Volume 11, Issue 7, July – 2026 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul186

New Green Synthesis of Acyclovir Prodrugs

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Publication Date: 2026/07/18

Abstract: Green synthesis of alkyl esters of acyclovir (acyclovir prodrugs) is described. Hexanoic, decanoic, dodecanoic and tetradecanoic acyclovir esters were synthesized reacting acyclovir and the respective acid anhydride in dimethyl sulfoxide (DMSO), in solvents from renewable sources and without solvent (T 30°C). Yields in prodrugs after 10 min of reaction were 95% using DMSO as solvent. The purification methodology was very simple,. The biosolvent, N,N-dimethylamide of decanoic acid, let us to obtain 95% yield in microwave oven. This oily biosolvent is not dermotoxic and the reaction crude can directly be used in topic formulations. Syntheses without solvent proceeded successfully for acyclovir esters. Indeed, dodecanoate and tetradecanoate yielding 98% conversion of reactants in 10 sec. In spite of requiring mild tempera ture (300 wat), substrate molar ratios were lowered to 1:1, thus conducing to a more efficient use of raw materials. The synthetic procedures were scaled up to a 500g batch (yield 98—99% isolated ester). These esters can be used as acyclovir prodrugs in topic formulations. The esters release from an oil/water micro-emulsion and a hydrogel formulation were tested with good results.

Keywords*: Acyclovir Prodrug; Green Chemistry; Transdermal Formulation.*

How to Cite: Dr. Kokane Balaji Digambar (2026) New Green Synthesis of Acyclovir Prodrugs. *International Journal of Innovative Science and Research Technology*, 11(7), 299-304. https://doi.org/10.38124/ijisrt/26jul186

I. INTRODUCTION

Acyclovir is a potent inhibitor of Herpes Simplex which also shows relatively fair inhibition to Varizella Zoster virus and to a less extent to Epstein Barr virus1) Its wide and continued clinical use as antiherpetic agent during the last 25 years has proved its safety2) Current antiherpetic treatments with acyclovir include tablets (200 mg, 400mg, 800mg or 1g), topical cream (5%), intravenous injection (25mg/ml) and ophthalmic ointment (3%). low serum half-life (2—3h),1,3,4) thus high doses and frequent administrations are required. Therefore, different prodrugs and topical formulations have been described in order to overcome these inconveniences. Transdermal administration of prodrugs is an interesting path to convey active principles systemically. This methodology directly competes with oral administration. Indeed, around 40% of drugs in clinical trials are intended to be used transdermally.5) This is due to the advantages that transdermal administration offers to achieve efficient and safe healing such as: avoiding first pass hepato-metabolic degradation,6) giving stable drug levels in plasma,7) this procedure is invasiveness8) and it can be applied for longer periods of time.9) The simplest transdermal technique is a passive diffusion which has the additional advantage of being more patient compliant than its counterparts such as iontophoretic, electroporation etc., which require more complex manufacturing and administering procedures. The most suitable kind of prodrugs for passive transdermal administration path is the linear alkyl esters due to their compatibility with the skin lipidic matrix. In addition the high activity of esterases in human skin favors the liberation of the drug by simple hydrolysis of acyclovir and the non-toxic fatty acid. Early attempts to synthesize acyclovir prodrugs date from early 80s with the work on 2,6-diamine-9-(2-hydroxy etoximethyl) purine10) and 6-deoxyacyclovir.11) In 1990, acetate and hexanoate of acyclovir were synthesized in 2—3h by Hardnen et al.12) using acid anhydrides as acyl donors in N,N-dimethylformamide (DMF) (toxic for the skin) and 4 N,N-dimethylaminopyridine (DMAP) as catalyst, obtaining 40% yield in monoester and diacyl derivatives as second ary products. In 1994, Shao et al.13) followed this methodology to synthesize some short chain esters of acyclovir but ex tended the reaction time up to 2—3d without reporting yields. A similar approach was described by Bando et al.14) in 1996 using acid chlorides instead of acid anhydrides as acyl donors but reduced the acyl chloride: acyclovir molar ratio to 3 : 1. This group obtained high purity compounds after 2 d and further precipitation in a NaOH solution. In a similar effort Kim et al.15) in 1998 synthesized short chain esters of 2-amino-6-fluoro-9-(2-hydroxymethoxy-methyl)purine, as potential prodrugs of acyclovir. These workers described a three-step

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul186

procedure with yields above 90%, but 5d were necessary to isolate the ester. In this procedure, the esterification step was achieved in 20min using 3eq of acid anhydrides and DMF as solvent. In 1999, Gao et al.16)conducted the synthesis of several short ester prodrugs of acyclovir using a modified Shao's procedure,13) reducing acid anhydride amount from 20 to 3 acyclovir equivalents and the re action time to 1.5d. In such work they reported yields around 80%, but they still observed 5—12% of double acylations. To the best of our knowledge, the syntheses of long chain esters of acyclovir (laurate and palmitate) have been referenced only in the Gao et al.17)review in which yields of 37% are re ported. Recently, Stankova et al.18,19)described the synthesis of acyclovir esters with peptidomimetics or with cinnamic acid using coupling reagents and evaluated in vitro for their antiviral activity against the replication of Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Solvents are necessary substances in all the chemical organic synthesis, so attention should be paid to choose the best suited and less harmful to the environment. Therefore, organic processes which make less use or substitute toxic solvents are desired. In this way, the enzyme-catalyzed acylation of nucleosides in 2-methyltetrahydrofuarne (obtained from biomass) instead of tetrahydrofuran (THF) has been re ported.20) In this work we present a series of alternative procedures to synthesize short and long acyclovir fatty acid esters (3a— f) in a more efficient and sustainable way to be incorporated in topical emulsions for transdermal administration use.

II. RESULTS AND DISCUSSION

Synthesis of Acyclovir Esters in acetonitrile as a greener synthesis, we substituted dermotoxic DMF & DMSO, used in all the described procedures above, by acetonitrile with no dermotoxicity and widely accepted as percutaneous penetrant and drug solvent and so, useful in creams for topical use.21—23)The synthesis of acyclovir esteres took place at room temperature using acetonitrile as the solvent, 8-diazobicycloundec-7-ene (DBU) in catalytic amounts and acid anhydrides as the acylating agents, obtaining near quantitative yields by prep-HPLC. Free fatty acids (with low reactivity) or acid chlorides (liberating HCl in the acylation which decomposes the prodrugs 3a—f) were not used as the acylating agents due to the low reactivity or to the dermotoxic HCl for mation, respectively. The reaction time was finished in 10 sec and no acylations on the amino group were observed in any case as can be deduced from NMR spectra and elemental analysis of the isolated compounds 3a—f. The described purification procedure was simple and straight forward by precipitation in water. The overall time to isolate pure acyclovir ester prodrugs in a solid form was reduced from over 1.5—5d as reported to one hour maximum improving the described syntheses. HPLC-MS analysis showed that only 0 % of acetonitrile remains in the dry powder. The scope of the synthesis is general because the yields are sustained regardless of the fatty acid chain size (Table 1). This methodology out performs the best results described by Gao and Mitra.16,17).

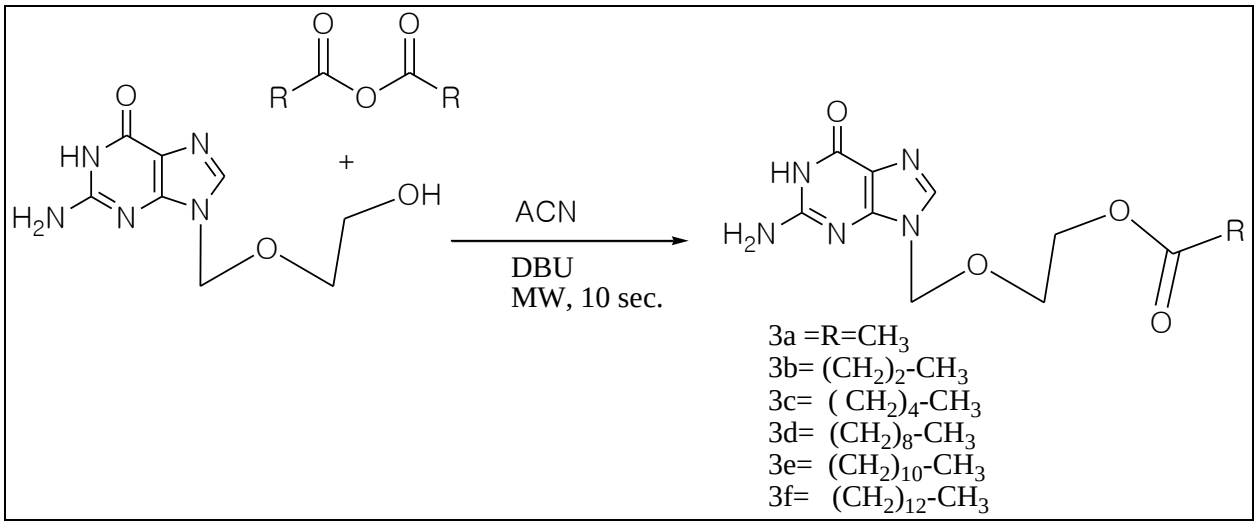

Fig 1 Reaction Scheme:

III. SYNTHESIS OF ACYCLOVIR ESTERS IN SOLVENTS OBTAINED FROM BIOMASS

An alternate approach was to use solvents obtained from renewable sources, as the reaction medium. N,N-dimethylamides of fatty acids, obtained from renewable sources (triglycerides) were used to carry out the synthesis of acyclovir esters. Three different solvents were used: N,N-dimethylamide of decanoic acid (DMAC10), a mixture of N,N dimethylamides of octanoic and decanoic acids (DMAA) and N,N-dimethylamide of lactic acid (DMALA). As we show in the Table 2, the three solvents provided a qualitatively positive outcome for the synthesis acyclovir alkyl esters but at slower reaction rates than in acetonitrile, probably due to the solvent viscosity which might create diffusion problems to substrates.24)TLC monitoring and HPLC analysis indicated

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul186

that only the monoester was synthesized. Despite this approach rendered slower reaction rates compared to acetonitrile, solvent DMAC10 offered a double function: as solvent and as a drug permeation enhancer for topical applications as will be discussed.

Table 1. Yields Obtained in the Esterification of Acyclovir (1) Using acetonitrile as Solvent Compared with the Best Described Yields16

Fatty Acid Anhydride	Compopund	Yield in Isolated Ester(%)	Reaction Time (sec)	Yield[16] (%)	Rreaction Time[16] (d)
Acetic	3a	98	10	75	1
Butyric	3b	94	10	-	-
Hexanoic	3c	95	10	5	1
Decanoic	3d	97	10	-	-
Dodecanoic	3e	96	10	10	1
Tetradecanoic	3f	99	10	-	

Table 2. Yields Obtained after 24h in the Synthesis of Acyclovir Alkyl Esters Using N,N-Dimethylamides of Fatty Acids as Green Solvents.

Compound		Solvent	Solvent	Solvent
		DMAC10	DMAA	DMLA
ACVC 6	3c	95	25	10
ACVC 10	3d	97	NL	15
ACVC 12	3e	94	NL	10
ACVC 14	3f	98	NL	10

IV. OPTIMIZATION OF THE SYNTHESIS CONDITIONS

In the synthesis of 3c(used as the model), we made slight further modifications in the reaction conditions in order to improve the process. We reduced both, the substrate molar ratio acyclovir/anhydride from 1/3 to 1/2, and the amount of solvent used (DMAC10). We increased the acyclovir concentration from 250 to 875mM. The reaction was complete at 10 sec in microwave oven at 300 watt and yielding almost 100% acyclovir monoester, with no signs of any sort of diacylation, identified and quantified by TLC and HPLC. This procedure guarantees the removal of catalyst, leaving any further purification just as a means to adjust the amount of solvent remaining in the final product. From an industrial standpoint, the use of a green solvent such as DMAC10 which serves also as a permeation enhancer for percutaneous applications, offers the advantage of avoiding the complete removal of the solvent from the reaction mix ture, and use this mixture as a permeation-enhancer-included product ready to use “as is,” in the following stages of trans dermic formulation. In an industrial setting, the recovery and recycling of DMAC10 can be achieved much easier than the recovery of DMSO from water, due to its water immiscibility. Following this positive outcome, the synthesis of the fatty acid acyclovir esters (3d—f) were carried out to explore the scope. In these cases, the solvent amount used was 20 ml and the temperature was raised to 40°C to help maintain the re action medium fluid. Reaction was completed (24h) with yields 98% (isolated product) and only the three monoesters were obtained. The purification steps followed were the same as in the synthesis of 3c stated above.

Synthesis without Solvent With the aim to develop a greener process, we performed the synthesis of acyclovir esters without solvent, using the anhydride as the reaction medium and using an anhydride/acyclovir ratio of 1/1. This substrate ratio was only achieved for long (C12 and C14) acyclovir anhydrides, because of their higher specific volume which, unlike shorter anhydrides, occupy a larger volume per weight and thus, are able to provide a large enough medium volume to carry out the reaction. Conversion of acyclovir into the respective ester, which reached over 98% in all cases, followed by TLC and HPLC, was achieved after 30min of the addition of acyclovir into a melted anhydride and catalyst mix (55 °C). The monoesters of acyclovir were purified by the same methodology described above.

V. EXPERIMENTAL

Acyclovir (1) was acquired from Cinfa S.A. Acid anhydrides, N,N-di methyl formamide and dimethyl sulfoxide were purchased from Sigma Aldrich. 4-N,N-Dimethylamino pyridine purchased from VWR International Eurolab S.L. Solvents from renewable sources, N,N-dimethylamide of decanoic acid (DMAC10) and the mixture of N,N-dimethylamides from octanoic, decanoic and dodecanoic acid (DMAA) were supplied from Cognis Iberica S.L. Reaction progress was followed by TLC on Macherey Nagel Alugram Sil G/UV254 sheets visualized under UV light, by with HPLC on a Fig. 3. Acyclovir Hexanoate Release Profile in O/W Emulsion with Sol vent DMAC10 as Promotion Enhancer, Using Polysulfone Synthetic Mem branes (Tuffryn®) Formulation includes DMAC10 (5% w/w) and acyclovir hexanoate (5%

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul186

w/w) into the O/W emulsion. The amount of acyclovir in ester form that crossed the membrane into the receptor phase was measured at 24 h.

VI. CONCLUSION

The synthesis of acyclovir esters—useful as prodrugs—have been performed by different methodologies more environmental friendly than those described in the literature. The substitution of dermotoxic and reprotoxic DMF by DMSO, a common permeation enhancer, as the reaction solvent let us to complete the synthesis in 10 min. The isolation of the monoesters as the unique product, was performed using water as a precipitating agent. The scale up of the synthesis of acyclovir hexanoate (3c) up to 300 g proves the feasabilty to implement it in industrial settings. The syntheses of medium and long chain esters of acyclovir (3c—f) carried out using DMAC10 solvents from renewable sources, rendered almost total conversion yields, yet at slower reaction rates but the se lectivity towards a single monoacylated product was retained. All the acyclovir esters syntheses were also performed without any solvent, using the melted acid anhydrides as solvent medium. For acyclovir dodecanoate and tetradecanoate, a re duction in the substrates ratio up to 1/1 was succesfully achieved.

- *Synthesis in Acetonitrile of the Acyclovir Esters:*

Acyclovir Acetate (3a) 2-Amino-9-[(2-acetyloxy)ethyl-oxy-methyl]-1,9-dihydro-6H-purin-6-one: The synthesis was carried out in a small flask under argon atmosphere. 2 Amino-1,9-dihydro-9-[(2-hydroxyyethoxy)methyl]-6H-purin-6-one, (1, acyclovir), (337 mg, 1.5 mmol) was dissolved in 6 ml of acetonitrile and 4-N,N-dimethylamino-pyridine (DMAP) (18mg, 0.15mmol) was added. Argon atmosphere was set and the solution was stirred until reactants were dissolved. The acetic anhydride (0.42 ml, 4.5 mmol) was added keeping the inert atmosphere. After 10 min, stirring is stopped and the reaction volume is transferred to a 10 ml syringe. The reaction medium was added dropwise to a vigorously agitated beaker with 600 ml of water (100 reaction volumes). The supernatant precipitate was then filtered and dried to r.t. 1H-NMR (250MHz, DMSO-d6) d: 10.6—the numbers of carbons and nitrogen in H NMR are in accordance with IUPAC acyclovir nomenclature—(1H, s broad, N1-H); 7.85 (1H s broad, C8H); 6.54 (2H, s broad, NH2); 5.36 (2H, s, C10H2); 4.07 (2H, t, 3J 7Hz, C13H2); 3.66 (2H, t, 3J 7Hz, C12H2); 1.96 (3H, t, 3J 7Hz, OOC-CH3). Elemental analysis Calcd for C10H13N5O4: C, 44.93; H, 4.90; N, 26.22. Found: C, 44.61, H: 5.01, N: 26.45.

- *Acyclovir Butyrate (3b):*

2-Amino-9-[(2-butanoyloxy)ethyl-oxy-methyl] 1,9-dihydro-6H-purin-6-one: The synthesis was carried out under the same conditions as in 3a. The butyric anhydride (0.716 ml, 4.5 mmol) was added keeping the inert atmosphere. 1H-NMR (250MHz, DMSO-d6) d: 10.7 (1H, s broad, N1-H); 7.94 (1H, s, C8H); 6.58 (2H, s broad, NH2); 5.36 (2H, s, C10H2); 4.09 (2H, t, 3J 7Hz, C13H2); 3.67 (2H, t, 3J 7Hz, C12H2); 2.20 (2H, t, 3J 7Hz, OOC-CH2); 1.47 (2H, c, 3J 7Hz, OOC-CH2CH2); 0.83 (3H, t, 3J 7Hz, OOC-(CH2)2-CH3). Elemental analysis Calcd for C12H17N5O4: C, 48.79; H, 5.80; N, 23.73. Found: C, 48.4, H, 5.89; N, 23.56. Acyclovir Hexanoate (3c): 2-Amino-9-[(2-hexanoyloxy)ethyl-oxy-methyl] 1,9-dihydro-6H-purin-6-one: The synthesis was carried out under the same conditions as 3a. The hexanoic anhydride (1.03 ml, 4.5 mmol) was added keeping the inert atmosphere. 1H-NMR (250MHz, DMSO-d6) d: 10.7 (1H, s broad, N1-H); 7.84 (1H, s, C8H); 6.54 (2H, s broad, NH2); 5.35 (2H, s, C10H2); 4.09 (2H, t, 3J 7Hz, C13H2); 3.66 (2H, t, 3J 7Hz, C12H2); 2.22 (2H, t, 3J 7Hz, OOC-CH2); 1.47 (2H, q, 3J 7Hz, OOC-CH2CH2); 1.22 (4H, mult, 2CH2); 0.84 (3H, t, 3J 7Hz, OOC-(CH2)4CH3). Elemental analy sis Calcd for C14H21N5O4: C, 51.99; H 6.54; N, 21.67. Found: C, 51.76; H, 6.68; N, 21.44.

- *Acyclovir Decanoate (3d):*

2-Amino-9-[(2-decanoyloxy)ethyl-oxy-methyl] 1,9-dihydro-6H-purin-6-one: The reaction was carried out under the same conditions as 3a. The decanoic anhydride (1.65 ml, 4.5 mmol) was added keeping the inert atmosphere. 1H-NMR (250MHz, DMSO-d6) d: 10.7 (1H, s broad, N1-H); 7.82 (1H, s, C8H); 6.60 (2H, s broad, NH2); 5.35 (2H, s, C10H2); 4.09 (2H, t, 3J 7Hz, C13H2); 3.66 (2H, t, 3J 7Hz, C12H2); 2.22 (2H, mult, OOC-CH2); 1.35 (2H, mult, OOC-CH2CH2); 1.35—1.24 (12H, mult, 6CH2); 0.84 (3H, t, OOC(CH2)8CH3). Elemental analysis Calcd for C18H29N5O4: C, 59.96; H, 7.70; N, 18.47. Found: C, 59.69; H, 7.85; N, 18.29.

- *Acyclovir Dodecanoate (3e):*

2-Amino-9-[(2-dodecanoyloxy)ethyl-oxy methyl]-1,9-dihydro-6H-purin-6-one: The synthesis was carried out under the same conditions as 3a. The dodecanoic anhydride (1.72 g, 4.5 mmol) was added keeping the inert atmosphere. 1H-NMR (250MHz, DMSO-d6) d: 10.65 (1H, s broad, N1-H); 7.82 (1H, s, C8H); 6.53 (2H, s broad, NH2); 5.35 (2H, s, C10H2); 4.08 (2H, t, 3J 7Hz, C13H2); 3.66 (2H, t, 3J 7Hz, C12H2); 2.22 (2H, mult, OOC-CH2); 1.35 (2H, comp, OOC-CH2CH2); 1.45—1.24 (16H, mult, 8CH2); 0.83 (3H, t, OOC(CH2)10CH3). Elemental analysis Calcd for C20H33N5O4: C, 58.93; H, 8.16; N, 17.19. Found: C, 58.78; H, 8.28; N, 17.01.

- *Acyclovir Tetradecanate (3f)*

2-Amino-9-[(2-tetradecanoyloxy)ethyl oxy-methyl]-1,9-dihydro-6H-purin-6-one: The synthesis was carried out under the same conditions as 3a. The dodecanoic anhydride (1.97g, 4.5 mmol) was added keeping the inert atmosphere. 1H-NMR (250MHz, DMSO-d6) d: 10.7 (1H, s broad, N1-H); 7.82 (1H, s, C8H); 6.56 (2H, s broad, NH2); 5.35 (2H, s, C10H2); 4.09 (2H, t, 3J 7Hz, C13H2); 3.66 (2H, t, 3J 7Hz, C12H2); 2.22 (2H, mult, OOC-CH2); 2.17 (2H, mult, OOC CH2CH2; 1.35 (20H, mult, 10CH2); 0.84 (3H, t, OOC(CH2)12CH3). Elemen tal analysis Calcd for C22H37N5O4: C, 60.65; H, 8.56; N, 16.09. Found: C, 60.38; H, 8.67; N, 15.89. Synthesis in Solvents from Biomass. Acyclovir Hexanoate (3c) Acy clovir, 1.97 g (8.75

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul186

mmol); hexanoic anhydride, 3.71 g (17.5 mmol); DMAP, 0.108g (0.88mmol); DMAC10, DMAA or DMALA, 10ml. Reaction tem perature was set to 40 °C. Reactants were agitated during 24h. In the purifi cation process 30 volumes (300ml) of a 50/50 acetonitrile/water mixture was added to the reaction mixture mainly to remove the DMAP and kept in agitation until a homogeneous suspension was observed. The suspension was filtered and allowed to dry to room temperature. HPLC method: iso cratic water/acetonitrile 60/40, 0.8 ml/min on a C18 30 cm 4.6 mm 5 mm col umn. Retention time: 6.2min. Acyclovir Decanoate (3d) Acyclovir, 1.97g (8.75mmol); decanoic an hydride, 5.71g (17.5mmol); DMAP, 0.108g (0.88mmol); DMAC10, DMAA or DMALA, 20ml and the reaction temperature was set to 40°C. Reactants were agitated during 24 h. In the purification process 30 volumes (300ml) of a 50/50 acetonitrile/water mixture was added to the reaction mixture mainly to remove the DMAP and kept in agitation until a homoge neous suspension was observed. The suspension was filtered and allowed to dry to ambient temperature. HPLC method: isocratic water/acetonitrile 25/75, 1.0 ml/min on a C18 30cm 4.6mm 5mm column. Retention time: 4.6min. Acyclovir Dodecanoate (3e) Acyclovir, 1.97g (8.75mmol); dodecanoic anhydride, 6.50g (17.5mmol); DMAP, 0.108g (0.88mmol); DMAC10, DMAA or DMALA 20ml. Reaction temperature was set to 40°C. Reactants were agitated during 24 h. In the purification process 30 volumes (300 ml) of a 50/50 acetonitrile/water mixture was added to the reaction mixture mainly to remove the DMAP and kept in agitation until a homogeneous suspension was observed. The suspension was filtered and allowed to dry to ambient temperature. HPLC method: isocratic water/acetonitrile 25/75, 1.0 ml/min on a C18 30cm 4.6mm 5mm column. Retention time: 7.1min. Acyclovir Tetradecanoate (3f) Acyclovir, 1.97g (8.75mmol); decanoic anhydride, 7.67g (17.5mmol); DMAP, 0.108g (0.88mmol); DMAC10, DMAA or DMALA 20ml. Reaction temperature was set to 40°C. Reactants were agitated during 24 h. In the purification process 30 volumes (300 ml) of a 50/50 acetonitrile/water mixture was added to the reaction mixture mainly to remove the DMAP and kept in agitation until a homogeneous suspension was observed. The suspension was filtered and allowed to dry to ambient temperature. HPLC method: isocratic water/acetonitrile 10/90, 1.3 ml/min on a C18 30cm 4.6mm 5mm column. Retention time: 5.7min. Synthesis without Solvents.

- *Acyclovir Dodecanoate (3e):*

Acyclovir, 1.97g (8.75mmol); dodecanoic anhydride, 3.25g (17.5mmol); DMAP, 0.108g (0.88mmol); reaction temperature was 30°C. After 30min the reac tion was finished resulting in a 98% yield analyzed by HPLC. The purifica tion process comprised the same steps as those used when DMSO was used as solvent. HPLC method: isocratic water/acetonitrile 25/75, 1.0 ml/min on a C18 30cm 4.6mm 5mm column. Retention time: 7.1min.

- *Acyclovir Tetradecanoate (3f):*

Acyclovir, 1.97g (8.75mmol); decanoic anhydride, 3.83 g (8.75 mmol); DMAP, 0.108g (0.88mmol); reaction tem perature was 30 °C. After 30 min of agitating reactants, the reaction was fin ished resulting in a 98% yield analyzed by HPLC. The purification stage comprised the same steps as those used when DMSO was used as solvent. HPLC method: isocratic water/acetonitrile 10/90, 1.3ml/min on a C18 30cm 4.6mm 5mm column. Retention time: 5.7 min.

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