C1-aryl); 121.02 (d, C1-aryl); 110.53 (C5); 110.47 (C5); 107.39 (C8); 85.13 (C4'); 85.09 (C1'); 75.18 (C3'); 75.11 (C3'); 68.75 (d, C5'); 68.71 (d, C5'); 67.51 (d, C-benzyl); 67.30 (d, C-benzyl); 56.52 (C2-Ile); 36.35 (C2'); 36.24 (C2'); 25.34 (C4-Ile); 15.08 (CH$_3$-C3-aryl); 14.99 (CH$_3$-C3-aryl); 14.48 (C4-Ile); 11.61 (C5-Ile); ^{31}P NMR (162 MHz, DMSO-d_6) δ -7.79; -7.87; MS (FAB) m/z 628.5; 630.5 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3436, 3261, 3249, 3180, 3068, 2967, 2931, 2884, 2854, 1685, 1639, 1596, 1467, 1284, 1201, 1132, 1056, 1024, 944, 800, 721, 657, 532; R_f value 0.32 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-L-phenylalanyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-L-Phe-BVDUMP) 4j:** yield 61%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.30–7.0 (m, 18H, H8, H4-aryl, H5-aryl,H6-aryl, H-aryl-Phe); 6.83 (d, 1H, H7); 6.81 (d, 1H, H7); 6.07–6.03 (m, 2H, H1'); 5.51–5.32 (m, 4H, H-benzyl); 5.14–5.08 (m, 2H, H3'); 4.32–4.22 (m, 4H, H5'); 3.91–3.88 (m, 2H, H2-Phe); 3.77–3.73 (m, 2H, H4'); 2.92–2.83 (m, 4H, H3-Phe); 2.41–2.23 (m, 4H, H2'); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.15 (C1-Phe); 160.96 (C4); 148.23 (C2); 139.26 (C6); 139.12 (C6); 131.14 (C4-aryl); 131.08 (C4-aryl); 130.12 (C4-Phe); 129.73 (C7); 129.42 (C5-Phe); 128.43 (C6-Phe); 126.98 (C3-aryl); 126.76 (C3-aryl); 124.21 (C5-aryl); 123.73 (C6-aryl); 121.16 (C1-aryl); 110.47 (C5); 110.43 (C5); 107.33 (C8); 84.97 (C4', C1'); 73.69 (C3'); 68.83 (C5'); 68.71 (C5'); 49.02 (C2-Phe); 35.67 (C2'); 30.78 (C3-Phe); 15.08 (CH$_3$-C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ -7.83; -7.85; MS (FAB) m/z 662.7; 630.7 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min}: 268.8 nm, 224.7 nm; IR (KBr) ν 3434, 3261, 3228, 3208, 3197, 3185, 3170, 3062, 3029, 2985, 2964, 2937, 2854, 2832, 1752, 1687, 1631, 1596, 1467, 1286, 1230, 1199, 1132, 1054, 1024, 1004, 944, 800, 759, 721, 659, 532; R_f value 0.51 (CH$_2$Cl$_2$/MeOH, 7:3); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-D-phenylalanyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-D-Phe-BVDUMP) 4k:** yield 50%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (s, 2H, NH-BVU); 9.24 (s, 4H, NH$_2$-Phe); 7.80 (s, 2H, H6); 7.30–7.0 (m, 18H, H8, H4-aryl, H5-aryl, H6-aryl, H-aryl-Phe); 6.82 (d, 1H, H7); 6.80 (d, 1H, H7); 6.05 (dd, 1H, H1'); 6.04 (dd, 1H, H1'); 5.43 (m, 4H, H-benzyl); 5.19 (m, 2H, H3'); 4.32 (m, 4H, H5'); 4.27 (m, 2H, H4'); 4.11 (s, 2H, H2-Phe); 3.61 (m, 4H, H3-Phe); 2.25 (m, 4H, H2'); 2.19 (s, 3H, CH$_3$-C3-aryl); 2.17 (s, 3H, CH$_3$-C3-aryl); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.15 (C1-Phe); 161.77 (C4); 149.34 (C2); 139.34 (C6); 139.23 (C6); 131.15 (C4-aryl); 131.10 (C4-aryl); 129.74 (C4-Phe); 129.73 (C7); 129.74 (C5-Phe); 128.82 (C6-Phe); 127.06 (C3-aryl); 126.98 (C3-aryl); 124.22 (C5-aryl); 123.75 (C6-aryl); 121.12 (C1-aryl); 110.53 (C5); 110.49 (C5); 107.40 (C8); 85.02 (C4'); 84.95 (C1'); 75.08 (C-benzyl); 74.83 (C-benzyl); 73.50 (C3'); 73.18 (C3'); 68.81 (C5'); 68.68 (C5'); 53.69 (C2-Phe); 53.45 (C2-Phe); 36.17 (C2'); 35.71 (C2'); 35.68 (C3-Phe); 35.53 (C3-Phe); 15.08 (CH$_3$-C3-aryl); 15.00 (CH$_3$-C3-aryl); ^{31}P NMR (202 MHz, DMSO-d_6) δ -7.84; -7.91; MS (FAB) m/z 662.7; 630.7 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3434, 3261, 3228, 3208, 3197, 3185, 3170, 3062, 3029, 2985, 2964, 2937, 2854, 2832, 1752, 1687, 1631, 1596, 1467, 1286, 1230, 1199, 1132, 1054, 1024, 1004, 944, 800, 759, 721, 659, 532; R_f value 0.51 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-L-prolinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-L-Pro-BVDUMP) 4l:** yield 43%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (s, 2H, NH-BVU); 9.25 (s, 2H, NH$_2$-Pro); 7.85 (s, 1H, H6); 7.84 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25–7.21 (m, 2H, H5-aryl); 7.08–7.06 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.81 (d, 1H, H7); 6.19 (dd, 1H, H1'); 6.17 (dd, 1H, H1'); 5.53–5.35 (m, 4H, H-benzyl); 5.32–

5.30 (m, 2H, H3'); 4.47–4.33 (m, 6H, H5', H2-Pro); 4.27–4.24 (m, 2H, H4'); 3.25–3.19 (m, 4H, H5-Pro); 2.45–2.39 (m, 4H, H2'); 2.28–2.17 (m, 4H, H3-Pro); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.93–1.86 (m, 2H, H4-Pro); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.40 (C1-Pro); 161.70 (C4); 149.33 (C2); 139.31 (C6); 139.21 (C6); 131.12 (C4-aryl); 131.08 (C4-aryl); 129.67 (C7); 127.03 (C3-aryl); 127.00 (C3-aryl); 124.21 (C5-aryl); 123.73 (C6-aryl); 123.71 (C6-aryl); 121.11 (d, C1-aryl); 121.04 (d, C1-aryl); 110.50 (C5); 110.44 (C5); 107.37 (C8); 85.19 (C4'); 85.15 (C4'); 81.82 (C1'); 81.70 (C1'); 75.55 (C3'); 75.45 (C3'); 68.72 (d, C5'); 68.63 (d, C5'); 67.64 (d, C-benzyl); 67.46 (d, C-benzyl); 58.83 (C2-Pro); 45.85 (C5-Pro); 36.07 (C2'); 35.90 (C2'); 27.76 (C3-Pro); 23.18 (C4-Pro); 15.08 (CH$_3$-C3-aryl); 14.99 (CH$_3$-C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ -7.77; -7.80; MS (FAB) m/z 612.1; 614.1 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3424, 3178, 3066, 3029, 2992, 2962, 2823, 1749, 1687, 1594, 1467, 1367, 1292, 1232, 1197, 1130, 1052,1024, 1006, 944, 827, 798, 773, 719, 659, 430; R_f value 0.70 (CH$_2$Cl$_2$/MeOH 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

***cyclo*(3-Methylsaligenyl)-5′-*O*-(*E*)-5-(2-bromovinyl)-2′-deoxy-3′-*O*-D-prolinyluridinyl)phosphate (3-Me-*cyclo*Sal-3′-D-Pro-BVDUMP) 4m:** yield 43%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.65 (s, 2H, NH-BVU); 9.25 (s, 2H, NH$_2$-Pro); 7.86 (s, 1H, H6); 7.85 (s, 1H, H6); 7.29 (d, 1H, H8); 7.28 (d, 1H, H8); 7.25–7.21 (m, 2H, H5-aryl); 7.08–7.06 (m, 4H, H4-aryl, H6-aryl); 6.83 (d, 1H, H7); 6.81 (d, 1H, H7); 6.20–6.16 (m, 2H, H1'); 5.52–5.35 (m, 4H, H-benzyl); 5.32–5.27 (m, 2H, H3'); 4.47–4.33 (m, 6H, H5', H2-Pro); 4.27–4.24 (m, 2H, H4'); 3.25–3.16 (m, 4H, H5-Pro); 2.45–2.39 (m, 4H, H2'); 2.28–2.17 (m, 4H, H3-Pro); 2.20 (s, 3H, CH$_3$-C3-aryl); 2.18 (s, 3H, CH$_3$-C3-aryl); 1.93–1.86 (m, 2H, H4-Pro); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.53 (C1-Pro); 161.78 (C4); 161.75 (C4); 149.41 (C2); 149.37 (C2); 148.05 (d, C2-aryl); 147.90 (d, C2-aryl); 139.35 (C6); 139.27 (C6); 131.13 (C4-aryl); 131.09 (C4-aryl); 129.70 (C7); 127.05 (C3-aryl); 126.97 (C3-aryl); 124.22 (C5-aryl); 123.75 (C6-aryl); 123.73 (C6-aryl); 121.14 (d, C1-aryl); 121.03 (d, C1-aryl); 110.53 (C5); 110.48 (C5); 107.41 (C8); 85.10 (C4'); 85.05 (C4'); 81.82 (C1'); 81.70 (C1'); 75.45 (C3'); 75.37 (C3'); 69.79 (C5'); 68.67 (C-benzyl); 68.60 (C-benzyl); 58.87 (C2-Pro); 58.81 (C2-Pro); 45.88 (C5-Pro); 45.74 (C5-Pro); 35.95 (C2'); 27.86 (C3-Pro); 27.82 (C3-Pro); 23.26 (C4-Pro); 15.07 (CH$_3$-C3-aryl); 14.98 (CH$_3$-C3-aryl); ^{31}P NMR (162 MHz, DMSO-d_6) δ -7.89; -7.83; (FAB) m/z 612.1, 614.1 (M + H$^+$); UV (H$_2$O/CH$_3$CN) λ_{max} 289.6 nm, 248.0 nm; λ_{min} 268.8 nm, 224.7 nm; IR (KBr) ν 3424, 3178, 3066, 3029, 2992, 2962, 2823, 1749, 1687, 1594, 1467, 1367, 1292, 1232, 1197, 1130, 1052, 1024, 1006, 944, 827, 798, 773, 719, 659, 430; R_f value 0.70 (CH$_2$Cl$_2$/MeOH, 9:1); analytical HPLC t_R 12.03 min (94%, gradient III).

Determination of the Partition Coefficients (log *P* Values). Log *P* values were determined as follows: a sample of the compounds **2**, **3**, or **4** was dissolved in 0.3 mL of 1-octanol. To this solution were added 0.3 mL of water. This mixture was vigorously vortexed for 10 min, and the two phases were separated by centrifugation (2 min at 13400 rpm). Aliquots were analyzed by analytical HPLC (Merck LiChroCART column, LiChrospher 100 reversed-phase silica gel RP-18 endcapped (5 μm), gradient 0–100% CH$_3$CN in water (0–20 min), 100% CH$_3$CN (20–22 min), 0% CH$_3$CN in water (22.1–35 min), flow 0.5 mL, UV detection at 250 nm). The *P* values were calculated by integration of the peaks of the aqueous and organic phase.

Kinetic Data. (a) Aqueous Buffers. 12 μL of DMSO stock solutions (50 mM) of the triesters were diluted in 300 μL of water or water/DMSO (c = 2.0 mM). 0.3 mL of this solution were added to 0.3 mL of aqueous buffer (50 mM phosphate buffer, pH 7.3 or 50 mM phosphate buffer, pH 6.8) containing 5 μL of an aqueous AZT solution (AZT as internal standard) at 37 °C. The final concentrations were 0.96 mM for the triesters and 25 mM for the aqueous buffer. Aliquots of 60 μL of the hydrolysis mixture were taken, and the hydrolysis was stopped by addition of 5 μL of glacial acetic acid and frozen in liquid air. After being thawed, samples were analyzed by

analytical HPLC (Merck LiChroCART column, LiChrospher 100 reversed-phase silica gel RP-18 endcapped (5 μm); UV detection at 250 nm). The hydrolysis of the compounds **2**−**4** was followed by integration of the peak areas in the HPLC chromatograms. The rate constants k were determined from slope of the logarithmic degradation curve. The half-lives ($t_{1/2}$) were calculated by using the rate constants k.

(b) P3HR-1 Cell Extract. 1.5 mM stock solution of the triesters in DMSO were prepared. 20 μL of this stock solution was mixed with 100 μL of cell extract and 20 μL of a 70 mM magnesium chloride solution. The hydrolysis process was stopped after 8 h by addition of 300 μL of acidic methanol and storage for 5 min at 0 °C. The mixtures were centrifuged by 13000 rpm for 10 min, and the supernatant was analyzed as mentioned above.

(c) Human Sera: The studies were performed as described in (b) but instead of cell extracts 10% of human serum in phosphate buffer, pH 6.8 a was used, and the data were collected in the same way.

Anti-EBV Evaluation. (a) Cell Cultures. The EBV producer cell line P3HR-1, the EBV genome carrying cell lines Raji and Namalwa as well as the EBV negative cell line Ramos were grown in RPMI-1640 medium supplemented with 10% heat-inactivated FCS, L-glutamine and antibiotics at 36.5 °C in a humidified 5% CO_2-containing atmosphere. The latter three cell lines served only as controls in the hybridization technique. Ramos is an EBV-negative cell line. Namalwa is an EBV genome carrying cell line with two EBV genome copies per cell. Raji cells are also EBV positive with about 30−60 EBV genome copies per cell. After hybridization with an EBV specific probe and detection Ramos cells give no signal, Namalwa cells give a very weak signal and Raji cells give a moderate signal.

(b) Exposure of P3HR-1 Cells to Drugs. Exponentially growing P3HR-1 cells were centrifuged, resuspended in fresh medium and seeded at a density of 10^6 cells/mL in 25 cm² cell culture flasks. The tumor promotor 12-*O*-tetradecanoylphorbol-13-acetate (TPA, Sigma) was added at a concentration of 20 ng/mL to induce virus production.[31] Cell cultures were incubated with compounds at different concentrations for 7 days.

(c) DNA Isolation. Control and drug treated cells were pelleted, washed twice with PBS, and resuspended in 200 μL of PBS. DNA was extracted using a DNA extraction kit (QIAamp DNA Blood Minikit, Qiagen). DNA concentration was determined by UV spectrometry.

(d) Slot Blot Hybridization. Ten micrograms of total cellular DNA of drug treated P3HR-1 cells and control cells were used to determine the EBV DNA content. The slot blot hybridization assay was done as described previously[32] using 30 ng/mL of a digoxigenin-11-dUTP-labeled probe specific for the Bam H1−W-fragment of the EBV genome. After hybridization chemiluminescence detection was carried out followed by 30 min exposition to a Kodak film. The amount of EBV DNA was measured using a densitometer (MWG Biotech). Then, the EBV DNA concentration was compared between drug-treated and nontreated P3HR-1 cells and the 50% effective concentration (EC_{50}) for inhibition of EBV replication was calculated by regression analysis.

(e) Determination of CC_{50} for Cell Growth. P3HR-1 cells were grown for 7 days in the presence of test compounds at different concentrations from an initial density of 2×10^5 cells/mL in 96-well plates. Cell numbers were determined using a Coulter Z-2 particle counter and 50% inhibitory concentrations for cell growth (CC_{50}) were calculated.

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