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SYNTHESIS AND BIOLOGICAL ASSESSMENT OF NOVEL HETEROCYCLIC NUCLEOSIDE ANALOGUES USING MICROWAVE-ASSISTED HANTZSCH REACTION

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Abstract – This paper reports a one-pot synthesis of 5-(1,4-dihydropyridyl) derivatives of 2'-deoxyuridines using Hantzsch condensation of 5-formyl-2'-deoxyuridine and NH_4OAc with diverse β-dicarbonyl compounds under solvent-free microwave irradiation conditions. The synthesized compounds were evaluated for their antiviral activities against human rhinovirus (HRV) and hepatitis C virus (HCV), as well as antibacterial activities against a series of Gram-positive and Gram-negative bacteria. The products carrying an unsymmetrical 1,4-dihydropyridyl moiety showed excellent antiviral activity against HCV.

INTRODUCTION

The diverse biological activities of 1,4-dihydropyridine derivatives (1,4-DHPs) make them an attractive target for drug discovery.[1,2] These compounds have shown promise as antihypertensive,[3] anticonvulsant,[4] anti-inflammatory,[5] antioxidant,[6] anticoagulant,[7] antitubercular,[8] antimicrobial,[9–11] anticancer[12] and antiviral[13] agents. Therefore, developing a rapid and practical method for synthesizing compounds that incorporate this ring system is of great interest.

To this end, we have developed a one-pot multicomponent reaction (MCR) that employs the Hantzsch reaction[14] under solvent-free and microwave irradiation conditions. This approach has enabled us to efficiently synthesize new C-5-1,4-dihydropyridinyl (1,4-DHP) nucleosides, which can significantly reduce the reaction time and improve the yield of the desired products.

In addition, all synthesized compounds have been screened for their antimicrobial activity and cytotoxicity. This is a crucial step in determining the potential of new compounds as antimicrobial agents and evaluating their safety and potential for therapeutic use.

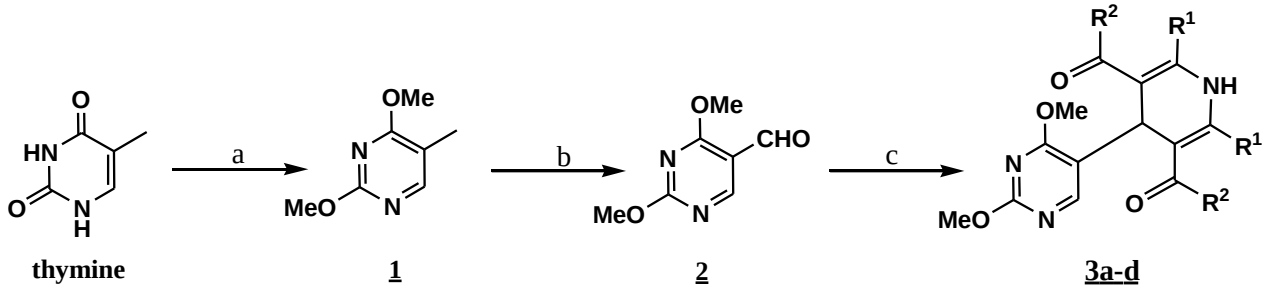
Overall, the present synthesis of the nucleosides incorporating the 1,4-dihydropyridine ring system at the C-5 position provides a promising avenue for the discovery of new and improved antimicrobial agents. However, further research and development are required to fully understand the potential of these compounds and their mechanism of action.

RESULTS AND DISCUSSION

Before embarking on the synthesis of 1,4-DHP substituted 2'-deoxyuridine, we aim to assess the feasibility of a three-component condensation with the known 5-formylpyrimidime 2, which would enable us to access pyrimidine 1,4-DHP derivatives at the C-5 position.

To synthesize these derivatives, we have devised a strategy as illustrated in the Scheme 1. Initially, to protect positions 2 and 4 of thymine, the Schmidt-Nickels and Johnson method[15] is employed, which involves chlorination of both positions with $POCl_3$ reagent followed by the introduction of methoxy groups in the presence of sodium methylate in methanol.

The synthesis of 2,4-dimethoxy-5-formylpyrimidine is then carried out with 2,6-lutidine and a solution of $K_2S_2O_8$ and $CuSO_4 \cdot 5H_2O$ in water, starting from the precursor 2,4-dimethoxy-5-methylpyrimidine using the method of coutouli-Argyropoulou et al.[16] After extraction and chromatographic purification on a silica gel column, the compound is obtained with a yield of 71%. The proton NMR spectrum confirms the structure of the aldehyde with the disappearance of the methyl group signal and the appearance of the aldehyde group signal at 10.11 ppm.



Scheme 1. Reagents and conditions: (a) $POCl_3$, reflux 5 h, MeONa/MeOH (b) $K_2S_2O_8$, $CuSO_4 \cdot 5H_2O$, 2,6-lutidine, H_2O/MeCN, 80 °C, 1 h (c) NH_4OAc, MW, 300 Hz, 140 °C, 5 min

The first attempt at the Hantzsch reaction was done through traditional heating. A mixture of 2,4-dimethoxy-5-formylpyrimidine, methyl acetoacetate, and ammonium acetate in the respective proportions of 1/2/2 was refluxed in ethanol for 18 h, resulting in only 60% of the pyrimidine-1,4-DHP derivative after

purification. This initial attempt prompted the study of the influence of the activation mode on the reaction yield, leading to the use of microwaves. With this, the desired product was formed after only 5 min of activation (P=300 Hz, T=140 °C) and without solvent in a yield of 70%. Afterwards, we proceeded with Hantzsch reactions using various alkyl acetoacetates, such as ethyl acetoacetate, isobutyl acetoacetate, and 1,3-cyclohexanedione.[17] The results are presented in Table 1.

Table 1. Synthesis of 2,4-dimethoxy-5(dihydropyridyl)pyrimidine derivatives by the Hantzsch reaction

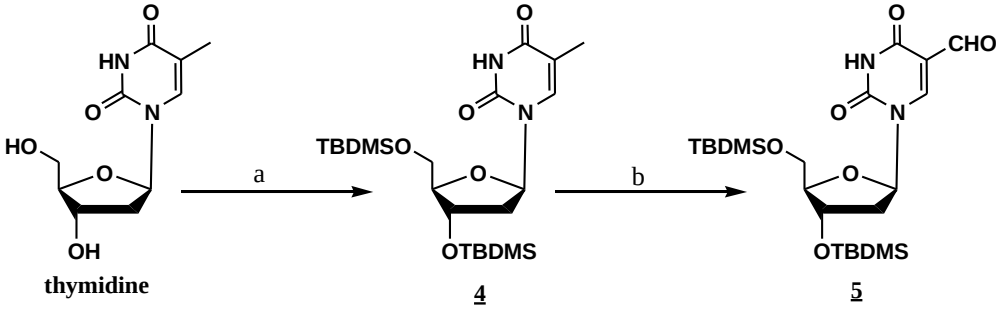
Entry	Product	R^1	R^2	Yield[a] (%)
1	**3a**	Me	OMe	70
2	**3b**	Me	OCH_2Me	74
3	**3c**	Me	$OCH_2CH(Me)_2$	65
4	**3d**	1,3-cyclohexanedione		78

[a] Isolated yields

Formylation of the C-5 position of thymidine

After determining the optimal conditions for the Hantzsch reaction under microwave irradiation, we used the same conditions to prepare other derivatives of 1,4-DHPs at the C-5 position of 2'-deoxyuridine, using a variety of differently substituted alkyl acetoacetates.

Firstly, we protect the 3' and 5' hydroxyl groups of the sugar part of thymidine are protected by *tert*-butyldimethylsilyl (TBDMS) groups in the presence of imidazole and *tert*-butyldimethylsilyl chloride (TBDMSCl) in DMF at room temperature.[18] After seven hours of stirring, the reaction is stopped by the addition of methanol, and compound **4** is obtained after extraction and simple purification with an excellent yield of 96%. Proton NMR analysis shows the presence of the *tert*-butyl protons of TBDMS at positions 3' and 5' at 0.78 ppm and 0.82 ppm, respectively.



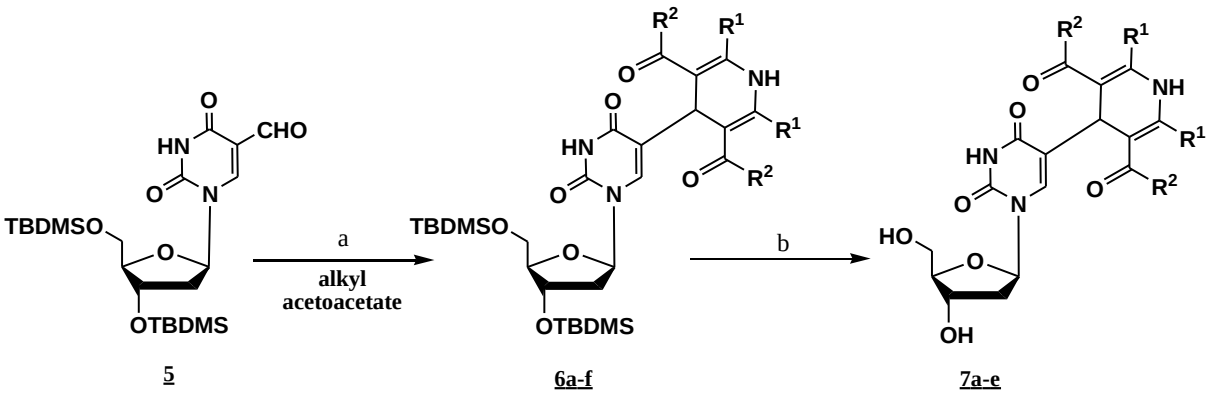
Scheme 2. Reagents and conditions: (a) TBDMSiCl, imidazole, DMF, 7 h (b) $K_2S_2O_8$, $CuSO_4 \cdot 5H_2O$, 2,6-lutidine, $MeCN/H_2O$, 2 h

The synthesis of C_5 (1,4-DHP) derivatives of 2'-deoxyuridine requires the preparation of the formylated precursor, 5-formyl-2'-deoxyuridine **5**. To achieve this, we adopted the same conditions described by

Matsuda et al.[19,20] which involves oxidation of the methyl group at C-5 position of thymidine to the formyl group (Scheme 2). The protected nucleoside is oxidized in the presence of 2 equivalents of $K_2S_2O_8$, 0.38 equivalents of $CuSO_4 \cdot 5H_2O$, and 3.58 equivalents of 2,6-lutidine in $MeCN/H_2O$ at 65 °C for 2 h. The analysis of the proton NMR spectrum shows the disappearance of the peak corresponding to the methyl protons and the appearance of a singlet corresponding to the aldehyde proton at C-5 of 2'-deoxyuridine at 9.91 ppm.

Synthesis of protected 5-(1,4-dihydropyridyl)-2'-deoxyuridines by Hantzsch condensation

After determining the optimal conditions for the Hantzsch reaction under microwave irradiation in the previous section, we used the same conditions to prepare other derivatives of 1,4-DHPs at the C-5 position of 2'-deoxyuridine, using a variety of differently substituted alkyl acetoacetates (Scheme 3). Thus, 5-formyl-2'-deoxyuridine **5** first reacts with alkyl acetoacetates (methyl acetoacetate, ethyl acetoacetate, methyl 4-methyl-3-oxopentanoate, isobutyl acetoacetate, and 1,3-cyclohexanedione) and ammonium acetate under microwave irradiation at 140 °C for 5 min, to yield C-5-(symmetric 1,4-dihydropyridyl)-2'-deoxyuridines. In a second step, we reacted **5** with two types of alkyl acetoacetates in order to access asymmetric 5-(1,4-dihydropyridyl)-2'-deoxyuridines (Scheme 3). The results obtained are shown in Table 2.

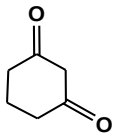
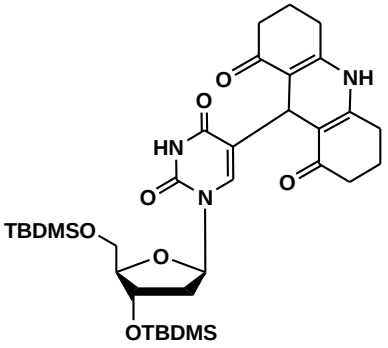
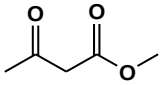
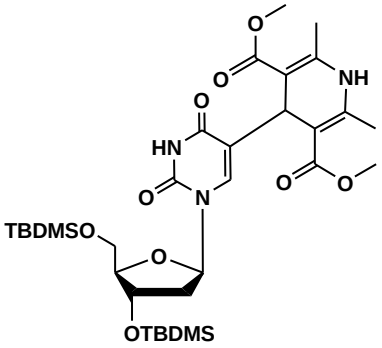
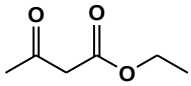
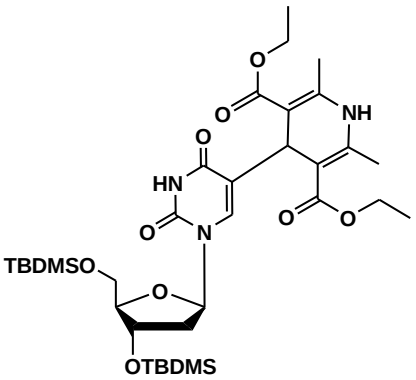
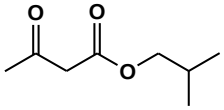
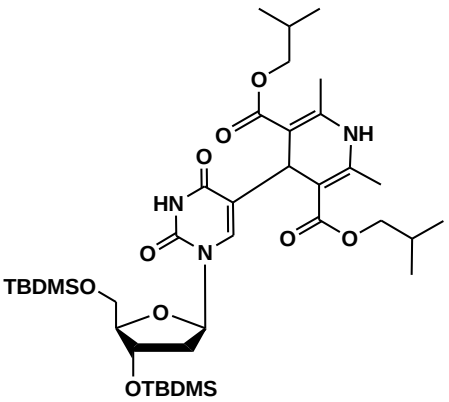


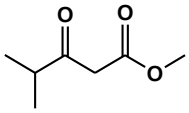
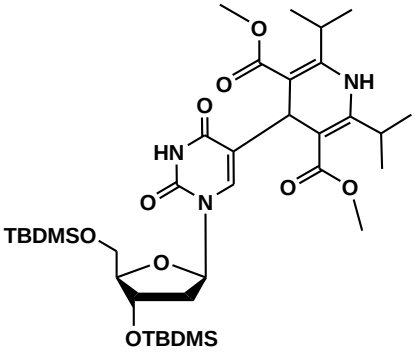
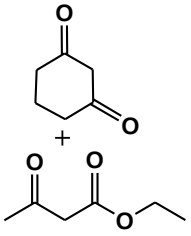
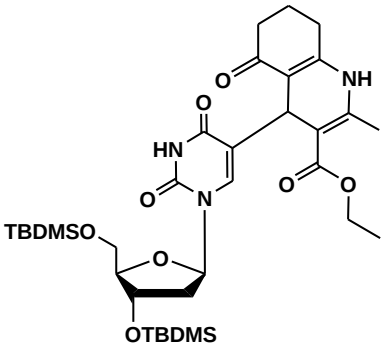
5 6a-f 7a-e

Scheme 3. Reagents and conditions: (a) NH_4OAc, MW, 300 Hz, 140 °C, 5 min; (b) TBAF/THF, 1 h

Expanding on the information provided in the first section regarding the 1,4-DHP-pyrimidine derivatives, it should be noted that the 5-(1,4-dihydropyridyl)-2'-deoxyuridine derivatives obtained can be characterized through ^1H NMR analysis. Specifically, the proton from the aldehyde function is no longer present and is replaced by the emergence of the protons from the 1,4-dihydropyridine nucleus, which is formed at C-5 of the 2'-deoxyuridine.

Table 2. Synthesis of 5-(1,4-dihydropyridyl)-2'-deoxyuridine derivatives via Hantzsch reaction under microwave irradiation

Entry	Alkyl Acetoacetate	Compound	Structure	Yield[a] (%)
1		**6a**		75
2		**6b**		80
3		**6c**		76
4		**6d**		63

5		**6e**		62
6		**6f**		65

[a] Isolated yields

Deprotection of the compounds 6a-f by desilylation

To achieve the intended objective, we carried out deprotection of compounds **6a-f** by desilylation of the glucidic part. The latter is performed using the TBAF system in THF at room temperature.[21] The deprotected 5-(1,4-dihydropyridyl)-2'-deoxyuridine derivatives **7a-e** were obtained within an hour with a good yield ranging from 80% up to 88%.

BIOLOGICAL EVALUATION

Antibacterial activity:

The minimum inhibitory concentration (MIC) values were used to determine the antibacterial activity of the compounds (**3a-d** and **7a-e**) against various bacterial strains. MIC values refer to the lowest concentration of an antimicrobial that visibly prevents bacterial growth after an overnight incubation. The bacterial strains tested included *Staphylococcus aureus* (ATCC 13709 in vivo, ATCC 25923, oxford, and MRSA in vivo), *Enterococcus faecalis* (ATCC 29212 VanS), *Enterococcus faecium* (Van A), *Streptococcus pneumoniae* (VanA, ATCC49619, PenR, and Blood effect), *Haemophilus influenzae* (ATCC 31517 MMSA), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). Standard techniques were used to evaluate the compounds in vitro antibacterial activity[22], and MIC values were determined and recorded greater than 64 µg/mL. The MIC values of the synthesized compounds against

Gram-positive and Gram-negative bacteria were compared with those of Ciprofloxacin and Linezolid, which were used as standard drugs.

Antiviral activity and cytotoxicity:

The compounds were also tested for their antiviral activity against viruses such as HCV and HRV in replicon systems of Hela and Huh cells (Table 3). Among all the synthesized compounds, only one compound (**7f**) showed significant activity against HCV with an effective concentration to reduce virus-induced cytopathicity by 50% (EC_{50}) of 16.4 µM. However, the rest of the molecules showed activity greater than 100 µM. As for the cytotoxic evaluation on different human cells, the majority of our compounds have a toxic effect, except for compounds **7a** and **7f**, which have a 50% cytotoxic concentration (CC_{50}) of 23.6 µM for Huh cells and 68.1 µM for Hela cells, respectively.

Table 3. Antiviral activities (EC_{50}, EC_{90}) and cytotoxicity (CC_{50})

Compound	HRV14 - Hela Rh - 2%FCS			HCV 1b - Huh 5,2 -10%FCS		
	EC_{50} (µM)	EC_{90} (µM)	CC_{50} (µM)	EC_{50} (µM)	EC_{90} (µM)	CC_{50} (µM)
3a	>100	ND	>100	>50	>50	>50
3b	>100	ND	>100	>50	>50	>50
3c	>100	>100	>100	>50	>50	>50
3d	>100	>100	>100	>50	>50	>50
7a	ND	ND	68.1	>50	>50	>50
7b	>100	ND	>100	>50	>50	>50
7c	>100	>100	>100	>50	>50	>50
7f	>100	>100	>100	16,4	ND	23,6

ND: not determined

CONCLUSION

The synthesis of 5-(1,4-dihydropyridyl)-2'-deoxyuridines via a one-pot, microwave-assisted multicomponent approach is a remarkable accomplishment in medicinal chemistry. The discovery of **7f** as a potent antiviral agent against HCV is promising and may lead to the development of more effective antiviral drugs. Moreover, compounds with lower cytotoxicity, specifically **7a** and **7f**, can be optimized to improve their therapeutic potential.

The outcomes of this study serve as a solid basis for future investigations in the field of drug discovery and development. The microwave-assisted, one-pot multicomponent approach is a viable technique for synthesizing novel compounds with potential therapeutic properties. In addition, the recognition of **7f** as a

potential starting point for drug development against HCV underscores the importance of exploring new chemical entities for treating viral diseases.

EXPERIMENTAL

Chemicals were procured from laboratory-grade sources such as Alfa Aesar, Acros, Aldrich, Sigma or Fluka. Solvents used were also of laboratory grade. Thin-layer chromatography was performed using aluminum sheets coated with silica gel 60 F254, while column flash chromatography was carried out using appropriate equipment. NMR spectra (^{1}H and ^{13}C) were recorded with TMS as the internal standard in $CDCl_3$ and DMSO-d_6, using Bruker AC 250 MHz and AC 400 MHz instruments. Chemical shifts were reported in ppm and *J* (spin-spin coupling constants) in Hz, with s, d, t, m, and br indicating singlet, doublet, triplet, multiplet, and broad, respectively. Mass spectra were obtained using ESI/MS and MALDI-TOF. Microwave irradiation experiments were conducted using a dedicated CEM-Discover mono-mode microwave apparatus that operated at a frequency of 2455 MHz and provided continuous irradiation power ranging from 0 to 300 W ± 10%.

2,6-Dimethoxy-5-methylpyrimidine

20 g of thymine was heated with 80 mL of $POCl_3$ at 110-120 °C for 5 h, where after the excess of phosphorus halide was removed by heating at 80 °C under vacuum. The cooled residue was then dissolved in Et_2O, the ethereal solution washed with water and diluted aqueous Na_2CO_3 and finally dried over Na_2SO_4. The pyrimidine was finally purified by distillation and boiled at 108-109 °C at 11 mm.

20 g of the dichloropyrimidine was dissolved in 100 mL of MeOH and the liquid poured into a solution of 7 g of Na in 100 mL of MeOH, whereupon NaCl separated immediately, the mixture becoming warm. The reaction was complete after heating for 5 min and after filtering from NaCl and distilling off excess of MeOH, the resulting oil was dissolved in Et_2O, washed with aqueous NaOH solution and then dried over Na_2SO_4. On evaporating the solvent the pyrimidine separated in crystalline form.

Oxidation of 2,6-dimethoxy-5-methylpyrimidine **1**

A solution of the 2,6-dimethoxy-5-methylpyrimidine (10 mmol) and 2,6-lutidine (4.1 mL, 35 mmol) in MeCN (40 mL) was added to a solution of $K_2S_2O_8$ (5.4 g, 20 mmol) and $CuSO_4 \cdot 5H_2O$ (1g, 4 mmol) in water (40 mL). The reaction mixture was heated in an oil bath at 80 °C and the reaction mixture was monitored by TLC. After 1 h TLC showed only traces of the starting methyl derivative and the heating was stopped. Applying longer reaction times at the same temperature or at lower temperatures side products were formed lowering the yield of the reaction. After cooling the reaction mixture was concentrated to half the initial volume and the remaining solution was extracted with EtOAc. The organic layer was successively

washed with water then aqueous 5% EDTA. The combined water layers were extracted with $CHCl_3$ then the organic layers were combined, dried over Na_2SO_4 and concentrated. The residue was chromatographed on a silica gel column with hexane-EtOAc as the eluent.

2,4-Diméthoxy-5-formylpyrimidine **2**

Yie*ld 6*5%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 8.72 (s, 1H, H-6), 10.11 (s, 1H, CHO). ^{13}C NMR (101 MHz, $CDCl_3$): δ 54.59 (OCH_3), 55.72 (OCH_3), 112.34 (C-5), 161.45 (C-6), 167.58 (C-2), 171.16 (C-4), 186.43 (CHO). ESIMS: *m/z* calcd for $C_7H_8N_2O_3$ [M+] 168.05 found 168.34.

A mixture of **2** (1 mmol) alkyl acetoacetate (2 mmol) and ammonium acetate (2 mmol) was taken in the glass reaction equipped with a magnetic stirrer. The glass reaction tube was then placed inside a CEM Discover microwave reactor, operated at 140 °C and 300 Hz for 5 min. After the reaction time, the reaction mixture was dissolved in EtOAc, and concentrated in vacuum. The crude compounds were purified by silica gel column chromatography eluting with MeOH/CH_2Cl_2 to get the desired compounds in pure form.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dimethoxypyrimidin-5-yl)pyridine-3,5-dicarboxylate **3a**

Yield 70%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.22 (s, 6H, 2 xCH_3), 3.55 (s, 6H, 2 xOCH_3), 3.88 (d, 6H, *J* = 3.36 Hz, 2 x$COOCH_3$), 4.97 (s, 1H, H4-DHP), 6.14 (s, 1H, NH), 7.98 (s, 1H, H-6).

^{13}C NMR (63 MHz, $CDCl_3$): δ 19.22 (2 xCH_3), 32.98 (C-4 DHP), 50.96 (2 x$OOCH_3$), 53.70 (OCH_3), 54.56 (OCH_3), 101.16 (C-3 and C-5 DHP), 119.92 (C-5), 145.20 (C-2 and C-6 DHP), 158.08 (C-6), 163.74 (C-2), 167.92 ($COOCH_3$), 168.62 (C-4). ESIMS: *m/z* calcd for $C_{17}H_{21}N_3O_6$ [M+H] 364.14 found, 364.2.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dimethoxypyrimidin-5-yl)pyridine-3,5-dicarboxylate **3b**

Yield 74%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.14 (t, 6H, *J* = 7.13 Hz, 2 xCH_3-), 2.23 (s, 6H, 2 xCH_3), 3.87 (s, 6H, 2 xOCH_3), 4.00 (q, *J* = 7.15 Hz, 2 x$COOCH_2$), 4.98 (s, 1H, H4-DHP), 5.72 (s, 1H, NH), 8.02 (s, 1H, H-6).^{13}C NMR (63 MHz, $CDCl_3$): δ 14.31 (2 x-CH_3), 19.44 (2 xCH_3), 32.97 (C-4 DHP), 53.59 (OCH_3), 54.55 (OCH_3), 59.69 (OCH_2-), 101.65 (C-3 and C-5 DHP), 120.24 (C-5), 144.77 (C-2 and C-6 DHP), 158.62 (C-6), 163.74 (C-2), 167.46 (2 x$COOCH_3$ and), 168.52 (C-4). ESIMS: *m/z* calcd for $C_{19}H_{25}N_3O_6$ [M+H] 392.17 found, 392.4.

Diisobutyl 1,4-dihydro-2,6-dimethyl-4-(2,4-dimethoxypyrimidin-5-yl)pyridine-3,5-dicarboxylate **3c**

Yield 65%,^{1}H NMR (250 MHz, $CDCl_3$): δ 0.84 (m, 12H, 2 x(-CH_3)$_2$), 1.84 (m, 2H, 2 x$CH(CH_3)_2$), 2.23 (s, 6H, 2 xCH_3), 3.74 (m, 4H, 2 xOCH_2-CH), 3.86 (s, 6H, 2 xOCH_3), 5.05 (s, 1H, H4-DHP), 5.93 (s, 1H, NH), 8.01 (s, 1H, H-6).^{13}C NMR (63 MHz, $CDCl_3$): δ 19.33 (2 xCH_3 and 2 x$(CH_3)_2$), 27.78 (2 xCH), 32.82

(C-4 DHP), 53.58 (OCH_3), 54.56 (OCH_3), 70.24 (2 xOCH_2-), 101.51 (C-3 and C-5 DHP), 119.93 (C-5), 144.96 (C-2 and C-6 DHP), 158.28 (C-6), 163.77 (C-2), 167.54 (2 x$COOCH_3$), 168.53 (C-4). ESIMS: *m/z* calcd for $C_{23}H_{33}N_3O_6$ [M+H] 448.24 found, 448.5.

9-(2,4-Dimethoxypyrimidin-5-yl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione **3d**

Yield 78%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97-1.78 (m, 4H, 2 xCH_2-CH_2), 2.24 (m, 4H, 2 xCH_2-C), 2.41 (m, 4H, 2 xCH_2-CO), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.42 (s, 1H, NH), 5.04 (s, 1H, H4-DHP), 8.22 (s, 1H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.29 (2 xCH_2), 27.15 (2 xCH_2), 28.38 (C-4 DHP), 37.18 (2 xCH_2-CO), 53.76 (OCH_3), 54.56 (OCH_3), 111.71 (C-3 and C-5 DHP), 118.85 (C-5), 151.96 (C-2 and C-6 DHP), 158.71 (C-6), 163.47 (C-2), 168.80 (C-4), 196.09 (2 xCO). ESIMS: *m/z* calcd for $C_{19}H_{21}N_3O_4$ [M+H] 356.15 found, 356.2.

Protecting the 3´, 5´-hydroxy groups of thymidine

Thymidine (5 g, 20.6 mmol) was added to imidazole (8.41 g, 123.6mmol) and TBDMSCl (9.31 g, 61.8 mmol) in 120 mL DMF at room temperature under argon atmosphere,and the mixture was stirred for 7 h. The reaction was quenched with 8 mL MeOH, diluted with EtOAc (400 mL). The solution was washed twice, each time with 200 mL H_2O, once with 200 mL sat. aq. $NaHCO_3$ and once with 200 mL brine, dried (Na_2SO_4), and concentrated to afford a solid mass, which was then purified by column chromatography on silica gel (elution with EtOAc/hexane (1.5/8.5)).

3´,5´-Bis-O-(tert-butyldimethylsilyl)thymidine **4**

Yield 96%, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.74 (br s, 1H, NH), 7.36 (s, 1H, H-6), 6.23 (dd, 1H, *J* = 7.8 and 5.8 Hz, H1'), 4.29 (m, 1H, H3'), 3.82 (dd, 1H, *J* = 4.7 and 2.2 Hz, H4'), 3.70 (ddd, 1H, *J* = 28.5, 11.3 and 2.4 Hz, H5'), 2.14 (ddd, 2H, *J* = 13.1, 5.8 and 2.5 Hz, H2'a), 1.89 (m, 1H, H2'b), 1.80 (s, 3H, CH_3), 0.82 (s, 9H, C–$(CH_3)_3$), 0.78 (s, 9H, C–$(CH_3)_3$), 0.00 (s, 6H, Si–$(CH_3)_2$), -0.03 (m, 6H, Si–$(CH_3)_2$).^{13}C NMR (63 MHz, $CDCl_3$) δ 163.75 (C4), 150.29 (C2), 135.45 (C6), 110.82 (C5), 87.83 (C4'), 84.85 (C1'), 72.25 (C3'), 62.99 (C5'), 41.39 (C2'), 25.95 (C–CH3), 25.76 (C–CH3), 18.41 (C– CH_3), 18.02 (C– CH3), 12.52 (CH_3), -4.62 (Si–CH_3), -4.82 (Si–CH_3), -5.35 (Si–CH3), -5.44 (Si–CH3). ESI-MS: *m/z* calcd for $C_{22}H_{42}N_2O_5Si_2$ [M+H] 471.26 found, 471.60.

Oxidation of 5-methyl group of thymidine **5**

Dissolve 6.0 g (12.75 mmol) **1** in 200 mL of 1:1 (v/v) MeCN/H_2O and add 6.89 g (25.5 mmol) $K_2S_2O_8$, 1.17 g (4.72 mmol) $CuSO_4 \cdot 5H_2O$, and 5.28 mL (45.6 mmol) 2,6-lutidine. Heat the mixture with stirring at 65 °C. Monitor the réaction by TLC in 1:2 (v/v) EtOAc/hexane, twice (Rf = 0.50). The starting compound

1 usually disappears after 2 to 3 h. A longer reaction time increases the amount of a more polar byproducts, so the reaction should be stopped before the complete disappearance of **1**. Filter off the reaction mixture through a Celite and dilute the filtrate with 500 mL EtOAc. Wash three times, each time with 300 mL of 10% aq. EDTA, twice with 200 mL 0.5 N HCl, twice with 200 mL sat. aq.$NaHCO_3$ and once with 200 mL brine. The organic layers were dried over Na_2SO_4. Evaporation of solvent followed by flash chromatography with EtOAc/hexane (2/8).

3´,5´-Bis-O-(tert-butyldimethylsilyl)-5-(formyl)-2´-deoxyuridine **5**

Yield 50%, ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.91 (s, 1H, CHO), 9.71 (br s, 1H, NH), 8.45 (s, 1H, H-6), 6.13 (dd, 1H, *J* = 7.5 and 5.8 Hz, H1'), 4.31 (dd, 1H, *J* = 3.3 and 2.2 Hz, H3'), 3.96 (d, 1H, *J* = 2.1 Hz, H4'), 3.73 (ddd, 2H, *J* = 28.4, 11.4 and 2.6 Hz, H5'), 2.35 (ddd, 1H, *J* = 13.1, 5.6 and 1.9 Hz, H2'a), 1.94 (ddd, 1H, *J* = 13.2, 7.5 and 5.8 Hz, H2'b), 0.79 (s, 9H, C–$(CH_3)_3$), 0.78 (s, 9H, C–$(CH_3)_3$), -0.01 (m, 12H, 2 x (Si–$(CH_3)_2$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 185.74 (CHO), 162.36 (C-4), 149.42 (C-2), 145.43 (C-6), 111.04 (C-5), 89.20 (C4'), 87.23 (C1'), 72.90 (C3'), 63.08 (C5'), 42.53 (C2'), 25.99 (C-CH_3), 25.78 (C-CH_3), 18.44 (Si-C), 18.04 (Si-C), -4.63 (Si–CH3), -4.80 (Si–CH_3), -5.47 (Si–CH_3), -5.60 (Si–CH_3). ESI-MS: *m/z* calcd for $C_{22}H_{40}N_2O_6Si_2$ [M+H] 485.24 found 485.6.

9-(1-(4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione **6a**

Yield 75%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.49 (s, 1H, NH), 7.27 (s, 1H, H-6), 6.30 (s, 1H, NH- DHP), 6.18 (dd, 1H, *J* = 8.17 and 5.64 Hz, $H_{1'}$), 4.62 (s, 1H, H4-DHP), 4.36 – 4.28 (m, 1H, $H_{3'}$), 3.84 ((m, 1H, $H_{4'}$), 3.79 – 3.58 (m, 2H, $H_{5'}$), 3.55 (s, 4H, 2 xCH_2), 2.16 (d, 4H *J* = 3.58 Hz, CH_2-DHP), 2.10 (dd, 1H, *J* = 5.60 and 2.18 Hz, $H_{2'a}$), 1.92 (m,1H, $H_{2'b}$), 0.85 (s, 9H, C–$(CH_3)_3$), 0.81 (s, 9H, C–$(CH_3)_3$), 0.00-0.04 (m, 12H, 2 x(Si–$(CH_3)_2$)). ^{13}C NMR (63 MHz, $CDCl_3$): δ 167.91 (CO-DHP), 167.80 (CO-DHP), 162.03 (C4), 150.01 (C2), 146.51 (C-2 and C-6 DHP), 137.75 (C6), 116.51 (C5), 98.82 (C-3 and C-5 DHP), 87.63 (C4'), 84.85 (C1'), 72.47 (C3'), 63.56 (C5'), 50.86 (C-4 DHP), 40.37 (C2'), 35.92 (CH_2), 26.03 (C–CH_3), 25.80 (C–CH_3), 19.76 (CH_2), 19.49 (CH_2), 18.50 (Si-C), 18.02 (Si-C), -4.60 (Si–CH_3), -4.72 (Si–CH_3), -5.23 (Si–CH_3), -5.39 (Si–CH_3). ESIMS: *m/z* calcd for $C_{34}H_{53}N_3O_7Si_2$ [M+H] 672.34 found, 672.9.

Dimethyl 4-(1-(4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **6b**

Yield 80%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.55 (s, 1H, NH), 7.27 (s, 1H, H-6), 6.34 (s, 1H, NH- DHP), 6.18 (dd, 1H, *J* = 8.18 and 5.63 Hz, $H_{1'}$), 4.61 (s, 1H, H4-DHP), 4.32 (m, 1H, $H_{3'}$), 3.84 (m, 1H, $H_{4'}$), 3.67 (ddd, 2H, *J* = 16.36, 10.93 and 4.79 Hz, $H_{5'}$), 3.55 (s, 6H, 2 xOCH_3), 2.12 (m, 7H, 2 xCH_3 and $H_{2'a}$), 1.92

(m, 1H, $H_{2'b}$), 0.85 (s, 9H, C–$(CH_3)_3$), 0.81 (s, 9H, C–$(CH_3)_3$), 0.02 (m, 12H, 2 x(Si–$(CH_3)_2$)). ^{13}C NMR (63 MHz, $CDCl_3$): δ 167.92 (CO-DHP), 167.82 (CO-DHP), 162.10 (C4), 150.03 (C-2 and C-6 DHP), 146.57 (C2), 137.76 (C6), 116.50 (C5), 98.77 (C-3 and C-5 DHP), 87.62 (C4'), 84.85 (C1'), 72.46 (C3'), 63.56 (C5'), 50.86 (2 xOCH_3), 40.38 (C2'), 35.91 (C-4 DHP), 26.04 (C–CH_3), 25.80 (C–CH_3), 19.75 (CH_3), 19.48 (CH_3), 18.50 (Si-C), 18.03 (Si-C), -4.60 (Si–CH_3), -4.72 (Si–CH_3), -5.23 (Si–CH_3), -5.38 (Si–CH_3). ESIMS: *m/z* calcd for $C_{32}H_{53}N_3O_9Si_2$ [M+H] 680.33 found, 680.9.

Diethyl 4-(1-(4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **6c**

Yield 76%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.60 (s, 1H, NH), 7.23 (s, 1H, H-6), 6.31 (s, 1H, NH- DHP), 6.11 (dd, 1H, *J* = 7.95 and 5.71 Hz, $H_{1'}$), 4.61 (s, 1H, H4-DHP), 4.28 (m, 1H, $H_{3'}$), 4.00 (m, 4H, 2 xOCH_2-), 3.81 (m, 1H, $H_{4'}$), 3.62 (m, 2H, $H_{5'}$), 2.10 (m, 7H, 2 xCH_3 and $H_{2'a}$), 1.92 (m, 1H, $H_{2'b}$), 1.13 (dt, 6H, *J* = 7.07, 7.03 and 2.34 Hz, 2 xCH_3), 0.80 (m, 18H, 2 x (C–$(CH_3)_3$)), -0.01 (m, 12H, 2 x(Si–$(CH_3)_2$)).^{13}C NMR (63 MHz, $CDCl_3$): δ 167.55 (CO-DHP), 167.47 (CO-DHP), 162.13 (C4), 150.03 (C-2 and C-6 DHP), 146.26 (C2), 137.94 (C6), 116.49 (C5), 98.79 (C-3 and C-5 DHP), 87.62 (C4'), 85.30 (C1'), 72.58 (C3'), 63.59 (C5'), 59.60 (2 xOCH_2), 40.12 (C2'), 36.02 (C-4 DHP), 26.02 (C–CH_3), 25.80 (C–CH_3), 19.91 (CH_3), 19.54 (CH_3), 18.50 (Si-C), 18.01 (Si-C), 14.57 (2 x-CH_3), -4.68 (2 x(Si–CH_3)), -5.32 (2 x(Si–CH_3)). ESIMS: *m/z* calcd for $C_{34}H_{57}N_3O_9Si_2$ [M+H] 708.36 found, 708.9.

Diisobutyl 4-(1-(4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **6d**

Yield 63%,^{1}H NMR (250 MHz, $CDCl_3$): δ 8.65 (s, 1H, NH), 7.26 (s, 1H, H-6), 6.37 (s, 1H, NH- DHP), 6.24 (dd, 1H, *J* = 8.2 and 5.6 Hz, $H_{1'}$), 4.76 (s, 1H, H4-DHP), 4.43 - 4.34 (m, 1H, $H_{3'}$), 3.83 - 3.67 (m, 5H, 2 xOCH_2 and $H_{4'}$), 3.6 (m, 2H, $H_{5'}$), 2.21 (m, 7H, 2 xCH_3 and $H_{2'a}$), 1.98 (m, 3H, 2 xCH and $H_{2'b}$), 1.12 - 1.18 (m, 12H, 2 x(-$CH_3)_2$), 0.94 - 0.90 (m, 18H 2 x C–$(CH_3)_3$), 0.10 (m, 12H, 2 x(Si–$(CH_3)_2$)).^{13}C NMR (63 MHz, $CDCl_3$): δ 167.62 (CO-DHP), 167.48 (CO-DHP), 161.79 (C4), 154.32 (C-2 DHP), 154.23 (C-6 DHP), 149.98 (C2), 137.13 (C6), 117.12 (C5), 97.34 (C-3 DHP), 97.24 (C-5 DHP), 87.52 (C4'), 84.88 (C1'), 72.47 (C3'), 63.59 (2 xOCH_2-), 63.70 (C5'), 39.81 (C2'), 36.12 (C-4 DHP), 27.83 (2 xCH), 26.02 (C–CH_3), 25.78 (C–CH_3), 20.51 - 18.48 (2 x(Si-C), 2 x(-$CH_3)_2$ and 2 xCH_3), 18.01 (Si-C), 14.13 (Si-C), -4.61 and -4.73 (2 x(Si–CH_3)), -5.24 and -5.38 (2 x(Si–CH_3)). ESIMS: *m/z* calcd for $C_{38}H_{65}N_3O_9Si_2$ [M+H] 764.43 found, 765.0.

Dimethyl 4-(1-(4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-diisopropyl-1,4-dihydropyridine-3,5-dicarboxylate **6e**

Yield 62%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.91 (s, 1H, NH), 7.36 (s, 1H, H-6), 6.66 (s, 1H, NH- DHP), 6.16 (dd, 1H, *J* = 7.7 and 5.9 Hz, $H_{1'}$), 4.76 (s, 1H, H4-DHP), 4.38 (m, 1H, $H_{4'}$), 3.97 – 3.74 (m, 3H, $2H_{5'}$, H3'), 2.21 - 2.23 (2 x s, 6H, 2 xOCH_3), 2.10 – 1.84 (m, 4H, 2 x–CH- , $H_{2'a}$, $H_{2'b}$), 0.8 - 0.97 (m, 30H, 2 x C–$(CH_3)_3$ and 2 x(-$CH_3)_2$), 0.09 (m, 12H, 2 x(Si–$(CH_3)_2$)). ^{13}C NMR (63 MHz, $CDCl_3$): δ 167.68 (CO-DHP), 167.58 (CO-DHP), 162.36 (C4), 150.04(C-2), 146.44 (C-6 DHP), 145.92 (C2), 138.11 (C6), 116.24 (C5), 98.93 - 98.56 (C-3 and C-5 DHP), 87.70 (C4'), 85.78 (C1'), 72.75 (C3'), 63.59 (C5'), 39.81 (OCH_3), 36.12 (C2'), 27.90 (C-4 DHP), 27.76 (CH), 26.02 (CH), 25.79 (CH), 19.90 (C–CH_3), 19.56 (C–CH_3), 19.45 (CH_3), 19.43 (CH_3), 18.44 (Si-C), 17.99 (Si-C), -4.64 (Si–CH_3), -4.73 (Si–CH_3), -5.30 (Si–CH_3). ESIMS: *m/z* calcd for $C_{36}H_{61}N_3O_9Si_2$ [M+H] 736.39 found, 736.9.

Ethyl 4-(1-(4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **6f**

The product is a mixture of two diasteroisomer in the ratio 0.5/0.5.
Yield 65%, ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.89 (m, 2H, 2 xNH), 7.43 (m, 2H, 2 xNH- DHP), 7.09 (m, 2H, 2 xH-6), 6.22 (m, 1H, $H_{1'}$), 6.05 (m, 1H, $H_{1'}$),4.68 (m, 2H, 2 xH4-DHP), 4.35 (m, 2H, 2 x$H_{3'}$), 4.02 (m, 4H, 2 xOCH_2-), 3.74 (m, 6H, 2 x$H_{4'}$ and 2 xH5'), 2.10 (m, 16H, 2 xCH_2, 2 xCH_2, 2 xCH_3 and 2 x$H_{2'a}$), 1.83 (m, 6H, 2 xCH_2 and 2 x$H_{2'b}$), 1.15 (dt, 6H, *J* = 6.98, 6.97 and 1.79 Hz, 2 xCH_3), 0.83 (m, 36H, 4x (C–$(CH_3)_3$)), 0.02 (m, 24H, 4x(Si–$(CH_3)_2$)).^{13}C NMR (63 MHz, $CDCl_3$): δ 167.40 (CO-DHP), 162.57 (C4), 152.25 (C-2 and C-6 DHP), 150.12 (C-2 and C-6 DHP), 146.37 (C2), 138.94 (C6), 115.37 (C5), 108.03 (C-3 and C-5 DHP), 100.48 (C-3 and C-5 DHP), 87.77 (C4'), 86.10 (C1'), 84.73 (C1'), 72.57 (C3'), 63.60 (C5'), 59.60 (OCH_2), 40.10 (C2'), 37.02 (C-4 DHP), 33.44 (CH_2), 27.12 (CH_2), 26.06 (C–CH_3), 25.81 (C–CH_3), 21.11 (CH_2), 19.56 (CH_3), 18.26 (2 x(Si-C)), 14.56 (CH_3), -4.66 (2 x(Si–CH_3)), -5.26 (2 x(Si–CH_3)). ESIMS: *m/z* calcd for $C_{34}H_{55}N_3O_8Si_2$ [M+H] 690.35 found, 690.9.

General procedure for the deprotection of 3´, 5´-hydroxy groups **7a-f**

General procedure for preparing **7a-e**: Compound (**7a-e**) (0.1 mmol) was dissolved in approximately 15 mL of THF and added (0.25 mmol) TBAF/THF/H_2O the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue obtained was purified on silica gel column CH_2Cl_2 and MeOH (9/1).

9-(1-(4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione **7a**

Yield 88%, yellow solid,[1]H NMR (250 MHz, DMSO-d_6): δ 10.84 (s, 1H, NH), 9.33 (s, 1H, NH- DHP), 7.43 (s, 1H, H-6), 6.08 (t, 1H, *J* = 6.73 Hz, $H_{1'}$), 5.25 (d, 1H, *J* = 3.93 Hz, $O_{3'}$-H), 4.89 (t, 1H, *J* = 5.12 Hz, $O_{5'}$-H), 4.54 (s, 1H, H4-DHP), 4.20 (m, 1H, $H_{3'}$), 3.75 (m, 1H, $H_{4'}$), 3.54 (m, 2H, $H_{5'}$), 2.38 (m, 4H, 2 xCH_2), 1.91 (m,10H,4xCH_2 and $H_{2'}$). ^{13}C NMR (63 MHz, DMSO-d_6): δ 194.61 (2 xCO-DHP), 161.25 (C4), 152.24 (C-2 and C-6 DHP), 150.16 (C2), 137.50 (C6), 116.94 (C5), 109.73 (C-3 and C-5 DHP), 87.35 (C4'), 84.05 (C1'), 70.70 (C3'), 61.93 (C5'), 40.49 (C2'), 39.39 (C-4 DHP), 36.79 (2 xCH_2-CO), 28.46 (C-4 DHP), 26.37 (2 xCH_2), 20.88 (2 xCH_2). MALDI-TOF: calcd for $C_{22}H_{25}N_3O_7$ 443.17 found, 443.11.

Dimethyl 4-(1-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **7b**

Yield 87%, yellow solid, [1]H NMR (250 MHz, DMSO-d_6): δ 11.01 (s, 1H, NH), 8.80 (s, 1H, NH- DHP), 7.27 (s, 1H, H-6), 6.12 (t, 1H, *J* = 6.83 Hz, $H_{1'}$), 5.23 (d, 1H, *J* = 4.03 Hz, $O_{3'}$-H), 4.89 (t, 1H, *J* = 5.04 Hz, $O_{5'}$-H), 4.64 (s, 1H, H4-DHP), 4.17 (m, 1H, $H_{3'}$), 3.75 (m, 1H, $H_{4'}$), 3.50 (m, 8H, 2 xOCH_3 and $H_{5'}$), 2.07 (m, 7H, 2 xCH_3 and $H_{2a'}$), 1.86 (m, 1H, $H_{2b'}$). ^{13}C NMR (63 MHz, DMSO-d_6): δ 167.40 (2 xCO-DHP), 161.74 (C4), 150.11 (C2), 146.18 (C-2 and C-6 DHP), 136.40 (C6), 117.15 (C5), 98.39 (C-3 and C-5 DHP), 87.32 (C4'), 83.86 (C1'), 70.88 (C3'), 61.91 (C5'), 50.50 (2 xOCH_3), 40.55 (C2'), 33.36 (C-4 DHP), 17.92 (2 xCH_3). MALDI-TOF: calcd for $C_{20}H_{25}N_3O_9$ 451.16 found, 452.73.

Diethyl 4-(1-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **7c**

Yield 85%, yellow solid, [1]H NMR (250 MHz, DMSO-d_6): δ 11.04 (s, 1H, NH), 8.76 (s, 1H, NH- DHP), 7.36 (s, 1H, H-6), 6.16 (dd, 1H, *J* = 7.64 and 6.08 Hz, $H_{1'}$), 5.27 (d, 1H, *J* = 4.01 Hz, $O_{3'}$-H), 4.92 (t, 1H, *J* = 4.94 Hz, $O_{5'}$-H), 4.67 (s, 1H, H4-DHP), 4.22 (m, 1H, $H_{3'}$), 4.04 (m, 4H, 2 xOCH_2-), 3.80 (d m, 1H, $H_{4'}$), 3.52 (m, 1H, $H_{5'}$), 2.11 (m, 7H, 2 xCH_3 and $H_{2'a}$), 1.89 (m, 1H, $H_{2'b}$), 1.16 (dt, 6H, *J* = 7.01 and 1.56 Hz, 2 xCH_3).[13]C NMR (63 MHz, DMSO-d_6): 166.97 (2 xCO-DHP), 161.61 (C4), 150.13 (C2), 146.00 (C-2 and C-6 DHP), 136.56 (C6), 117.67 (C5), 98.63 (C-3 and C-5 DHP), 87.31 (C4'), 83.89 (C1'), 70.92 (C3'), 61.85 (C5'), 58.80 (2 xOCH_2), 40.54 (C2'), 33.46 (C-4 DHP), 18.06 (2 xCH_3), 14.25 (2 x-CH_3). MALDI-TOF: calcd for $C_{22}H_{29}N_3O_9$ 479.19 found, 479.88.

Diisobutyl 4-(1-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **7d**

Yield 83%, yellow solid, [1]H NMR (250 MHz, DMSO-d_6): δ 11.09 (s, 1H, NH), 8.87 (s, 1H, NH- DHP), 7.15 (s, 1H, H-6), 6.13 (m, 1H, $H_{1'}$), 5.30 (d, 1H, *J* = 4.04 Hz, $O_{3'}$-H), 4.87 (t, 1H, *J* = 5.31 Hz, $O_{5'}$-H), 4.82 (s, 1H, H4-DHP), 4.18 (m, 1H, $H_{3'}$), 3.77 (m, 5H, 2 xOCH_2 and $H_{4'}$), 3.46 (m, 2H, $H_{5'}$), 2.13 (m, 7H,

2 xCH_3 and $H_{2'a}$), 1.87 (m, 3H, 2 xCH and $H_{2'b}$), 0.89 (m, 12H, 2 x(-CH_3)$_2$).^{13}C NMR (63 MHz, DMSO-d_6): δ 167.00 (2 xCO-DHP), 161.70 (C4), 150.07 (C2), 146.03 (C-2 DHP), 145.42 (C-6 DHP), 135.83 (C6), 117.93 (C5), 99.25 (C-3 DHP), 98.71 (C-5 DHP), 87.24 (C4'), 83.87 (C1'), 70.84 (C3'), 69.14 (2 xOCH_2-), 61.96 (C5'), 40.52 (C2'), 32.59 (C-4 DHP), 27.28 (2 xCH), 19.06 (2 x(-CH_3)$_2$), 17.94 (2 xCH_3). ESIMS: *m/z* calcd for $C_{26}H_{37}N_3O_7$ [M-H] 534.25 found, 534.60.

Ethyl 4-(1-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **7f**

The product is a mixture of two diasteroisomers in the ratio 0.53/0.47

Yield 80%, yellow solid, ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.99 (s, 2H, NH), 9.14 (m, 2H, NH- DHP), 7.41 (s, 1H, H-6), 7.34 (s, 1H, H-6), 6.14 (m, 2H, $H_{1'}$), 5.30 (d, 2H, *J* = 3.45 Hz, $O_{3'}$-H), 4.95 (m, 2H, $O_{5'}$-H), 4.68 (s, 1H, H4-DHP), 4.65 (s, 1H, H4-DHP), 4.24 (m, 2H, 2 x$H_{3'}$), 4.00 (m, 4H, 2 xOCH_2-), 3.79 (m, 2H, 2 x$H_{4'}$), 3.54 (m, 4H, 4x$H_{5'}$), 2.51 (m, 16H, 2 xCH_2, 2 x CH_2, 2 xCH_3 and 2 x$H_{2'a}$), 2.44 (m, 4H, 4x$H_{2'}$), 1.91 ((m, 4H, 2 xCH_2), 1.16 (dt, 6H, *J* = 7.02, 7.02 and 1.77 Hz, 2 xCH_3). ^{13}C NMR (63 MHz, DMSO-d_6): δ 167.07 (CO-DHP), 161.41 (C4), 152.71 (C-2 and C-6 DHP), 150.14 (C-2 and C-6 DHP), 144.80 (C2), 136.99 (C6), 118.36 (C5), 107.77 (m), 87.29 (C-3 and C-5 DHP), 83.89 (C4'), 70.82 (C3'), 61.84 (C5'), 58.87 (OCH_2), 40.55 (C2'), 36.74 (C-4 DHP), 31.11 (CH_2), 26.18 (CH_2), 20.90(CH_2), 19.21 (CH_3), 14.17 (CH_3). MALDI-TOF: calcd for $C_{22}H_{27}N_3O_8$ 461.18 found, 463.81.

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REFERENCES AND NOTES

1. P. Talwan, S. Chaudhary, K. Kumar, and R. K. Rawal, C*urr. Bioact. Compd.*, 2017, **13**, 109.
2. M. M. Heravi and V. Zadsirjan, *ChemistrySelect*, 2022, **7**, e202104032.
3. A. Bryzgalov, T. Tolstikova, B. Koshcheev, and A. Maksimov, *Results in Chemistry*, 2023, **5**, 100705.
4. S. Begum and K. Sirisha, *Indian J. Chem. - B*, 2021, **60 B**, 433.
5. J. M. Madar, L. A. Shastri, S. L. Shastri, M. Holiyachi, N. S. Naik, P. Gudimani, V. Pawar, A. K. Shettar, S. D. Joshi, and V. A. Sungar, *Indian J. Chem.*, 2022, **61**, 159.

6. P. Anaikutti and P. Makam, *Bioorg. Chem.*, 2020, **105**, 104379.
7. R. S. Kumar, A. Idhayadhulla, A. J. Abdul Nasser, and J. Selvin, *Eur. J. Med. Chem.*, 2011, **46**, 804.
8. K. N. Venugopala, P. K. Deb, M. Pillay, D. Chopra, S. Chandrashekharappa, M. A. Morsy, B. E. Aldhubiab, M. Attimarad, A. B. Nair, N. Sreeharsha, M. Kandeel, R. Venugopala, and V. Mohanlall, *Curr. Top. Med. Chem.*, 2021, **21**, 295.
9. R. Kumar, D. Kumar, R. K. Upadhyay, N. Deswal, P. Takkar, A. Kareem, V. Kumar, and L. S. Kumar, *ChemistrySelect*, 2022, **7**, e202202928.
10. S. M. Gomha, M. M. Edrees, Z. A. Muhammad, N. A. Kheder, S. Abu- Melha, and A. M. Saad, *Polycycl. Aromat. Compd.*, 2022, **42**, 173.
11. A. González, J. Casado, M. G. Gündüz, B. Santos, A. Velázquez-Campoy, C. Sarasa-Buisan, M. F. Fillat, M. Montes, E. Piazuelo, and Á. Lanas, *Front. Microbiol.*, 2022, **13**, 874709.
12. A. Fassihi, Z. Azadpour, N. Delbari, L. Saghaie, H. R. Memarian, R. Sabet, A. Alborzi, R. Miri, B. Pourabbas, J. Mardaneh, P. Mousavi, B. Moeinifard, and H. Sadeghi-aliabadi, *Eur. J. Med. Chem.*, 2009, **44**, 3253.
13. P. S. Mahajan, S. J. Smith, S. H. Hughes, X. Zhao, and T. R. Burke Jr., *Molecules*, 2023, **28**, 1428.
14. A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1881, **14**, 1637.
15. W. Schmidt-Nickels and T. B. Johnson, *J. Am. Chem. Soc.*, 1930, **52**, 4511.
16. E. Coutouli-Argyropoulou and C. Zachariadou, *J. Heterocycl. Chem.*, 2005, **42**, 1135.
17. L. Öhberg and J. Westman, *Synlett*, 2001, **8**, 1296.
18. K. L. Gangadhara, P. Srivastava, J. Rozenski, H.-P. Mattelaer, V. Leen, W. Dehaen, J. Hofkens, E. Lescrinier, and P. Herdewijn, *J. Syst. Chem.*, 2014, **5**, 1.
19. A. Matsuda, M. Inada, H. Nara, E. Ohtsuka, and A. Ono, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2751.
20. K. Sato, W. Hirose, A. Matsuda, Synthesis of 5-formyl-2'-deoxyuridine and its incorporation into oligodeoxynucleotides. Current Protocols in Nucleic Acid Chemistry, Chapter *1*, Unit 1.21, 2008.
21. H. Oguri, S. Hishiyama, T. Oishi, and M. Hirama, *Synlett*, 1995, **12**, 1252.
22. CLSI- Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that grow Aerobically 7th edition Approved Standard M7-A7 Wayne PA: CLSI 2006.