Journal of Siberian Federal University. Chemistry 2020 13(4): 465–478
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DOI: 10.17516/1998-2836-0199

УДК 547.455.522

Ribose Moieties Acylation and Characterization of Some Cytidine Analogs

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Received 03.10.2020, received in revised form 10.11.2020, accepted 03.12.2020

Abstract. Modification of naturally occurring nucleosides is an important area in the search for new agents with therapeutic potential. In this study, nucleoside molecules, that is, cytidine analogs bearing ribose moieties were successfully synthesized to obtain 5′-O-acyl cytidine (2), which in turn was converted into 2′,3′-di-O-acyl cytidine (3–7) through direct acylation. Similarly, several cytidine analogs (8–15) were formed using the aforementioned technique. Physicochemical properties and spectroscopic methods were used to characterize the newly synthesized cytidine analogs. X-ray powder diffraction was employed for quantitatively identifying crystalline compounds. Hence, these synthesized derivatives can be used as potential antimicrobial agents and promising drug candidates.

Keywords: ribose, acylation, analogs, cytidine, spectroscopy.

Citation: Rana K.M., Ferdous J., Hosen A., Kawsar S.M.A. Ribose moieties acylation and characterization of some cytidine analogs, J. Sib. Fed. Univ. Chem., 2020, 13(4), 465–478. DOI: 10.17516/1998-2836-0199

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Ацилирование рибозных фрагментов и характеристики некоторых аналогов цитидина

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Аннотация. Модификация природных нуклеозидов – важная область в поиске новых агентов с терапевтическим потенциалом. В этом исследовании нуклеозидные молекулы, являющиеся аналогами цитидина, с рибозными фрагментами были успешно использованы для синтеза 5-0-ацил цитидина (2), который в свою очередь был превращен в 2,3-ди-0-ацил цитидин (3-7) путем прямого ацилирования. Точно так же, с использованием вышеописанного метода, получено несколько аналогов цитидина (8-15). Синтезированные новые аналоги цитидина были охарактеризованы физико-химическими методами. Для количественной идентификации кристаллических соединений применили метод порошковой рентгеновской дифракции. Эти синтезированные производные могут быть использованы как потенциальные антимикробные агенты и перспективные лекарственные препараты.

Ключевые слова: рибоза, ацилирование, аналоги, цитидин, спектроскопия.

Цитирование: Рана, К.М. Ацилирование рибозных фрагментов и характеристики некоторых аналогов цитидина / К.М. Рана, Дж. Фердоус, А. Хосен, С.М.А. Кавсар // Журн. Сиб. федер. ун-та. Химия, 2020. 13(4). С. 465–478. DOI: 10.17516/1998-2836-0199

Introduction

Nucleosides and their analogues are of enormous importance. They are an established class of clinically useful medicinal agents, possessing antiviral and anticancer activity [1-3]. A number of different types of nucleosides have been synthesized from time to time which are reported to be biologically active, for example, ribavirin or virazole is an important such nucleoside. It has been reported as one of the most powerful synthetic antiviral agent's active against DNA viruses [4]. Virazole has been approved by the FDA for the treatment of viral infections [5]. The 5-azacytidine has been shown to possess promising activity against adult non-lymphocytic leukemia. It can either be synthesized chemically or produced microbiologically. It mainly affects the synthesis and function of DNA [6]. 2′,3′-Dideoxycytidine also been reported to inhibit HIV and its clinical trials have been successfully carried out at NIH in AIDS patients [7]. Structural modifications of nucleosides have

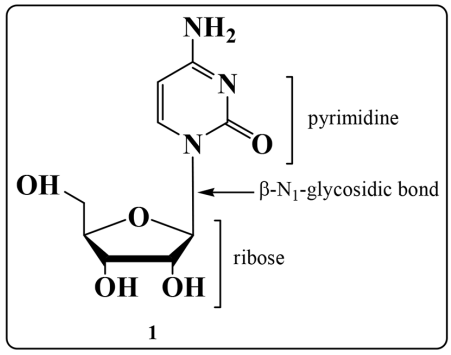

Fig. 1. Structure of cytidine

given rise to widely used drugs such as zidovudine [8] and acyclovir [9], which demonstrates that this strategy offers interesting opportunities to synthesize new therapeutically useful compounds.

Cytidine (Fig. 1) is a nucleoside that consists of a sugar part, ribose, which is linked to the pyrimidine base cytosine via a β-glycosidic bond. Cytidine is a component of RNA and a precursor for uridine. When RNA-rich food is consumed, RNA is broken down into ribosyl pyrimidines (cytidine and uridine) and its basic elements are released for absorption from intestine [10]. RNA-rich foods are considered good cytidine sources. The supplementation of dietary cytidine (5′)-diphosphocholine protects against the development of memory deficits [11].

Modifications in the sugar moiety of nucleosides have resulted in various effective therapeutic applications. In the last few years, many researchers have investigated the selective acylation of the hydroxyl groups of the ribose moieties of nucleosides and nucleotides by using various methods [12, 13]. Different methods for nucleoside acylation have been successfully developed and employed [14, 15]. Among those, a direct method is most encouraging for nucleoside acylation [16].

Encouraged by the literature [17, 18] and our findings [19-21], we synthesized some selectively acylated analogs of cytidine (schemes 1–4) containing various substituents in a single molecular framework and X-ray diffraction studies on them for the first time.

Experimental

Materials and methods

Thin layer chromatography (TLC) was performed on Kieselgel GF_{254}, and visualization was achieved by spraying plates with 1% H_2SO_4 followed by heating the plates at 150–200 °C until coloration occurred. Melting points (m.p.) were determined using an electrothermal melting point apparatus and were uncorrected. Evaporation was performed using a Büchi rotary evaporator under diminished pressure. Analytical grade solvents were employed and purified using standard procedures. Infrared (IR) spectral analyses were conducted using a Fourier transform IR (FTIR) spectrophotometer (IR Prestige-21, Shimadzu, Japan) within 200–4000 cm^{-1} at the Department of Chemistry, University of Chittagong, Bangladesh. The mass spectra of the synthesized compounds were recorded through liquid chromatography electrospray ionization-tandem mass spectrometry in the positive ionization mode (LC/ESI(+)-MS/MS) by using a system comprising a JASSO LC (JASCO, Japan). A Brucker advance DPX 400 MHz with tetramethylsilane as an internal standard was used to record ^{1}H-NMR

spectra in $CDCl_3$ (δ in ppm) at WMSRC, JU, Bangladesh. XRD patterns were obtained using an XRD-53 analyzer, Rigaku, Japan diffractometer, with a back monochromator and Cu target and Kα (λ = 1.5406 nm) in 2θ = 2°–70° at CARS, Dhaka University, Bangladesh. Column chromatography was performed with silica gel G_{60}. $CHCl_3/CH_3OH$ was employed as the solvent system for TLC analyses was in different proportions. All reagents used were commercially available (Aldrich) and used without further purification unless otherwise specified.

Synthesis

Over past several years, our laboratory has been synthesizing nucleoside derivatives containing various acyl groups to explore their antimicrobial properties [30, 31].

In dry DMF (*N*,*N*-dimethylformamide) (3 ml), a cytidine (1) (70 mg, 0.287 mmol) solution was cooled to −5 °C when decanoyl chloride (65 mg, 1.1 molar eq.) was added. The solution was stirred at this temperature for 5 to 6 h and then was allowed to stand at room temperature overnight. Reaction progress was monitored through TLC, which indicated the complete conversion of the starting material into a single product. A few pieces of ice were added to the flask to stop the reaction. Subsequently, the solvent was evaporated using a high pressure vacuum evaporator, and the resulted product was passed through silica gel column chromatography and eluted with (1:24), which provided the decanoyl derivative (2) (92 mg). The recrystallization of ($CHCl_3$–C_6H_{14}) led to the formation of the title derivative (2) as needles. The compound was sufficiently pure for subsequent use without further treatment and identification.

5′-*O*-Decanoylcytidine (2): Yield 83.8% as crystalline solid, M.P. 85–87 °C ($CHCl_3$–C_6H_{14}), R_f = 0.51 ($CHCl_3/CH_3OH$ = 24/1, v/v). FTIR: ν_{max} 1731, 1714 (-CO), 3550 (-NH), 3420 cm^{-1} (-OH). ^{1}H -NMR (400 MHz, $CDCl_3$): δ_H 9.02 (1H, s, -NH), 7.44 (1H, d, J = 7.8 Hz, H-6), 6.56 (1H, d, J = 3.0 Hz, H-1′), 6.49 (1H, s, 2′-OH), 6.01 (1H, dd, J = 2.4 and 12.3 Hz, H-5′a), 5.56 (1H, dd, J = 2.4 and 12.3 Hz, H-5′b), 5.45 (1H, s, 3′-OH), 4.85 (1H, dd, J = 2.4 and 5.6 Hz, H-4′), 4.60 (2H, s, $-NH_2$), 4.45 (1H, d, J = 3.2 Hz, H-2′), 4.31 (1H, dd, J = 3.6 and 5.8 Hz, H-3′), 3.80 (1H, d, J = 7.2 Hz, H-5), 2.38 {2H, m, $CH_3(CH_2)_7CH_2CO$-}, 1.59 {2H, m, $CH_3(CH_2)_6CH_2CH_2CO$-}, 1.32 {12H, m, $CH_3(CH_2)_6(CH_2)_2CO$-}, 0.85 {3H, m, $CH_3(CH_2)_8CO$-}. MS $[M+1]^+$ 398.10.

Anal Calcd. for $C_{19}H_{31}N_3O_6$: % C, 72.54, H, 7.81; found: % C, 72.53, H, 7.82.

General procedure for the direct 2′,3′-di-O-acylation of 5′-O-decanoylcytidine (2) derivatives (3–7)

In DMF (3 ml), octanoyl chloride (0.185 ml, 4 molar eq.) was added to a cooled (0 °C) and stirred solution of the decanoyl derivative (**2**) (110 mg, 0.276 mmol). The mixture was stirred at 0 °C for 8 h and then allowed to stand overnight at room temperature. TLC analyses showed the complete conversion of reactants into a single product. A few pieces of ice were added to the reaction flask to eliminate the excess reagent, and the reaction mixture was evaporated using the high-pressure vacuum evaporator to remove the solvent. The percolation of the resulting product achieved by passing through a silica gel column with the $CHCl_3$–CH_3OH eluant led to the formation of the octanoyl derivative (**3**) (163 mg) as a crystalline solid.

A similar reaction and purification procedure was employed to prepare compounds (**4**), (**5**), (**6**), and (**7**).

5′-*O*-Decanoyl-2′,3′-di-*O*-octanoylcytidine (3): Yield 77.6% as a white crystalline solid, M.P. 89–91 °C ($CHCl_3$–C_6H_{14}), R_f = 0.51 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1729, 1716 (-CO), 3470 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.18 (1H, s, -NH), 7.27 (1H, d, J = 7.8 Hz, H-6), 6.54 (1H, d, J = 3.2 Hz, H-1′), 5.45 (1H, m, H-2′), 4.82 (1H, dd, J = 3.5 and 5.6 Hz, H-3′), 4.67 (1H, dd, J = 2.4 and 12.2 Hz, H-5′a), 4.58 (2H, s, -NH_2), 4.55 (1H, dd, J = 2.4 and 12.2 Hz, H-5′b), 4.38 (1H, dd, J = 2.4 and 5.5 Hz, H-4′), 3.70 (1H, d, J = 7.2 Hz, H-5), 2.37 {4H, m, 2×$CH_3(CH_2)_5CH_2$CO-}, 1.64 {4H, m, 2×$CH_3(CH_2)_4CH_2CH_2$CO-}, 1.29 {16H, m, 2×$CH_3(CH_2)_4(CH_2)_2$CO-}, 0.89 {6H, m, 2×$CH_3(CH_2)_6$CO-}. MS $[M+1]^+$ 650.09.

Anal Calcd. for $C_{35}H_{59}O_8N_3$: % C, 64.71, H, 9.09; % found: C, 64.73, H, 9.06.

5′-*O*-Decanoyl-2′,3′-di-*O*-palmitoylcytidine (4): Yield 91.2% as a white crystalline solid, M.P. 78–79 °C ($CHCl_3$–C_6H_{14}), R_f = 0.54 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1696 (-CO), 3500 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.10 (1H, s, -NH), 7.29 (1H, d, J = 7.7 Hz, H-6), 6.52 (1H, d, J = 3.2 Hz, H-1′), 5.48 (1H, m, H-2′), 4.86 (1H, dd, J = 3.5 and 5.6 Hz, H-3′), 4.67 (1H, dd, J = 2.4 and 12.1 Hz, H-5′a), 4.58 (2H, s, -NH_2), 4.56 (1H, dd, J = 2.4 and 12.1 Hz, H-5′b), 4.41 (1H, dd, J = 2.4 and 5.5 Hz, H-4′), 3.81 (1H, m, H-5), 2.36 {4H, m, 2×$CH_3(CH_2)_{13}CH_2$CO-}, 1.27 {52H, m, 2×$CH_3(CH_2)_{13}CH_2CH_2$CO-}, 0.91 {6H, m, 2×$CH_3(CH_2)_{14}$CO-}. MS $[M+1]^+$ 874.30.

Anal Calcd. for $C_{51}H_{91}O_8N_3$: % C, 70.10, H, 10.42; found: % C, 70.13, H, 10.40.

5′-*O*-Decanoyl-2′,3′-di-*O*-stearoylcytidine (5): Yield 85.3% as crystalline solid, M.P. 95–97 °C ($CHCl_3$–C_6H_{14}), R_f = 0.50 ($CHCl_3$/CH_3OH = 23/1, v/v). FTIR: ν_{max} 1709 (-CO), 3490 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.08 (1H, s, -NH), 7.28 (1H, d, J = 7.7 Hz, H-6), 6.68 (1H, d, J = 3.2 Hz, H-1′), 6.48 (1H, m, H-2′), 6.21 (1H, dd, J = 3.5 and 5.6 Hz, H-3′), 6.07 (1H, dd, J = 2.4 and 12.1 Hz, H-5′a), 5.51 (1H, dd, J = 2.4 and 12.1 Hz, H-5′b), 5.21 (1H, dd, J = 2.4 and 5.5 Hz, H-4′), 4.88 (2H, s, -NH_2), 4.11 (1H, m, H-5), 2.36 {4H, m, 2×$CH_3(CH_2)_{15}CH_2$CO-}, 1.65 {4H, m, 2×$CH_3(CH_2)_{14}CH_2CH_2$CO-}, 1.27 {56H, m, 2×$CH_3(CH_2)_{14}CH_2CH_2$CO-}, 0.90 {6H, m, 2×$CH_3(CH_2)_{16}$CO-}. MS $[M+1]^+$ 930.23.

Anal Calcd. for $C_{55}H_{99}O_8N_3$: % C, 71.0, H, 10.60; % found: C, 71.03, H, 10.63.

5′-*O*-Decanoyl-2′,3′-di-*O*-(triphenylmethyl)cytidine (6): Yield 84.3% as a white crystalline solid, M.P. 102–104 °C ($CHCl_3$–C_6H_{14}), R_f = 0.52 ($CHCl_3$/CH_3OH = 22/1, v/v). FTIR: ν_{max} 1686 (-CO), 3496 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.02 (1H, s, -NH), 7.58 (12H, m, 2×Ar-H), 7.36 (18H, m, 2×Ar-H), 7.22 (1H, d, J = 7.6 Hz, H-6), 6.61 (1H, d, J = 3.2 Hz, H-1′), 5.47 (1H, d, J = 3.2 Hz, H-2′), 4.88 (1H, dd, J = 3.6 and 5.6 Hz, H-3′), 4.68 (1H, dd, J = 2.3 and 12.1 Hz, H-5′a), 4.60 (2H, s, -NH_2), 4.57 (1H, dd, J = 2.4 and 12.1 Hz, H-5′b), 4.49 (1H, dd, J = 2.4 and 5.5 Hz, H-4′), 3.92 (1H, m, H-5). MS $[M+1]^+$ 882.12.

Anal Calcd. for $C_{57}H_{59}O_6N_3$: % C, 77.60, H, 6.71; % found: C, 77.62, H, 6.73.

5′-*O*-Decanoyl-2′,3′-(4-*tert*-butylbenzoyl)cytidine (7): Yield 90.4% as crystalline solid, M.P. 109–111 °C ($CHCl_3$–C_6H_{14}), R_f = 0.52 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1712 (-CO), 3501 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.03 (1H, s, -NH), 8.06 (4H, m, 2×Ar-H), 7.51 (4H, m, 2×Ar-H), 7.28 (1H, d, J = 7.7 Hz, H-6), 6.68 (1H, d, J = 3.2 Hz, H-1′), 5.57 (1H, m, H-2′), 4.96 (1H, dd, J = 3.5 and 5.6 Hz, H-3′), 4.66 (1H, dd, J = 2.4 and 12.1 Hz, H-5′a), 4.54 (2H, s, -NH_2), 4.52 (1H, dd, J = 2.4 and 12.1 Hz, H-5′b), 4.25 (1H, dd, J = 2.4 and 5.5 Hz, H-4′), 4.01 (1H, m, H-5), 1.33, 1.28 {18H, 2×s, 2×$(CH_3)_3C$-}. MS $[M+1]^+$ 718.11.

Anal Calcd. for $C_{41}H_{55}O_8N_3$: % C, 68.60, H, 7.60; % found: C, 68.63, H, 7.58.

In dry DMF (3 ml), a cytidine (**1**) (70 mg, 0.287 mmol) solution was cooled to −5 °C and treated with 1.1 molar equivalent of triphenylmethyl chloride (85 mg) with continuous stirring at the same temperature for 5 to 6 h. Stirring was continued overnight at room temperature. Reaction progress was monitored through TLC. A few pieces of ice were added to the flask to terminate the reaction. Subsequently, the solvent was evaporated using the high-pressure vacuum evaporator. The resulting syrupy mass was purified through silica gel column chromatography (with $CHCl_3$–CH_3OH, 1:24 eluant) to acquire the title compound (**8,** 107 mg) as a crystalline solid.

5′-*O*-(Triphenylmethyl)cytidine (8): Yield 81.2% as a white crystalline solid, M.P. 75–77 °C) ($CHCl_3$–C_6H_{14}), R_f = 0.50 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1701 (-CO), 3547 (-NH), 3416-3468 (br) cm^{-1} (-OH). ^{1}H -NMR (400 MHz, $CDCl_3$): δ_H 9.01 (1H, s, -NH), 7.35 (6H, m, Ar-H), 7.30 (9H, m, Ar-H), 7.23 (1H, d, J = 7.8 Hz, H-6), 6.61 (1H, d, J = 3.0 Hz, H-1′), 6.48 (1H, s, 2′-OH), 5.30 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 5.26 (1H, dd, J = 2.2 and 12.2 Hz, H-5′b), 5.15 (1H, s, 3′-OH), 4.85 (1H, dd, J = 2.2 and 5.6 Hz, H-4′), 4.50 (2H, s, -NH_2), 4.25 (1H, d, J = 3.2 Hz, H-2′), 4.01 (1H, dd, J = 3.6 and 5.8 Hz, H-3′), 3.91 (1H, d, J = 7.2 Hz, H-5). MS $[M+1]^+$ 486.08.

Anal Calcd. for $C_{28}H_{27}O_5N_3$: % C, 69.28, H, 5.56; % found: C, 69.27, H, 5.53.

General procedure for the direct 2′,3′-di-O-acylation of 5′-O-(triphenylmethyl)cytidine derivatives (9–15)

The triphenylmethyl derivative (**8**, 60 mg, 0.124 mmol) was dissolved in dry DMF (3 ml), and the solution was cooled to 0 °C when hexanoyl chloride (0.067 ml, 4 molar eq.) was added. The mixture was stirred at 0 °C for 6 h and at room temperature overnight. The conventional work-up procedure and subsequent chromatographic purification with the $CHCl_3$–CH_3OH (1:24) eluant led to the formation of 2',3'-di-*O*-hexanoyl derivative (**9**) (157 mg).

2′,3′-Di-*O*-hexanoyl-5′-*O*-(triphenylmethyl)cytidine (9): Yield 81.5% as crystalline solid, M.P. 100–102 °C, R_f = 0.52 ($CHCl_3$/CH_3OH = 22/1, v/v). FTIR: ν_{max} 1710 (-CO), 3503 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.08 (1H, s, -NH), 7.32 (6H, m, Ar-H), 7.28 (9H, m, Ar-H), 7.21 (1H, d, J = 7.6 Hz, H-6), 6.51 (1H, d, J = 3.2 Hz, H-1′), 5.47 (1H, m, H-2′), 4.88 (1H, dd, J = 3.2 and 5.4 Hz, H-3′), 4.61 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 4.54 (2H, s, -NH_2), 4.48 (1H, dd, J = 2.2 and 12.2 Hz, H-5′b), 4.35 (1H, dd, J = 2.2 and 5.4 Hz, H-4′), 3.81 (1H, d, J = 7.1 Hz, H-5), 2.31 {4H, m, 2×$CH_3(CH_2)_3CH_2$CO-}, 1.62 {4H, m, 2×$CH_3(CH_2)_2CH_2CH_2$CO-}, 1.26 {8H, m, 2×$CH_3(CH_2)_2CH_2CH_2$CO-}, 0.88 {6H, m, 2×$CH_3(CH_2)_4$CO-}. MS $[M+1]^+$ 682.05.

Anal Calcd. for $C_{40}H_{47}O_7N_3$: % C, 70.40, H, 6.90; % found: C, 70.42, H, 6.91.

A similar reaction and purification method were employed to synthesize compounds (**10**) (164 mg), (**11**) (152 mg), (**12**) (109.5 mg), (**13**) (100.4 mg), (**14**) (132 mg), and (**15**) (111 mg).

2′, 3′-Di-*O*-heptanoyl-5′-*O*-(triphenylmethyl)cytidine (10): Yield 78.9% as crystalline solid, M.P. 98–99 °C ($CHCl_3$–C_6H_{14}), R_f = 0.50 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1715 (-CO), 3506 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.03 (1H, s, -NH), 7.30 (6H, m, Ar-H), 7.28 (9H, m, Ar-H), 7.20 (1H, d, J = 7.4 Hz, H-6), 6.44 (1H, d, J = 3.2 Hz, H-1′), 5.50 (1H, d, J = 3.2 Hz, H-2′), 5.24 (1H, dd, J = 3.2 and 5.4 Hz, H-3′), 5.06 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 4.65 (2H, s, -NH_2), 4.02 (1H, dd, J = 2.1 and 12.1 Hz, H-5′b), 3.95 (1H, dd, J = 2.2 and 5.3 Hz, H-4′), 3.80 (1H, m, H-5), 2.41 {4H, m, 2×$CH_3(CH_2)_4CH_2$CO-}, 1.62 {4H, m, 2×$CH_3(CH_2)_3CH_2CH_2$CO-}, 1.35 {12H, m, 2×$CH_3(CH_2)_3CH_2CH_2$CO-}, 0.91 {6H, m, 2×$CH_3(CH_2)_5$CO-}. MS $[M+1]^+$ 710.14.

Anal Calcd. for $C_{42}H_{53}O_7N_3$: % C, 71.00, H, 7.10; % found: C, 71.02, H, 7.09.

2′,3′-Di-*O*-lauroyl-5′-*O*-(triphenylmethyl)cytidine (11): Yield 93.2% as a white crystalline solid, M.P. 107–109 °C ($CHCl_3$–C_6H_{14}), R_f = 0.50 ($CHCl_3$/CH_3OH = 23/1, v/v). FTIR: ν_{max} 1735 (-CO), 3500 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.00 (1H, s, -NH), 7.36 (6H, m, Ar-H), 7.31 (9H, m, Ar-H), 7.28 (1H, d, J = 7.3 Hz, H-6), 6.47 (1H, d, J = 3.3 Hz, H-1′), 5.57 (1H, d, J = 3.2 Hz, H-2′), 5.27 (1H, dd, J = 3.2 and 5.4 Hz, H-3′), 5.11 (1H, dd, J = 2.1 and 12.1 Hz, H-5′a), 4.58 (2H, s, -NH_2), 4.11 (1H, dd, J = 2.2 and 12.2 Hz, H-5′b), 3.99 (1H, dd, J = 2.1 and 5.2 Hz, H-4′), 3.85 (1H, d, J = 7.1 Hz, H-5), 2.37 {4H, m, 2×$CH_3(CH_2)_9CH_2$CO-}, 1.68 {4H, m, 2×$CH_3(CH_2)_8CH_2CH_2$CO-}, 1.29 {32H, m, 2×$CH_3(CH_2)_8CH_2CH_2$CO-}, 0.89 {6H, m, 2×$CH_3(CH_2)_{10}$CO-}. MS $[M+1]^+$ 850.23.

Anal Calcd. for $C_{52}H_{71}O_7N_3$: % C, 73.50, H, 8.36; % found: C, 73.49, H, 8.35.

2′,3′-Di-***O***-myristoyl-5′-***O***-(triphenylmethyl)cytidine (12): Yield 88.75.3% as a crystalline solid, M.P. 96–98 °C ($CHCl_3$–C_6H_{14}), R_f = 0.51 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1726 (-CO), 3470 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.09 (1H, s, -NH), 7.38 (6H, m, Ar-H), 7.33 (9H, m, Ar-H), 7.29 (1H, d, J = 7.4 Hz, H-6), 6.40 (1H, d, J = 3.2 Hz, H-1′), 5.51 (1H, d, J = 3.2 Hz, H-2′), 5.20 (1H, dd, J = 3.1 and 5.2 Hz, H-3′), 5.01 (1H, dd, J = 2.1 and 12.1 Hz, H-5′a), 4.59 (2H, s, -NH_2), 4.10 (1H, dd, J = 2.1 and 12.1 Hz, H-5′b), 3.89 (1H, dd, J = 2.1 and 5.2 Hz, H-4′), 3.87 (1H, d, J = 7.1 Hz, H-5), 2.38 {4H, m, 2×$CH_3(CH_2)_{11}CH_2$CO-}, 1.68 {4H, m, 2×$CH_3(CH_2)_{10}CH_2CH_2$CO-}, 1.29 {40H, m, 2×$CH_3(CH_2)_{10}CH_2CH_2$CO-}, 0.95 {6H, m, 2×$CH_3(CH_2)_{12}$CO-}. MS $[M+1]^+$ 906.04.

Anal Calcd. for $C_{56}H_{79}O_7N_3$: % C, 74.25, H, 8.73; % found: C, 74.27, H, 8.74.

2′,3′-Di-*O*-pivaloyl-5′-*O*-(triphenylmethyl)cytidine (13): Yield 91.4% as crystalline solid, M.P. 96–97 °C ($CHCl_3$–C_6H_{14}), R_f = 0.55 ($CHCl_3$/CH_3OH = 24/1, v/v). FTIR: ν_{max} 1718 (-CO), 3501 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.04 (1H, s, -NH), 7.33 (6H, m, Ar-H), 7.30 (9H, m, Ar-H), 7.20 (1H, d, J = 7.5 Hz, H-6), 6.36 (1H, d, J = 3.1 Hz, H-1′), 5.50 (1H, d, J = 3.1 Hz, H-2′), 5.10 (1H, dd, J = 3.2 and 5.2 Hz, H-3′), 5.00 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 4.89 (2H, s, -NH_2), 4.11 (1H, dd, J = 2.2 and 12.1 Hz, H-5′b), 3.92 (1H, dd, J = 2.2 and 5.4 Hz, H-4′), 3.90 (1H, d, J = 7.1 Hz, H-5), 1.26 {18H, s, 2×$(CH_3)_3$CCO-}. MS $[M+1]^+$ 654.01.

Anal Calcd. for $C_{38}H_{43}O_7N_3$: % C, 69.83, H, 6.58; % found: C, 69.84, H, 6.60.

2′,3′-Di-*O*-(4-chlorobenzoyl)-5′-*O*-(triphenylmethyl) cytidine (14): Yield 78.3% as a white crystalline solid, M.P. 99–101 °C ($CHCl_3$–C_6H_{14}), R_f = 0.52 ($CHCl_3$/CH_3OH = 22/1, v/v). FTIR: ν_{max} 1711 (-CO), 3505 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.01 (1H, s, -NH), 7.98 (4H, m, Ar-H), 7.58 (4H, m, Ar-H), 7.32 (6H, m, Ar-H), 7.28 (9H, m, Ar-H), 7.21 (1H, d, J = 7.5 Hz, H-6), 6.44 (1H, d, J = 3.1 Hz, H-1′), 5.58 (1H, d, J = 3.2 Hz, H-2′), 5.12 (1H, dd, J = 3.2 and 5.2 Hz, H-3′), 5.02 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 4.60 (2H, s, -NH_2), 4.10 (1H, dd, J = 2.1 and 12.1 Hz, H-5′b), 4.00 (1H, dd, J = 2.2 and 5.4 Hz, H-4′), 3.92 (1H, d, J = 7.1 Hz, H-5). MS $[M+1]^+$ 763.22.

Anal Calcd. for $C_{42}H_{33}O_7N_3Cl_2$: % C, 66.14, H, 4.33; % found: C, 66.12, H, 4.32.

2′,3′-Di-*O*-cinnamoyl-5′-*O*-(triphenylmethyl)cytidine (15): Yield 88.5% white crystalline solid, M.P. 102–104 °C ($CHCl_3$–C_6H_{14}), R_f = 0.50 ($CHCl_3$/CH_3OH = 22/1, v/v). FTIR: ν_{max} 1678 (-CO), 3492 cm^{-1} (-NH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 9.02 (1H, s, -NH), 7.85 (4H, m, Ar-H), 7.40 (6H, m, Ar-H), 7.60, 7.57 (2×1H, 2×d, J = 16.1 Hz, 2×PhC*H*=CHCO-), 7.36 (6H, m, Ar-H), 7.31 (9H, m, Ar-H), 7.28 (1H, d, J = 7.4 Hz, H-6), 6.45 (1H, d, J = 3.2 Hz, H-1′), 6.48, 6.42 (2×1H, 2×d, J = 16.1 Hz, 2×PhCH=C*H*CO-), 5.68 (1H, d, J = 3.3 Hz, H-2′), 5.34 (1H, dd, J = 3.3 and 5.3 Hz, H-3′), 4.97 (1H, dd, J = 2.2 and 12.2 Hz, H-5′a), 4.61 (2H, s, -NH_2), 4.31 (1H, dd, J = 2.2 and

12.2 Hz, H-5′b), 4.15 (1H, dd, J = 2.2 and 5.4 Hz, H-4′), 3.62 (1H, d, J = 7.1 Hz, H-5). MS $[M+1]^+$ 743.30.

Anal Calcd. for $C_{46}H_{36}O_7N_3$: % C, 74.39, H, 4.85; % found: C, 74.41, H, 4.84.

X-ray powder diffraction

X-ray powder diffraction was performed using Rigaku Dmax2200PC diffractometer (Rigaku Corporation, Tokyo, Japan) and Cu Kα-radiation [22]. The X-ray intensity was measured in the range of $5° \leq 2\theta \leq 90°$ with a scan speed of $2°{\cdot}min^{-1}$. The peak position of the 002 coke peak was measured. By using Bragg's law, the interlayer d-spacing was calculated. The improved Langford method was employed to calculate the stacking disorder degree, P.

Results and discussion

Chemistry

In this study, regioselective decanoylation (Fig. 2 and 3) and triphenylmethylation (Fig. 4 and 5) of cytidine (**1**) were performed using the direct method. The resulting decanoylation and triphenylmethylation products were converted into numerous analogs by employing various acylating agents.

Characterization and selective decanoyl of cytidine

Cytidine **1** was initially converted into the 5′-*O*-decanoylcytidine derivative **2** through treatment with dry pyridine, and this product after the reaction with decanoyl chloride, followed by solvent removal and silica gel column chromatographic purification, produced 5′-*O*-decanoyl derivative (**2**) with 83.8% yield as needles and m.p. of 85–87 °C). The FTIR spectrum of compound **2** showed the following absorption bands: 1731, 1714 cm^{-1} (due to –CO), 3420 cm^{-1} (due to –OH), and 3550 cm^{-1} (due to –NH) stretching. In its ^{1}H-NMR spectrum, two two-proton multiplets observed at δ 2.38 $\{CH_3(CH_2)_7CH_2CO–\}$ and δ 1.59 $\{CH_3(CH_2)_6CH_2CH_2CO–\}$, a twelve-proton multiplet appearing at δ 1.32 $\{CH_3(CH_2)_6(CH_2)_2CO–\}$, and a three-proton multiplet seen at δ 0.85 $\{CH_3(CH_2)_8CO–\}$ were caused by the presence of one decanoyl group in the molecule. The downfield shift of C-5′ proton to δ 6.01 (as dd, J = 2.4 and 12.3 Hz, H-5′a) and to δ 5.56 (as dd, J = 2.4 and 12.3 Hz, H-5′b) from their general values [23] in the precursor compound (**1**) and the resonances of other protons in their anticipated positions indicated the presence of the decanoyl group at position 5′. The formation of 5′-*O*-decanoylcytidine (**2**) might be caused by the high reactivity of the sterically less hindered

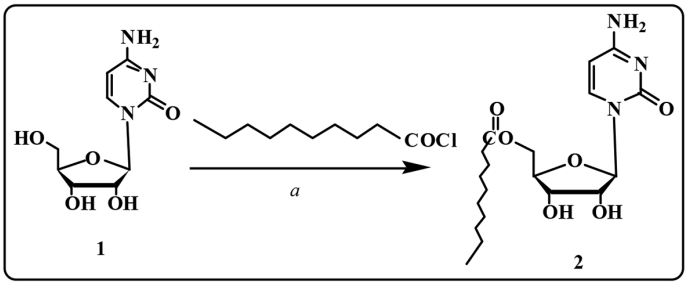

Fig. 2. *Reagents and conditions*: (*a*) dry C_6H_5N, −5 °C, 6 to 7 h; **2** = decanoyl derivative

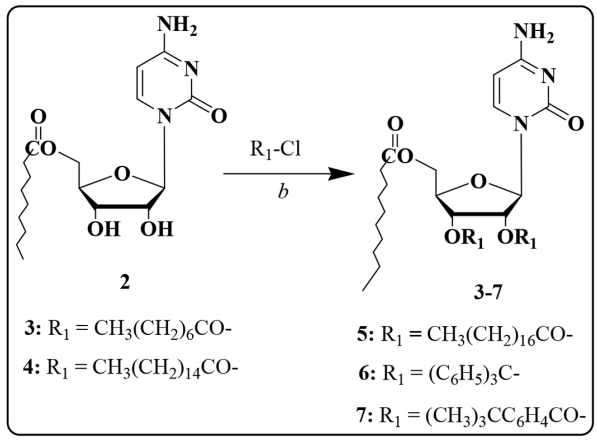

Fig. 3. (*b*) dry pyridine, 0 °C to room temperature, DMAP, stir for 6–8 h, R_1 = different acyl halides (**3**–**7**)

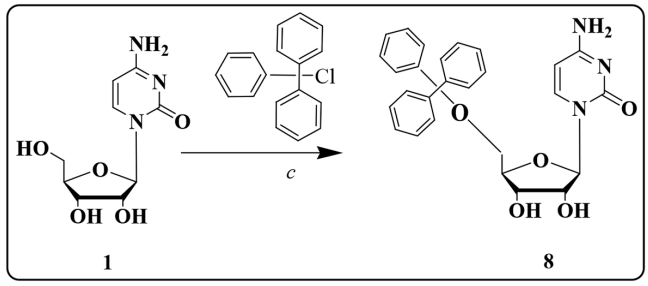

Fig. 4. *Reagents and conditions*: (*c*) dry C_6H_5N, 0–5°C, 6 h; **8** = triphenylmethyl derivative

primary hydroxyl group of the ribose moiety of cytidine (**1**). Mass spectrometry provided a molecular ion peak at *m/z* $[M+1]^+$ 398.10, which corresponded to the aforementioned molecular formula. From the complete analysis of FTIR, ^{1}H-NMR, and elemental data, the structure of this compound was assigned as 5′-*O*-decanoylcytidine (**2**).

Furthermore, the structure of compound (**2**) was confirmed through the preparation of its octanoyl derivatives (**3**) (77.6%) as the crystalline solid with the m.p. of 89–91 °C. In its ^{1}H-NMR spectrum, two four-proton multiplets appearing at δ 2.37 {2 × $CH_3(CH_2)_5CH_2CO$–} and 1.64 {2 × $CH_3(CH_2)_4CH_2CH_2CO$–}, sixteen-proton multiplet observed at δ 1.29 {2×$CH_3(CH_2)_4(CH_2)_2CO$–}, and six-proton multiplet obtained at δ 0.89 {2 × $CH_3(CH_2)_6CO$–} were caused by the presence of two octanoyl groups in the molecule. The downfield shift of H-2′ and H-3′ protons to δ 5.45 and δ 4.82 from their precursor values (**2**) [24] indicated the attachment of two octanoyl groups at positions 2′ and 3′. The structure of octanoyl derivatives (**3**) was confirmed as 5′-*O*-decanoyl-2′,3′-**di-***O*-octanoylcytidine (**3**)through the complete analysis of their FTIR, ^{1}H-NMR, and elemental data.

Through the palmitoylation of compound (**2**) by using palmitoyl chloride as acylating agent in C_5H_5N at room temperature, we isolated compound **4** in good yield. The following resonance peaks ascertained the presence of two palmitoyl groups in the molecule: δ 2.36 {4H, m, 2 × $CH_3(CH_2)_{13}CH_2CO$–}, δ 1.27 {52H, m, 2 × $CH_3(CH_2)_{13}CH_2CO$–}, and δ 0.91 {6H, m, 2 × $CH_3(CH_2)_{14}CO$–}. The introduction of palmitoyl groups at position 2′ and 3′ was indicated by appearance of H-2′ and H-3′ resonance peaks

at δ 5.48 (as m) and δ 4.86 (as dd, J = 3.5 and 5.6 Hz), which were deshielded considerably from their precursor diol (**2**) peaks. The decanoyl derivative **2** was further transformed easily into the 2′,3′**-di-***O*-stearoyate **5**, 2′,3′-di-*O*-(triphenylmethyloate) **6**, and 2′,3′-(4-*tert*-butylbenzoate) **7**.

Characterization and selective triphenylmethylation of cytidine

Cytidine (**1**) was then transformed into the 5′-*O*-(triphenylmethyl)cytidine derivative **8** through a treatment with a unimolecular amount of triphenylmethyl chloride in anhydrous pyridine at −5 °C. The conventional work-up procedure, followed by solvent removal and silica gel column chromatographic purification, produced high yields of the triphenylmethyl derivative (**8**) as the crystalline solid. In its ^{1}H-NMR spectrum, two characteristic six-proton multiplets appearing at δ 7.35 (Ar–H) and nine-proton multiplets observed at δ 7.30 (Ar–H) were caused by three phenyl protons of the triphenylmethyl group in the molecule. The downfield shift of C-5′ proton to δ 5.30 (as dd, J = 2.2 and 12.2 Hz, H-5′a) and to 5.26 (as dd, J = 2.2 and 12.2 Hz, H-5′b) from their usual values (~4.00 ppm) in the precursor compound (**1**) and the resonances of other protons at their anticipated positions showed the presence of the triphenylmethyl group at position 5′. This finding is in accordance with the mechanism proposed by Kawsar *et al*. [25] based on similar nucleoside derivatives.

The preparation and identification of hexanoyl derivative **9** further supported the structure of compound **8**. The ^{1}H-NMR spectra exhibited two four-proton multiplets at δ 2.31 {2 × $CH_3(CH_2)_3CH_2CO$–} and at δ 1.62 {2 × $CH_3(CH_2)_2CH_2CH_2CO$–}, eight-proton multiplet at δ 1.26 {2 × $CH_3(CH_2)_2CH_2CH_2CO$–}, and six-proton multiplet at δ 0.88 {2 × $CH_3(CH_2)_4CO$–}, which showed the attachment of two hexanoyl groups indicating the formation of 2′,3′-di-*O*-hexanoate **9**.

Compound **8** was then converted into heptanoyl derivative **10** by using similar procedures, and a high yield of heptanoate **10** was isolated as needles, (m.p. 98–99 °C). From the complete analysis of the FTIR, ^{1}H-NMR, and elemental data, the structure of this compound was confirmed as 2′,3′**-di-***O*-heptanoyl -5′-*O*-(triphenylmethyl)cytidine (**10**). Similarly, compound **8** was converted into numerous acylated derivatives (**11**–**15**) to obtain newer compounds for antimicrobial evaluation studies. The structures of these derivatives were ascertained through the complete interpretation of their FTIR and ^{1}H-NMR spectra.

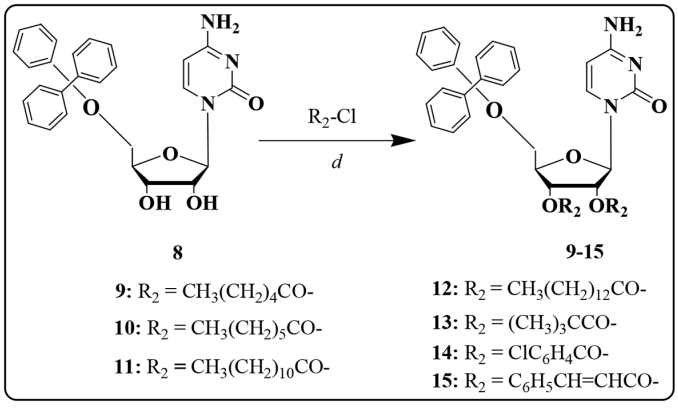

Fig. 5. *Reagents and conditions*: (*d*) anhydr. pyridine, 0 °C to room temperature, DMAP, stir for 6 to 7 h, R_2 = several acyl halides (**9**–**15**)

Thus, cytidine (**1**) acylation by applying the direct method was unique, and the reaction provided a single mono-substituted product in reasonably high yields. These newly synthesized products may be used as important precursors to modify cytidine molecules at different positions. All the prepared products were employed as test compounds for evaluating their antimicrobial and anticancer activities and for computational investigations.

XRD measurements

XRD is mainly performed for quantitatively identifying crystalline compounds, whereas single crystal XRD is conducted for structure determination. If h, k, and l represent the miller indices, the rules of the determination of crystal lattice type are as follows (Table 1).

The XRD patterns of the pure compounds synthesized under the optimized conditions were obtained in the 2θ range of (0°–50°). The peaks observed at 2θ of 19.653 and 21.506 (h,k,l:112 & 220), 6.010 and 21.472 (h,k,l:320 & 100), 8.386 and 20.212 (h,k,l:100 & 100), and 7.427 and 12.360 (h,k,l:100 & 111) corresponded to compounds **4**, **5**, **13,** and **15,** respectively. These peaks indicated the formation of typical phases of compounds **4**, **5**, **13,** and **15**. According to the phase analysis, the compounds synthesized using this method have high purity, and no impurities were detected in the XRD pattern. Moreover, compounds **4**, **5**, **13,** and **15** show many lines with high intensity in their XRD patterns, which indicated that all the compounds are highly crystalline (Fig. 6). By applying the rules (Table 1) of the determination of the lattice type, we assigned the lattice structures to the synthesized

Table 1. Rules of the determination of crystal lattice type

Lattice type	Rules for reflection to be observed
Primitive, P	None
Body centered, I	hkl; h+k+l= 2n
Face centered, F	hkl; h,k,l either all odd or all even
Side centered, C	hkl; h+k= 2n
Rhombohedral	hkl; -h+k+l= 3n or h-k+l= 3n

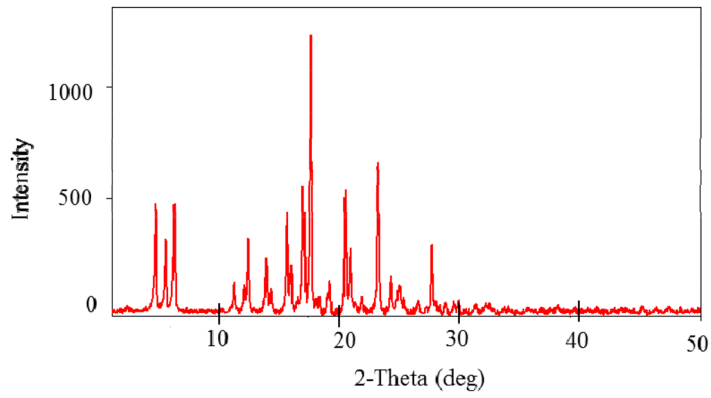

Fig. 6. XRD pattern of 2′,3′-di-*O*-pivaloyl-5′-*O*-(triphenylmethyl)cytidine (**13**)

compounds. Compound **4** satisfied the rule, h + k + l = 2n and was assigned the body centered lattice, while compounds **5**, **13**, and **15** were assigned primitive, for which no rule was provided.

Conclusion

In conclusion, an efficient method was proposed for synthesizing cytidine analogs. Moreover, acylation reactions are highly promising because considerably high yields of a single mono-substituted product were isolated through all the reactions. XRD pattern showed that the compounds **4**, **5**, **13** and **15** exhibited many lines with high intensity and suggested these compounds are well crystalline.

Author Contributions

S.M.A.K. designed and planned the experiments; K.M.R., and A.H. performed the synthetic experiment and determined XRD. S.M.A.K. interpreted the data and wrote the paper. All authors have read and approved the final version of the manuscript.

Acknowledgment

The authors are grateful to the Ministry of Science and Technology (MOST), the Government of the People's Republic of Bangladesh for providing financial support (*Ref.: 39.00.0000. 09.06.024.19/ Phy's-544-560, 2019-2020)* to conduct this research.

Declaration of interest

The authors declare no conflict of interest.

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