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Simple and rapid synthesis of some nucleoside derivatives: structural and spectral characterization

Shagir A. Chowdhury[a], Mohammad M. R. Bhuiyan[b], Yasuhiro Ozeki[c] and Sarkar M. A. Kawsar[a,c]*

[a]*Laboratory of Carbohydrate and Protein Chemistry, Department of Chemistry, Faculty of Science, University of Chittagong, Chittagong-4331, Bangladesh*
[b]*Department of Chemistry, School of Science and Technology, University of New England, Armidale NSW 2351, Australia*
[c]*Laboratory of Glycobiology and Marine Biochemistry, Department of Life and Environmental System Science, Graduate School of NanoBio Sciences, Yokohama City University, 22-2 Seto, Kanazawa-ku, Yokohama 236-0027, Japan*

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A B S T R A C T

In our present investigation a new series of nucleoside derivatives (**2-13**) were synthesized from uridine (**1**) via only two step reactions by direct acylation method. Firstly, uridine (**1**) was treated with 4-t-butylbenzoyl chloride in pyridine at -5ºC and afforded the 5′-*O*-(4-t-butylbenzoyl)uridine derivative (**2**) in an excellent yield. In order to obtain newer products, the 5′-*O*-uridine derivative was further transformed to a series of 2′,3′-di-*O*-acyl derivatives (**2-13**) containing a wide variety of functionalities in a single molecular framework. The yields of the compounds were more than 80%. The synthesized titled compounds were characterized by their physical properties, FTIR (Fourier transform infrared spectroscopy), 1H-NMR (Nuclear magnetic resonance) spectroscopy and elemental analysis.

1. Introduction

Nucleotides and nucleosides are key compounds involved in major biological processes, such as nucleic acids and protein synthesis, cell signaling, enzyme regulation, and metabolism. Nucleosides and their analogues are of enormous importance. They are an established class of clinically useful medicinal agents possessing antiviral and anticancer activity;[1-4] at the same time they are one class of compounds worthy of further investigation as antibacterial agents since some derivatives have shown moderate to good activity against specific bacterial strains.[5] The chemical modification of naturally occurring nucleoside and nucleotide structures is an important field in nucleic acid and medicinal chemistry. This has led to our interest in the search for new nucleoside derivatives that may be screened for a broad-spectrum of biological activities.

* Corresponding author. Tel.: +88 01762717081, Fax: +88 031 2606014
E-mail address: akawsarabe@yahoo.com (S. M. A. Kawsar)

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Uridine has crucial role in the pyrimidine metabolism of the brain. It supplies nervous tissue with the pyrimidine ring, and in turn, participates in a number of important metabolic pathways. Uridine and its nucleotide derivatives may also have an additional role in the function of the central nervous system as signaling molecules.[6] There are established signaling molecules in the brain, such as amino acids, and adenosine, which are also available in large pools as metabolites.[7, 8]

Nucleosides and carbohydrates can also be acylated selectively using a number of suitable methods to give newer derivatives, some of which show effective biological activity. Selective acylation is very important in the field of nucleoside chemistry because of its usefulness for the synthesis of biologically active products. During the last few years, many workers have investigated selective acylation of hydroxyl groups of the carbohydrate moieties of nucleosides and nucleotides using various methods.[9,10] Different methods for acylation of carbohydrates and nucleosides have so far been developed and employed successfully.[11,12] Of these, a direct method has been found to be the most encouraging method for acylation of carbohydrates and nucleosides.[13]

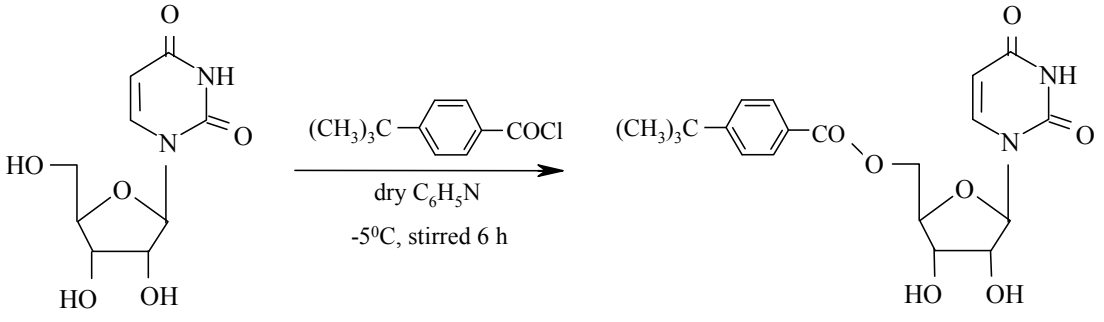
It was found from the literature survey that nitrogen, sulphur and halogen containing heterocyclic compounds showed marked antimicrobial activities.[14] When heterocyclic part become attached to carbohydrates,[15] their efficiency to inhibit bacteria or fungi sharply increased. A large number of biologically active compounds also possess aromatic, heteroaromatic and acyl substituents.[15] It is also known that if an active nucleus is linked to another active nucleus, the resulting molecule may possess greater potential for biological activity.[15-17]

From our previous works we also observed that in many cases the combination of two or more acyl substituents in a single molecular framework enhances the biological profile many fold comparing to their parent nuclei.[18-24] Encouraged by our own findings and previous reports, we synthesized a series of nucleoside i.e., uridine derivatives deliberately incorporating a wide variety of probable biologically active components to the ribose moiety. We report here the synthetic part of the work whereas the biological evaluation part will be the subject of a forthcoming communication.

2. Results and Discussion

Chemistry and spectral characterization

The main aim of the research work presented in this paper was to carry out selective 4-*t*-butylbenzoylation of uridine (**1**) with 4-*t*-butylbenzoyl chloride using the direct method. A series of derivatives of the resulting 4-*t*-butylbenzoylation product were prepared using non-traditional eleven acylating agents (**Schemes 1** and **2**). The structure of all acylated products were ascertained by analyzing their FTIR, ^{1}H-NMR spectra, elemental and physicochemical data (**Table 1**). The 4-*t*-butylbenzoate **2** and its derivatives were employed as test chemicals for antimicrobial studies and the results will be reported later.



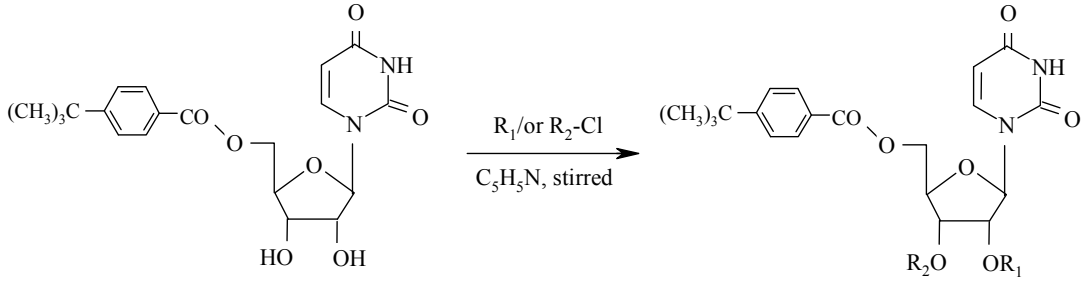
Uridine (**1**)

5/-*O*-(4-*t*-Butylbenzoyl)uridine (**2**)

Scheme 1. Synthesis of 5/-*O*-(4-*t*-butylbenzoyl)uridine (**2**)

Our initial effort was to carry out the reaction of uridine (**1**) with 1.1 molar amount of 4-*t*-butylbenzoyl chloride in dry pyridine at -5^{0}C. Conventional work-up procedure, followed by silica gel column chromatographic separation, we were able to purify 4-*t*-butylbenzoyl derivative (**2**) as needless. The IR spectrum of compound **2** showed absorption bands at: 1785 cm^{-1} (-CO stretching), 3530 cm^{-1} (-OH stretching). The ^{1}H-NMR spectrum of compound **2** displayed the following characteristic peaks at δ 7.96 (2H, d, J = 8.5 Hz), δ 7.34 (2H, d, J=8.5 Hz) and δ 1.28 (9H, s), indicating the presence of one 4-*t*-butylbenzoyl group in the molecule. The introduction of this group to position 5$^/$ was shown by deshielding of the C-5$^/$ proton to δ 5.78 (as dd, J = 2.2 and 12.3 Hz, 5$^/$a) and 5.74 (as dd, J = 2.1 and 12.2 Hz, 5$^/$b) from its value in the precursor diol (**2**). By complete analysis of the IR and ^{1}H-NMR spectra of this compound was in agreement with the structure accorded as 5$^/$-*O*-(4-*t*-butylbenzoyl)uridine (**2**).

Further support for the structure of the 4-*t*-butylbenzoate **2** was achieved by the conversion to acetyl derivative **3** and its identification. Thus, acetylation of compound **2** with acetic anhydride in pyridine, followed by usual procedure and purification, provided the di-*O*-acetyl derivative (**3**) as crystalline solid. Recrystallization from ethyl acetate-hexane gave the pure compound (**3**) as prism m.p. 106-108^{0}C. The IR spectrum of compound **3** showed the following absorption bands: 1765, 1748 and 1680 cm^{-1} stretching due to –CO groups. The presence of two three-proton singlets at δ 2.10 and δ 2.04 in the ^{1}H-NMR spectrum of compound **3** was attributed to the methyl protons of two acetyloxy (C*H*$_3$CO-) groups. The downfield shifts of H-2$^/$ and H-3$^/$ to δ 5.61 (as m) and δ 5.49 (as dd, J = 7.2 and 5.6 Hz), as compared to the precursor compound **2** (δ 4.22, d, J = 5.5 Hz, H-2$^/$; δ 4.10, dd, J = 7.4 and 5.4 Hz, H-3$^/$) indicated the attachment of the acetyl groups at positions 2$^/$ and 3$^/$. The complete analysis of the IR and ^{1}H-NMR spectra of the acetyl derivative was assigned as 2$^/$,3$^/$-di-*O*-acetyl-5$^/$-*O*-(4-*t*-butylbenzoyl)uridine (**3**).



5$^/$-*O*-(4-*t*-Butylbenzoyl)uridine (**2**) 2$^/$,3$^/$-di-*O*-acyl uridine derivatives (**3-13**)

2: $R_1 = R_2 = H$

3: $R_1 = R_2 = CH_3CO$-

4: $R_1 = R_2 = CH_3(CH_2)_3CO$-

5: $R_1 = R_2 = CH_3(CH_2)_4CO$-

6: $R_1 = R_2 = CH_3(CH_2)_8CO$-

7: $R_1 = R_2 = CH_3(CH_2)_{10}CO$-

8: $R_1 = R_2 = CH_3(CH_2)_{12}CO$-

9: $R_1 = R_2 = CH_3(CH_2)_{14}CO$-

10: $R_1 = R_2 = CH_3SO_2$-

11: $R_1 = R_2 = 3\text{-Cl.C}_6H_4CO$-

12: $R_1 = R_2 = 4\text{-Cl.C}_6H_4CO$-

13: $R_1 = R_2 = 2,6\text{-di.Cl.C}_6H_4CO$-

Scheme 2. Synthesis of uridine derivatives (**3-13**)

Pentanoylation of the compound **2** with pentanoyl chloride using the conventional work-up and purification procedure provided the pentanoyl derivative (**4**) as thick syrup. IR spectrum showed the absorption band at 1735 cm^{-1} for carbonyl stretching. In its ^{1}H-NMR spectrum, the resonance peaks three four-proton multiplet at δ 2.36 {2×$CH_3(CH_2)_2CH_2CO$-} and δ 1.63 {2×$CH_3CH_2CH_2CH_2CO$-} and δ 1.40 {2×$CH_3CH_2(CH_2)_2CO$-} and one six-proton multiplet at δ 0.88 {2×$CH_3(CH_2)_3CO$-} showed

the presence of two pentanoyl groups. The deshielding of H-2′, and H-3′ protons to δ 4.52 (as d, J= 5.2 Hz) and δ 4.48 (as dd, J= 7.6 and 5.5 Hz) from their precursor compound **2** indicated the introduction of the two pentanoyl groups at positions 2′ and 3′. Reaction of compound **2** with hexanoyl chloride in dry C_5H_5N, provided the hexanoyl derivative (**5**) as needles m.p. 60-62^{0}C (ethyl acetate-hexane). The IR spectrum of this compound showed the characteristics absorption bands at 1780, 1708 cm^{-1} (-CO) stretching. The ^{1}H-NMR spectrum of compound **5** displayed characteristics two four-proton multiplet at δ 2.38 {2×$CH_3(CH_2)_3CH_2CO$-}, and δ 1.64 {2×$(CH_3)_2CH_2CH_2CO$-}, a eight-proton multiplet at δ 1.29 {2×$CH_3(CH_2)_2CH_2CH_2CO$-} and one six-proton multiplet at δ 0.96 {2×$CH_3(CH_2)_4CO$-} showing the attachment of two hexanoyl groups in the compound. The resonance for H-2′, and H-3′ protons appeared at δ 4.52 (as d, J= 5.2 Hz) and δ 4.47 (as dd, J= 7.8 and 5.6 Hz) which shifted downfield from their precursor compound **2** indicating the attachment of the hexanoyl groups at positions 2′ and 3′. The rest of the IR and ^{1}H-NMR spectra enabled us to assign the structure of the hexanoyl derivative as 5′-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-hexanoyluridine (**5**).

Table 1. List of physicochemical properties of the synthesized uridine derivatives (**2**-**13**).

Compd.	Solvent system	Time (h)	R_f	Yield (mg)	%	mp. (ºC)
2	CH_3OH-$CHCl_3$ (1:12)	7	0.50	243	48	159-161
3	CH_3OH-$CHCl_3$ (1:20)	6.5	0.50	56	92	106-108
4	CH_3OH-$CHCl_3$ (1:18)	6.5	0.50	62	87	Thick syrup
5	CH_3OH-$CHCl_3$ (1:17)	6.0	0.50	67	89	60-62
6	CH_3OH-$CHCl_3$ (1:20)	6.5	0.51	74	85	Pasty mass
7	$C_2H_5COOCH_3$-*n*hexane (1:18)	6.0	0.50	72	75	Semi-solid
8	CH_3OH-$CHCl_3$ (1:20)	6.5	0.50	68	82	Pasty mass
9	CH_3OH-$CHCl_3$ (1:19)	6.0	0.50	69	78	118-120
10	CH_3OH-$CHCl_3$ (1:18)	6.5	0.50	52	84	122-124
11	CH_3OH-$CHCl_3$ (1:20)	6.5	0.50	74	87	126-128
12	CH_3OH-$CHCl_3$ (1:22)	6.0	0.50	54	79	158-160
13	CH_3OH-$CHCl_3$ (1:20)	6.0	0.50	76	81	Pasty mass

Additional support for the structure accorded to compound **2** was achieved by preparation and identification of decanoyl derivative (**6**) in good yield. The infrared spectrum of compound **6** showed the absorption band at 1760 cm^{-1} due to -CO stretching. The ^{1}H-NMR spectrum of compound **6** displayed two four-proton multiplets at δ 2.37 {2×$CH_3(CH_2)_7CH_2CO$-} and 1.66 {2×$CH_3(CH_2)_6CH_2CH_2CO$-}, a twenty four-proton multiplet at δ 1.24 {2×$CH_3(CH_2)_6(CH_2)_2CO$-} and a six-proton multiplet at δ 0.88 {2×$CH_3(CH_2)_8CO$-} showing the attachment of two decanoyl groups in the molecule. By similar procedure, the lauroyl derivative (**7**) was obtained as semi-solid. The IR spectrum displayed absorption bands at 1758 cm^{-1} due to carbonyl stretching. In the ^{1}H-NMR spectrum of **7** two four-proton multiplet at 2.36 {2×$CH_3(CH_2)_9CH_2CO$-}, δ 1.62 {2×$CH_3(CH_2)_8CH_2CH_2CO$-} a thirty two-proton multiplet at δ 1.27 {2×$CH_3(CH_2)_8(CH_2)_2CO$-} and a six-proton multiplet at δ 0.87 {2×$CH_3(CH_2)_{10}CO$-}, therefore, indicating the presence of two lauroyl groups in the compound **7**. The downfield shift of H-2′ and H-3′ protons to δ 5.09 (as d, J= 5.8 Hz) and δ 4.97 (as dd, J=7.2 and 5.5 Hz) from its values of the precursor diol **2** (δ 4.22 and δ 4.10) showed the attachment of the two lauroyl groups at positions 2′ and 3′. The rest of the IR and ^{1}H-NMR spectrum also supports to make this assumption.

Compound **2** was then allowed to react with myristoyl chloride in dry pyridine under direct acylation conditions and obtained compound **8**. IR spectrum showed the band at 1680 cm^{-1} for -CO stretching. In its ^{1}H-NMR spectrum, a four-proton multiplet at δ 2.33 {2×$CH_3(CH_2)_{11}CH_2CO$-}, a forty four-proton multiplet at δ 1.27 {2×$CH_3(CH_2)_{11}CH_2CO$-} and a six-proton multiplet at δ 0.88 {2×$CH_3(CH_2)_{12}CO$-} were due to the presence of two myristoyl groups in the compound. The downfield shift of the H-2′ and H-3′ protons to δ 5.45 (as m) and δ 5.33 (as dd, J=7.3 and 5.3 Hz) from their values and the resonances of other protons in their anticipated positions showed the attachment of myristoyl groups at positions 2′ and 3′. We next treated compound **2** with palmitoyl chloride under similar conditions and following the same work-up and purification procedures. The targeted compound **9** was isolated as crystalline solid, m.p. 118-120^{0}C (ethyl acetate-hexane). The IR spectrum

displayed the characteristic absorption band at 1718 for –CO stretching. The ^{1}H-NMR spectrum of compound **9** displayed following resonance peaks at: δ 2.32 {4H, m, 2×$CH_3(CH_2)_{13}CH_2$CO-}, δ 1.21 {52H, m, 2×$CH_3(CH_2)_{13}CH_2$CO-} and δ 0.89 {6H, m, 2×$CH_3(CH_2)_{14}$CO-} corresponding to two plamitoyl groups. The introduction of the palmitoyl groups at position 2′ and 3′ were indicated by appearance of H-2′ and H-3′ resonance peaks at δ 5.23 (as m) and δ 5.09 (as dd, J= 7.2 and 5.2 Hz), deshielded considerably from its precursor diol (**2**) By complete analysis of the spectrum of compound **9**, we confidentially assign as 5'-*O*-(4-t-butylbenzoyl)-2′,3′-di-*O*-palmitoyluridine (**9**).

The structure of compound **2** was also supported by its transformation to and identification of the methanesulphonyl derivative (**10**). Compound **10** was prepared as needles m.p. 122-124^{0}C (ethyl acetate-hexane) by using methanesulphonyl chloride in pyridine at freezing temperature. Its IR spectrum exhibited absorption band at 1710 cm^{-1} due to –CO stretching. The presence of two methanesulphonyl groups in the molecule was demonstrated by its ^{1}H-NMR spectrum which displayed two three-proton singlets at δ δ 3.10 and δ 3.04 due to the methyl protons of two methanesulphonyloxy (CH_3SO_2-) groups. Also, the H-2′ and H-3′ protons shifted downfield to δ 5.21 (as d, J=5.8 Hz) and δ 5.03 (as dd, J= 7.7 and 5.6 Hz) from its precursor compound **2** (δ 4.22 and δ 4.10), thereby suggesting the attachment of the two methanesulphonyl groups. We then derivatized the 4-*t*-butylbenzoate **2** using 3-chlorobenzoyl chloride and 4-chlorobenzoyl chloride by applying the direct acylation method. The corresponding 2′,3′-di-substitution products, **11** (87%, as solid mass) and **12** (79%, 158-160^{0}C, ethyl acetate-hexane) were isolated in good yields. Complete analysis of their IR and ^{1}H-NMR spectra clearly demonstrated the formation of the corresponding 2′,3′-di-*O*-substitution products.

Final confirmation of the structure of the compound **2** was provided by preparation of its 2,6-di-chlorobenzoyl derivative (**13**). Reaction of compound **2** with 2,6-dichlorobenzoyl chloride in pyridine, as usual procedure gave the dichlorobenzoyl derivative (**13**) as pasty mass. The IR spectrum of this compound showed absorption band at 1778 cm^{-1} for carbonyl stretching. The ^{1}H-NMR spectrum displayed a six proton multiplet at δ 7.69 (as m, Ar-H) corresponded to two 2,6-dichlorobenzoyl groups present in the compound. The H-2′ and H-3′ protons resonated at δ 5.22 (as d, J= 5.6 Hz) and δ 5.03 (as m) shifted downfield from their precursor compound (**2**), which were indicative of the attachment of the 2,6-dochlorobenzoyl groups at 2′ and 3′ positions. Complete analysis of the IR and ^{1}H-NMR spectrum was in accord with the structure of this compound assigned as 5′-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-(2,6-dichlorobenzoyl)uridine (**13**).

Thus, selective acylation of uridine (**1**) with a number of acylating agents by applying the direct method was unique in that all the reactions provided a single mono-substitution product in reasonably high yield. These acylation products and their derivatives may further be utilized as probable starting materials for the synthesis of newer derivatives. These acylating agents, though seldom used by other workers for selective acylation of nucleosides, were found to be very encouraging in terms of high selectivity and good yields. All these substitution products were subjected to antimicrobial evaluation studies and the results will be reported later in our forthcoming paper.

3. Conclusions

In this article, we have presented the initial efforts to synthesize novel nucleoside derivatives obtained from the direct acylation method. This method demonstrates a very simple, rapid and efficient method for the synthesis. The synthesized compounds 2′,3′-di-*O*-acetyl-5′-*O*-(4-*t*-butylbenzoyl)uridine (**3**) and 5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-hexanoyluridine (**5**) were found to be encouraging in terms of high selectivity and excellent yields as 92% and 89%, respectively.

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4. Experimental

4.1. Materials and methods

Uridine and all reagents used were commercially available (Aldrich and Merck) and were used as received, unless otherwise specified. ^{1}H-NMR (400 MHz) spectra were recorded for solutions in $CDCl_3$ using TMS as internal standard with a Bruker DPX-400 spectrometer. Evaporations were carried out under reduced pressure using VV-1 type vacuum rotary evaporator (Germany) with a bath temperature below 40^{o}C. Melting points were determined on an electro-thermal melting point apparatus (England) and are uncorrected. Column chromatography was performed with silica gel G_{60}. Thin layer chromatography (t.l.c) was performed on Kieselgel GF_{254} and spots were detected by spraying the plates with 1% H_2SO_4 and heating at 150-200^{o}C until coloration took place. The reaction pathways have been summarized in Schemes 1 and 2.

4.2. Synthesis

To a cooled (-5ºC) and stirred solution of uridine (**1**) (3g, 12.3 mmol) in anhydrous pyridine (36 ml) was treated with 4-*t*-butylbenzoyl chloride (2.55 ml, 13.01 mmol) and stirring was continued at this temperature for 7 hrs. The progress of the reaction was checked by t.l.c (methanol-chloroform, 1:12) which indicated full conversion of the starting material into a single product (R_f = 0.50). A few pieces of ice were added to the reaction and flask with constant shaking and then contents extracted with chloroform. The chloroform layer was washed successively with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate and water. The organic layer was concentrated with dried $MgSO_4$ and then the residue was subjected to silica gel column chromatographic purification (methanol-chloroform, 1:12) to furnish the 4-*t*-butylbenzoyl derivative (**2**) (243 mg, 48%) yield as a solid. Recrystallization from ethyl acetate-*n*-hexane gave the 5′-*O*-(4-*t*-butylbenzoyl)uridine (**2**) as needles mp. 159-161°C.

5′-*O*-(4-*t*-butylbenzoyl)uridine (**2**). Colorless crystalline solid, FTIR ($CHCl_3$, ν cm^{-1}): 1785 (-CO), 3530 (-OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (1H, s, -NH), 7.96 (2H, d, J = 8.5 Hz, Ar-H), 7.81 (1H, d, J = 7.8 Hz, H-6), 7.34 (2H, d, J = 8.5 Hz, Ar-H), 5.91 (1H, d, J = 5.4 Hz, H-1′), 5.81 (1H, s, 2′-OH), 5.78 (1H, dd, J = 2.2 and 12.3 Hz, H-5′a), 5.74 (1H, dd, J = 2.1 and 12.2 Hz, H-5′b), 5.68 (1H, d, J = 8.0 Hz, H-5), 5.42 (1H, s, 3′-OH), 4.48 (1H, dd, J = 2.2 and 5.4 Hz, H-4′), 4.22 (1H, d, J = 5.5 Hz, H-2′), 4.10 (1H, dd, J = 7.4 and 5.4 Hz, H-3′), 1.28{9H, s, (CH_3) $_3$C-}. Anal. Calcd for $C_{20}H_{24}N_2O_7$ %: C, 59.42; H, 5.98; Found: C, 59.47; H, 6.02.

*4.3. General procedure for the synthesis of 5′-O-(4-t-butylbenzoyl)uridine derivatives (**3-13**)*

A cooled (0°C) and stirred solution of the 5′-*O*-(4-*t*-butylbenzoyl)uridine (**2**) (50 mg, 0.13 mmol) in dry pyridine (3 ml) was separately treated with acetic anhydride (0.046 ml, 0.39 mmol), pentanoyl chloride (0.057 ml, 0.43 mmol), hexanoyl chloride (0.065 ml, 0.54 mmol), decanoyl chloride (0.116 ml, 0.52 mmol), lauroyl chloride (0.14 ml, 0.39 mmol), myristoyl chloride (0.195 ml, 0.67 mmol), palmitoyl chloride (0.15 ml, 0.59 mmol), methanesulfonyl chloride (0.165 ml, 0.73 mmol), 3-chlorobenzoyl chloride (0.1 ml, 0.017 mmol), 4-chlorobenzoyl chloride (0.13 ml, 0.018 mmol) and 2,6-di-chlorobenzoyl chloride (0.14 ml, 0.019 mmol), respectively and stirring was continued at 0°C for 6-7.5 hrs. The progress of the reaction was monitored by t.l.c., which indicated formation of a single product. The reaction mixture was then allowed to stand at room temperature overnight. Excess reagent

was decomposed by addition of a few pieces of ice to the flask. The contents in the flask were extracted with chloroform (3×10 ml). The organic layer was washed with dilute hydrochloric acid, followed by saturated aqueous sodium hydrogen carbonate solution and distilled water. The organic layer was dried magnesium sulfate, filtered and concentrated to dryness. The resulting syrupy residue was passed through a silica gel column and eluted with methanol-chloroform and ethyl acetate-*n*-hexane at different ratio (Table 1) to yield compound **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12** and **13**, respectively.

4.4. Physical and spectral data

2′,3′-di-*O*-acetyl-5′-*O*-(4-*t*-butylbenzoyl)uridine (**3**). White needles (ethyl acetate-hexane), FTIR ($CHCl_3$, ν cm^{-1}): 1765, 1748 and 1680 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (1H, s, -NH), 7.94 (2H, d, J = 8.5 Hz, Ar-H), 7.85 (1H, d, J = 7.8 Hz, H-6), 7.39 (2H, d, J = 8.6 Hz, Ar-H), 5.93 (1H, d, J = 5.5 Hz, H-1′), 5.73 (2H, m H-5′) 5.64 (1H, d, J = 7.9 Hz, H-5), 5.61 (1H, m, H-2′) , 5.49 (1H, dd, J = 7.2 and 5.6 Hz, H-3′), 4.45 (1H, m, H-4′), 2.10, 2.04 (2 × 3H, 2 × s, 2×C*H*$_3$CO-). 1.27 {9H, s, (C*H*$_3$) $_3$C-}. Anal. Calcd for $C_{24}H_{28}N_2O_9$ %: C, 59.01; H, 5.77; Found: C, 59.04; H, 5.81.

5′-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-pentanoyluridine (**4**). Colorless thick syrup, FTIR ($CHCl_3$, ν cm^{-1}): 1735 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (1H, s, -NH), 7.92 (2H, d, J = 8.6 Hz, Ar-H), 7.48 (1H, d, J = 7.8 Hz, H-6), 7.35 (2H, m, Ar-H), 6.19 (1H, d, J = 5.5 Hz, H-1′), 5.72 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 5.63 (1H, dd, J = 2.1 and 12.2 Hz, H-5′b), 5.48 (1H, d, J = 7.8 Hz, H-5), 4.52 (1H, d, J = 5.2 Hz, H-2′), 4.48 (1H, dd, J = 7.6 and 5.5 Hz, H-3′), 4.39 (1H, m, H-4′), 2.36 {4H, m, 2×$CH_3(CH_2)_2C$*H*$_2$CO-}, 1.63 (4H, m, 2×CH_3CH_2C*H*$_2CH_2$CO-), 1.40 {4H, m, 2×CH_3C*H*$_2(CH_2)_2$CO-}, 1.28 {9H, s, (C*H*$_3$)$_3$C-}, 0.88 {6H, m, 2×C*H*$_3(CH_2)_3$CO-}. Anal. Calcd for $C_{32}H_{40}N_2O_9$ %: C, 64.0; H, 7.39; Found: C, 64.07; H, 7.44.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-hexanoyluridine (**5**). White needles (ethyl acetate-hexane), FTIR ($CHCl_3$, ν cm^{-1}): 1780, 1708 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (1H, s, -NH), 7.98 (2H, d, J = 8.4 Hz, Ar-H), 7.80 (1H, d, J = 7.8 Hz, H-6), 7.51 (2H, d, J = 8.6 Hz, Ar-H), 6.14 (1H, d, J = 5.4 Hz, H-1′), 5.69 (1H, dd, J = 2.1 and 12.2 Hz, H-5′a), 5.64 (1H, dd, J = 2.2 and 12.2 Hz, H-5′b), 5.50 (1H, d, J = 7.7 Hz, H-5), 4.52 (1H, d, J = 5.2 Hz, H-2′), 4.47 (1H, dd, J = 7.8 and 5.6 Hz H-3′), 4.46 (1H, dd, J = 2.2 and 5.3 Hz, H-4′), 2.38 {4H, m, 2×$CH_3(CH_2)_3C$*H*$_2$CO-}, 1.64 {4H, m, 2×$CH_3(CH_2)_2C$*H*$_2CH_2$CO-}, 1.29 {8H, m, 2×$CH_3(C$*H*$_2)_2CH_2CH_2$CO-}, 1.27{9H, s, (C*H*$_3$)$_3$C-}, 0.96 {6H, m, 2×C*H*$_3(CH_2)_4$CO-}. Anal. Calcd for $C_{32}H_{44}N_2O_9$ %: C, 64.15; H, 7.34; Found: C, 64.19; H, 7.39.

5′-*O*-(4-*t*-butylbenzoyl)-2,′3′-di-*O*-decanoyluridine (**6**). White syrup, FTIR ($CHCl_3$, ν cm^{-1}): 1760, (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (1H, s, -NH), 7.78 (2H, d, J = 8.5 Hz, Ar-H), 7.74 (1H, d, J = 7.8 Hz, H-6), 7.53 (2H, d, J = 8.5 Hz, Ar-H), 5.79 (1H, m, H-1′), 5.69 (2H, m, H-5a′ and H-5′b), 5.60 (1H, d, J = 7.9 Hz, H-5), 5.08 (1H, d, J = 6.0 Hz, H-2′), 4.91 (1H, m, H-3′), 4.58 (1H, m, H-4′), 2.37 {4H, m, 2×$CH_3(CH_2)_7C$*H*$_2$CO-}, 1.66 {4H, m, 2×$CH_3(CH_2)_6C$*H*$_2CH_2$CO-}, 1.26{9H, s, (C*H*$_3$)$_3$C-}, 1.24 {24H, m, 2×$CH_3(C$*H*$_2)_6CH_2CH_2$CO-}, 0.88 {6H, m, 2×C*H*$_3(CH_2)_8$CO-}. Anal. Calcd for $C_{40}H_{60}N_2O_9$ %: C, 67.55; H, 8.48; Found: C, 67.59; H, 8.53.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-lauroyluridine (**7**). Colorless pasty mass, FTIR ($CHCl_3$, ν cm^{-1}): 1758 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (1H, s, -NH), 7.79 (1H, d, J = 8.5 Hz, Ar-H), 7.70 (1H, m, H-6), 7.54 (2H, d , J = 8.6 Hz , Ar-H), 5.69 (1H, m, H-1′), 5.54 (2H, m, H-5′a and H-5′b), 5.46 (1H, d, J = 8.0 Hz, H-5), 5.09 (1H, d, J = 5.8 Hz, H-2′), 4.97 (1H, dd, J = 7.2 and 5.5 Hz , H-3′), 4.70 (1H, m, H-4′), 2.36 {4H, m, 2×$CH_3(CH_2)_9C$*H*$_2$CO-}, 1.62 {4H, m, 2×$CH_3(CH_2)_8C$*H*$_2CH_2$CO-}, 1.29 {9H, s, (C*H*$_3$)$_3$C-}, 1.27 {32H, m, 2×$CH_3(C$*H*$_2)_8CH_2CH_2$CO-}, 0.87 {6H, m, 2×C*H*$_3(CH_2)_{10}$CO-}. Anal. Calcd for $C_{44}H_{68}N_2O_9$ %: C, 68.72; H, 8.91; Found: C, 68.77; H, 8.99.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-myristoyluridine (**8**). White pasty, FTIR ($CHCl_3$, ν cm^{-1}): 1680(-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (1H, s, -NH), 7.98 (2H, d, J = 8.6 Hz, Ar-H), 7.51 (1H, d, J = 7.9 Hz, H-6), 7.45 (2H, m, Ar- H), 6.13 (1H, d, J = 5.8 Hz, H-1′), 6.07 (1H, m, H-5′a), 5.78

(1H, m, H-5′b), 5.49 (1H, d, J = 7.6 Hz , H-5), 5.45 (1H, m, H-2′), 5.33 (1H, dd, J = 7.3 and 5.3 Hz, H-3′), 4.45 (1H, m, H-4′), 2.33 {4H, m, 2×$CH_3(CH_2)_{11}CH_2$CO-}, 1.29 {9H, s, (CH_3)$_3$C-}, 1.27 {44H, m, 2×$CH_3(CH_2)_{11}CH_2$CO-}, 0.88 {6H, m, 2×$CH_3(CH_2)_{12}$CO-}. Anal. Calcd for $C_{48}H_{76}N_2O_9$ %: C, 69.87; H, 9.28; Found: C, 69.91; H, 9.30.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-palmitoyluridine (**9**). White crystalline solid (ethyl acetate-hexane), FTIR ($CHCl_3$, ν cm^{-1}): 1718 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (1H, s, -NH), 7.78 (2H, d, J = 8.5 Hz, Ar-H), 7.66 (1H, m, H-6), 7.50 (2H, m, Ar-H), 5.70 (1H, d, J = 5.7 Hz H-1′), 5.50 (1H, dd, J = 2.2 and 12.2 Hz H-5′a), 5.48 (1H, dd, J = 2.1 and 12.2 Hz, H-5′b), 5.45 (1H, d, J = 8.0 Hz, H-5), 5.23 (1H, m, H-2′), 5.09 (1H, dd, J = 7.2 and 5.2 Hz , H-3′), 4.90 (1H, m, H-4′), 2.32 {4H, m, 2×$CH_3(CH_2)_{13}CH_2$CO-}, 1.26 {9H, s, (CH_3)$_3$C-}, 1.21{52H, m, 2×$CH_3(CH_2)_{13}CH_2$CO-}, 0.89 {6H, m, 2×$CH_3(CH_2)_{14}$CO-}. Anal. Calcd for $C_{52}H_{84}N_2O_9$ %: C, 70.87; H, 9.60; Found: C, 70.89; H, 9.66.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-methensulfonyluridine (**10**). White needles (ethyl acetate-hexane), FTIR ($CHCl_3$, ν cm^{-1}): 1710 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (1H, s, -NH), 7.98 (2H, d, J = 8.8 Hz, Ar-H), 7.68 (1H, d ,J = 7.8 Hz, H-6), 7.53 (2H, d ,J = 8.7 Hz, Ar-H), 6.10 (1H, d, J = 5.7 Hz H-1′), 5.73 (1H, dd, J = 2.2 and 12.0 Hz, H-5′a), 5.55 (1H, dd, J = 2.0 and 12.0 Hz H-5′b), 5.35 (1H, d, J = 7.7 Hz, H-5), 5.21 (1H, d, J = 5.8 Hz, H-2′), 5.03 (1H, dd, J = 7.7 and 5.6 Hz, H-3′), 4.62 (1H, m, H-4′), 3.10, 3.04 {2×3H, 2×s, 2×CH_3SO_2-}, 1.27{9H, s, (CH_3)$_3$C-}. Anal. Calcd for $C_{24}H_{28}N_2O_{13}S_2$ %: C, 46.76; H, 4.57; Found: C, 46.81; H, 4.58.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-(3-chlorobenzoyl)uridine (**11**). Colorless crystalline solid (ethyl acetate-hexane), FTIR ($CHCl_3$, ν cm^{-1}): 1728 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (1H, s, -NH), 7.96 (2H, d, J = 8.5 Hz, Ar-H), 7.92 (2H, d, J = 7.8 Hz, Ar-H), 7.88 (2H, s, Ar-H), 7.81 (1H, d, J = 7.8 Hz, H-6), 7.79 (2H, d, J = 7.8 Hz, Ar-H), 7.48 (2H, t, J = 7.6 Hz, Ar -H), 7.35 (2H, d, J = 8.6 Hz, Ar -H), 5.92 (1H, d, J = 5.8 Hz, H-1′), 5.68 (1H, m, H-5′a), 5.53 (1H, m, H-5′b), 5.40 (1H, d, J = 8.2 Hz, H-5), 5.20 (1H, d, J = 6.0 Hz, H-2′), 5.01 (1H, m, H-3′), 4.64 (1H, dd, J = 2.2 and 5.6 Hz, H-4′), 1.27{9H, s, (CH_3)$_3$C-}. Anal. Calcd for $C_{34}H_{30}N_2O_9Cl_2$ %: C, 60.17; H, 4.42; Found: C, 60.22; H, 4.44.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-(4-chlorobenzoyl)uridine (**12**). White solid (ethyl acetate-hexane), FTIR ($CHCl_3$, ν cm^{-1}): 1748 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (1H, s, -NH), 8.02 (4H, m, Ar-H), 7.95 (2H, d, J = 8.8 Hz, Ar-H), 7.77 (1H, d, J = 8.0 Hz, H-6), 7.68 (4H, m, Ar-H), 7.51 (2H, m, Ar-H), 6.10 (1H, d, J = 5.7 Hz, H-1′), 5.89 (2H, m, H-5′a and H-5′b), 5.50 (1H, d, J = 7.7 Hz, H-5), 5.33 (1H, m, H-2′), 4.97 (1H, dd, J = 7.4 and 5.4 Hz, H-3′), 4.63 (1H, dd, J = 2.2 and 5.6 Hz, H-4′), 1.29 {9H, s, (CH_3)$_3$C-}. Anal. Calcd for $C_{34}H_{30}N_2O_9Cl_2$ %: C, 60.17; H, 4.42; Found: C, 60.21; H, 4.46.

5'-*O*-(4-*t*-butylbenzoyl)-2′,3′-di-*O*-(2,6-dichlorobenzoyl)uridine (**13**). Colorless pasty mass, FTIR ($CHCl_3$, ν cm^{-1}): 1778 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (1H, s, -NH), 7.98 (2H, d, J = 8.8 Hz, Ar-H), 7.81 (1H, m, H-6), 7.69 (6H, m , Ar-H), 7.53 (2H, d, J = 8.5 Hz, Ar -H), 5.92 (1H, d, J = 5.5 Hz, H-1′), 5.72 (1H, m, H-5′a), 5.61 (1H, dd, J = 2.2 and 12.2 Hz, H-5′b), 5.47 (1H, m, H-5), 5.22 (1H, d, J = 5.6 Hz H-2′), 5.03 (1H, m, H-3′), 4.38 (1H, dd, J = 2.4 and 5.8 Hz, H-4′), 1.28{9H, s, (CH_3)$_3$C-}. Anal. Calcd for $C_{34}H_{28}N_2O_9Cl_4$ %: C, 59.42; H, 5.98; Found: C, 59.43; H, 6.01.

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