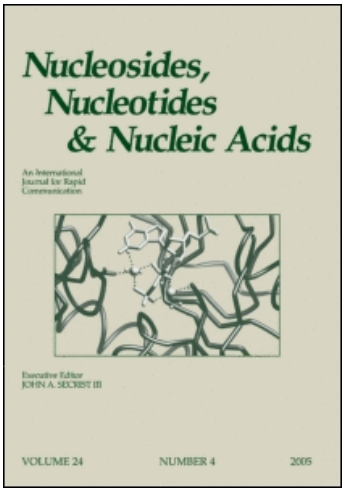

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Ionic Liquid Mediated Synthesis of 5-Halouracil Nucleosides: Key Precursors for Potential Antiviral Drugs

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IONIC LIQUID MEDIATED SYNTHESIS OF 5-HALOURACIL NUCLEOSIDES: KEY PRECURSORS FOR POTENTIAL ANTIVIRAL DRUGS

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□ *Synthesis of antiviral 5-halouracil nucleosides, also used as key precursors for the synthesis of other potential antiviral drugs, has been demonstrated using ionic liquids as convenient and efficient reaction medium.*

Keywords Ionic liquids; antiviral; Idoxuridine; 5-halouracil nucleosides

INTRODUCTION

The rational variation at C-5 position of uracil nucleosides can enhance their properties in terms of oral bioavailability, metabolic stability, pharmacokinetics, etc. 5-Halouracil nucleosides are of great pharmaceutical interest and have been extensively investigated due to their anti-neoplastic and anti-viral properties.[1] Idoxuridine, also known as 5-iodo-2′-deoxyuridine and marketed as Herples and Stoxil, is one of the drugs used for conjunctival and corneal disease associated with feline herpes virus. Some of the 5-chlorouracil nucleoside derivatives have shown selective anti-HIV activity.[2] 5-Halouracil nucleosides are important intermediates for the synthesis of a wide range of modified nucleosides showing activity, mainly against HSV-1 and HSV-2 (herpes simplex virus type 1 and 2) and VZV (varicella-zoster virus).[3] Radioactive halogenated uracil nucleosides have been used as

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mechanistic probes for DNA metabolism studies.[4] Therefore, new methods for the synthesis of 5-halouracil nucleosides are of great interest in nucleoside chemistry.

One approach to synthesize 5-halouracil nucleosides is the coupling of a protected chlorosugar and a halogenated base, but this method requires multiple steps and often results in the mixture of α and β anomers.[5] The other method is direct halogenation of protected or unprotected nucleosides.[6] Prusoff et al. were the first to report iodination of uridine (U) and 2′-deoxyuridine (2′-dU) at the C-5 position using I_2/HNO_3 or KI/H_2SO_4.[7] Later, Lipkin et al. carried out iodination of nucleosides with N-iodosuccinimide or iodine monochloride (ICl) in DMSO or N-ethylacetamide using different catalysts.[8] In a similar attempt, N-chlorosuccinimide has been used with an excess of pyridine to obtain 5-chlorouracil nucleosides.[2] Dale et al. reported iodination of 5-mercurouridines in aqueous alcohol.[9] Chlorination of different nucleosides including uridine and 2′-deoxyuridine has been carried out using an acyl chlorides/DMF/MCPBA system in moderate yields.[10] Recently, Kumar et al. have reported halogenation of protected and unprotected uracil nucleosides using N-halosuccinimides and ICl in the presence of excess sodium azide, which required reaction times up to 48 hours.[11] All the methods mentioned above have disadvantages, that is, harsh reaction conditions, longer reaction time, use of toxic oxidizing agents or catalysts (e.g., HNO_3, H_2SO_4, sodium azide, etc.), highly toxic and high boiling solvents (e.g., DMSO, DMF, pyridine, acetic acid, etc.), which are difficult to remove and often get contaminated with product which makes the workup procedure of these reactions more tedious. Asakura and Robins reported a simple approach of 5-halogenation of U and dU with iodine and lithium halides in the presence of ceric ammonium nitrate (CAN) using acetic acid/acetonitrile as solvent.[12] This method required a highly acidic solvent and lots of extraction steps in the workup. In this article, we have used the same reagents in ionic liquids and observed superior results.

Over the last decade, ionic liquids (ILs) have emerged as effective alternatives to conventional organic solvents due to their attractive properties viz. negligible vapor pressure, recyclability, high thermal stability and their ability to dissolve a wide range of compounds.[13] The possibilities of their structural variations help in designing ideal solvents suitable for any particular process.[14] We have recently designed ILs that provide high solubility for nucleosides and that were found to be efficient reaction media for their selective modifications, giving high yields under ambient conditions.[15] Herein we are reporting an improved, convenient, and safe method for 5-halogenation of protected and unprotected U and dU using lithium halides as halogenating agents in the presence of ceric ammonium nitrate (CAN) with an ionic liquid as the reaction medium.

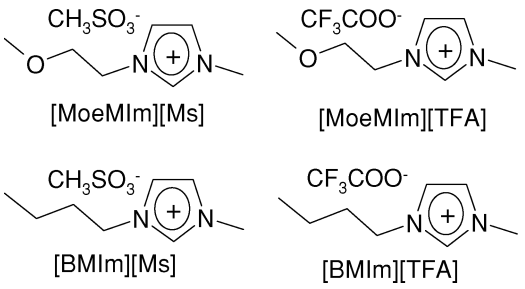
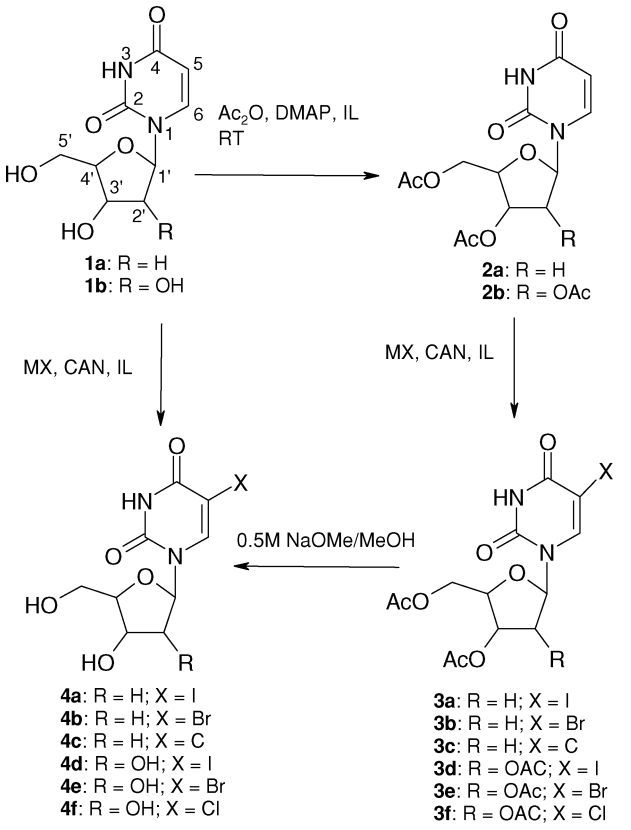


FIGURE 1 Ionic liquids used for halogenation of U and 2′dU.

RESULTS AND DISCUSSION

The ionic liquids utilized are 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MoeMIm][Ms]), 1-methoxyethyl-3-methylimidazolium trifluoroacetate ([MoeMIm][TFA]), 1-butyl-3-methylimidazolium methanesulfonate ([BMIm][Ms]) and 1-butyl-3-methylimidazolium trifluoroacetate ([BMIm][TFA]) (Figure 1). The hydroxyl groups of 2′-deoxyuridine (2′-dU) (**1a**) and uridine (U) (**1b**) were first acetylated to give 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2a**) and 2′,3′,5′-tri-*O*-acetyluridine (**2b**), respectively. Usually, these reactions are carried out in pyridine/DMAP[16] or acetonitrile/Et_3N/DMAP[17] with an excess of acetic anhydride, and the reaction time varies from 2 to 12 hours. We carried out this reaction in ILs [MoeMIm][Ms], [MoeMIm][TFA] and [BMIm][TFA] at room temperature using DMAP as catalyst and a stoichiometric amount of acetic anhydride as the acylating agent. The IL [BMIm][Ms] was not used for these reactions as it is a solid at room temperature. The reactions with all three ILs were completed in 20–25 minutes to give the acetylated derivative in high yields as a single product (Scheme 1). Moreover, no purification was required and the product was obtained by simple extraction. All three ILs were reused up to four times for this reaction with no loss in product yield (Table 1).

All four ILs were then screened for 5-iodination of **2a** under conditions reported earlier in the literature i.e. using iodine or lithium iodide in the presence of CAN at 80°C (Table 2). In ILs [MoeMIm][TFA] and [BMIm][TFA] having a trifluoroacetate anion, the reactions were slow. Although, the conversion was relatively fast with iodine in both the ILs as compared to that with lithium iodide, but the reactions were not 100% complete and the deacetylated products started to form over time. At this point the reactions were stopped and products were isolated (Table 2). In IL [BMIm][Ms] also, the conversion was very slow and incomplete with lithium iodide and the yield was only 10% but no deacetylation products was observed on TLC (entry 6, Table 2), however, the reaction is fast in the case of iodine and completed in 45 minutes to give the product in 80%



SCHEME 1 Synthesis of 5-halouridines and 5-halo-2′-deoxyuridines.

yield (entry 7, Table 2). The best results were obtained in IL [MoeMIm][Ms] where 100% conversion was observed in 20 minutes with lithium iodide and in 1 hour with iodine to give the iodinated products in 96% (entry 1, Table 2) and 95% (entry 1, Table 2), respectively. The reaction time was less than half as compared to the literature method in the case of lithium iodide and yields were also better with both iodine and lithium iodide (Table 2).

TABLE 1 Recycling of ILs for acetylation reaction of U and 2′-dU

	Reaction time (min)/yield (%)					
	[MoeMIm][Ms]		MoeMIm][TFA]		[BMIm][TFA]	
Cycle	1a to 2a	1b to 2b	1a to 2a	1b to 2b	1a to 2a	1b to 2b
0	20/91	25/93	25/90	30/92	25/90	30/93
1	20/90	25/92	25/90	30/91	30/89	30/92
2	25/90	30/91	35/89	3091	30/89	35/90
3	25/89	30/91	35/89	35/90	35/85	35/89

TABLE 2 5-Iodination of **2a** (0.5 mmol) in different ILs at 80°C

Entry	Solvent	MX (mol equiv.)	CAN (mol equiv.)	Time (h)	Yield (%)
1	[MoeMIm][Ms]	LiI (1.2)	2.0	20 min	96
2	[MoeMIm][Ms]	I_2 (0.6)	0.5	1	95
3	[MoeMIm][TFA]	I_2 (0.6)	0.5	3	70[a]
4	[MoeMIm][TFA]	LiI (1.2)	2.0	12	15[a]
5	[BMIm][TFA]	I_2 (0.6)	0.5	3	65[a]
6	[BMIm][TFA]	LiI (1.2)	2.0	12	20[a]
7	[BMIm][Ms]	I_2 (0.6)	0.5	45 min	80
8	[BMIm][Ms]	LiI (1.2)	2.0	12	10[b]
9	MeCN	I_2 (0.6)	0.5	1	92[c]
10	MeCN	LiI (1.2)	2.0	1	93[c]

[a]Starting material left and deacetylation starts after this time.
[b]Starting material left and no change in conversion was observed on TLC after this time.
[c]Literature data from.[13]

The reaction proceeds through oxidation of halide salts by CAN resulting in the generation of electron deficient halogen species which attack at C-5 position of the uracil moiety.[12b] It is also known that the kinetics of this reaction depends on the concentration of CAN and the temperature.[12a] To study these effects, we first carried out the iodination of **2a** using iodine at different concentration of CAN and at different temperatures. The results show that the reaction rate increases with an increase in the concentration of CAN (Table 3). Also, for the same concentration of CAN, the reaction rate increased with an increase in temperature. It is important to note that at higher temperatures the decomposition starts taking place over time, as indicated by multiple spots on the TLC (entry 4, Table 3). The best results were obtained with 1.0 equivalent of CAN where the reaction is completed in 4 hours at room temperature to give 91% yield (entry 11, Table 3) and in 10 minutes at 100°C to give 94% yield (entry 14, Table 3). Similar effects of CAN concentration and temperature were also observed with iodination of **2a** with lithium iodide (Table 4). No reactions were observed with 0.2 and 0.5 equivalents of lithium iodide at 80°C (entry 1 and 2, Table 4), and the conversion is incomplete (only 20%) with 1.0 equivalent of lithium iodide (entry 3, Table 4). The best results with lithium iodide were obtained with 2.0 equivalent of CAN where the reaction is completed in 20 minutes at 80°C and in 10 minutes at 100°C to give the product in 96 and 94% yields, respectively (entry 7 and 8, Table 4).

After thoroughly screening the reaction conditions, we carried out halogenation of both protected and unprotected 2′-dU and U using lithium halides (1.2 equiv.) and CAN (2.0 equiv.) at 80°C. The results are summarized in Table 5. The iodination and bromination of all the substrates i.e. 2′-dU (**1a**) (entry 1 and 2, Table 5), U (**1b**) (entry 7 and 8, Table 5), 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2a**) (entry 4 and 5, Table 5), 2′,3′,5′-tri-*O*-acetyluridine (**2b**) (entry 10 and 11, Table 5) were achieved in comparable

TABLE 3 Effect of CAN concentration and temperature on 5-iodination of **2a** (0.5 mmol) using iodine (0.6 mol equiv.) in IL [MoeMIm][Ms]

Entry	CAN (mol equiv.)	Temp (°C)	Time (h)	Yield%
1	0.1	80	4.0	82
2	0.1	100	1.0	90
3	0.1	150	1.0	75[a]
4	0.1	150	3.0	[b]
5	0.2	80	1.5	90
6	0.2	100	45 min	94
7	0.5	RT	4.0	30[c]
8	0.5	50	1.2	93
9	0.5	80	1.0	93
10	0.5	100	30 min	95
11	1.0	RT	4.0	91
12	1.0	50	35 min	94
13	1.0	80	20 min	95
14	1.0	100	10 min	94

[a]Starting material left.
[b]Decomposition was observed on TLC indicated by multiple spots.
[c]Starting material left and no change in conversion was observed on TLC after this time.

yields in less time as compared to the reported method. The yields were lower in the case of the chlorination reaction because of competitive decomposition, which was also observed in the reported method. Moreover, no product could be isolated for the chlorination of uridine (**1b**) using LiCl in literature method, while our method afforded the desired product in 32% isolated yields (entry 9, Table 5). The deacetylation reactions were carried out using 0.5 M NaOMe/MeOH in quantitative yields. The overall yields of

TABLE 4 Effect of CAN concentration and temperature on 5-iodination of **2a** (0.5 mmol) using lithium iodide (1.2 mol equiv.) in IL [MoeMIm][Ms]

Entry	CAN (mol equiv.)	Temp. (°C)	Time (h)	Yield%
1	0.2	80	24.0	no reaction[a]
2	0.5	80	24.0	no reaction[a]
3	1.0	80	2.0	20[b]
8	1.5	50	6.0	30[b]
4	1.5	80	40 min	95
5	1.5	100	30 min	94
6	2.0	50	4.0	90
7	2.0	80	20 min	96
8	2.0	100	10 min	94

[a]No reaction.
[b]Starting material left and no change in conversion was observed on TLC after this time.

TABLE 5 5-Halogenation of acetylated and unacetylated 2′-dU and U in IL [MoeMIm][Ms] using lithium halides (1.2 mol equiv.)

Entry	Substrate (0.5 mmol)	MX	Time (h)	Product (% Yield)
1	**1a**	LiI	10 min	**4a** (82)
			30 min[a]	**4b** (73)[a]
2	**1a**	LiBr	20 min	**4b** (86)
			30 min[a]	**4b** (81)[a]
3	**1a**	LiCl	5.0	**4c** (30)[b]
4	**2a**	LiI	20 min	**3a** (95) **4a** (90)[c]
			1.0[a]	**3a** (93)[a]
5	**2a**	LiBr	30 min	**3b** (94) **4b** (88)[c]
			1.5[a]	**3b** (90)[a]
6	**2a**	LiCl	2.5	**3c** (58)[d] **4c** (55)[c]
			6.0[a]	**3c** (95)[a]
7	**1b**	LiI	20 min	**4d** (80)
			30 min[a]	**4d** (78)[a]
8	**1b**	LiBr	20 min	**4e** (80)
			30 min[a]	**4e** (82)[a]
9	**1b**	LiCl	5.0	**4f** (32)[b]
			4.0[a]	Decomposition[a]
10	**2b**	LiI	20 min	**3d** (92) **4d** (76)[c]
			1.0[a]	**3d** (96)[a]
11	**2b**	LiBr	30 min	**3e** (93) **4e** (76)[c]
			1.5[a]	**3e** (91)[a]
12	**2b**	LiCl	2.0	**3f** (32)[d] **4f** (30)[c]
			24.0[a]	**3f** (90)[a]

[a]Literature data from ref[13] using acetic acid/MeCN as solvent.

[b]Starting material left and decomposition of product was also observed as indicated by multiple spots on TLC.

[c]Overall yield from **2a** or **2b**.

[d]Decomposition was taking place simultaniously.

compounds **4a**, **4b**, **4c** from **2a** and that of compounds **4d**, **4e** and **4f** from **2b** are given in Table 5 (entry 4, 5, 6, 10, 11, and 12). It is also important to note that all the reported methods for halogenation of nucleosides require 10–15 ml of highly polar and high boiling solvents (viz. DMSO, DMF, acetic acid, etc) to dissolve 1 mmol of substrate.[7–13] But in our reactions only 1 ml of IL was required to dissolve the same amount of substrate because of their highly solubilizing nature. This 10-fold decrease in the solvent requirement makes this protocol more benign. In comparison to the multiple extraction and chromatography steps required in earlier reports, the workup procedure of our method is very simple. The reaction mixture, being very low in the volume, was directly loaded on silica gel column and the products were isolated by using methanol/dichloromethane as eluents

in increasing order of polarity, however the ionic liquids could not be recovered in this process.

CONCLUSION

In summary, we have successfully synthesized 5-halo derivatives of both protected and unprotected U and 2′dU using ionic liquids as reaction medium. The acetyl protection of hydroxyl groups of U and 2′dU was also carried out in ILs and all the ILs were successfully recovered and reused for up-to 4 cycles without any loss in yields. The lower reaction volume of IL mediated reactions makes the workup procedure very convenient.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400MR spectrometer at 400 and at 101 MHz, respectively using TMS as internal standard. The LC-MS were done on Agilent 1200 series system equipped with Agilent 6210 Time-Of-Flight mass detector. All chemicals used were purchased either from Sigma-Aldrich Corp. (St. Louis, MO, USA) and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated Merck silica gel $60F_{254}$ plates; the spots were detected under ultraviolet (UV) light or by charring with 5% H_2SO_4/ethanol solution. Purification of all the products was done on Teledyne ISCO Combiflash Companion flash chromatography system. Ionic liquid 1-butyl-3-methylimidazolium methanesulfonate ([BMIm][Ms]) was purchased from Sigma-Aldrich Ionic liquids 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MoeMIm][Ms]), 1-methoxyethyl-3-methylimidazolium triflruoroacetate ([MoeMIm][TFA]) and 1-butyl-3-methylimidazolium triflruoroacetate ([BMIm][TFA]) were prepared following the literature protocol.[5b]

General procedure for acetylation of 1a and 1b in ionic liquids: 1a (1g, 4.38 mmol) or **1b** (1g, 4.09 mmol) was dissolved in IL (3 ml) at 50°C and the mixture was then cooled down to room temperature (substrate does not precipitate at room temperature once it is dissolved) followed by addition of 4-dimethylaminopyridine (DMAP) (100 mg) and acetic anhydride (9.20 mmol for **1a** and 13.09 mmol for **2a**). The reaction mixture was stirred at room temperature. After completion (TLC), water (15 ml) was added to reaction mixture and product was extracted with ethyl acetate (5 × 25 ml). The water layer was concentrated on rotary evaporator to recover the IL which was dried in vacuum oven overnight and was further used for the same reaction. The combined organic layers were first washed with saturated

sodium bicarbonate solution followed by water and then dried over sodium sulfate and finally concentrated on rotary evaporator and dried overnight under vacuum to get the desired acetoxy derivatives **2a** and **2b** as off-white solids.

General procedure for iodination of 2a using iodine in ionic liquids: **2a** (0.5 mmol) was taken in a vial and dissolved in ionic liquid (1 ml) at 50°C. The mixture was then cooled down to room temperature (no precipitation of substrate was observed at room temperature) followed by the addition of CAN and iodine. The reaction mixture was then stirred at the desired temperature. To check the reaction progress, a small amount of reaction mixture was taken out by capillary tube and dissolved in methanol and this solution was used to check the TLC (5% $MeOH/CH_2Cl_2$). After completion, the reaction mixture was diluted by CH_2Cl_2 (5 ml), loaded on a silica gel column, which was eluted with $MeOH/CH_2Cl_2$ in increasing order of polarity. The fractions containing the pure product were mixed together and concentrated under vacuum to get the desired product **3a**. The reaction temperature, different ionic liquids used, and amount of CAN and iodine (with respect to the substrate) for different reactions along with the isolated yields are given in Tables 2 and 3.

General procedure for halogenation of nucleosides using lithium halides in ionic liquids: Compound **1a**, **1b**, **2a**, or **2b** (0.5 mmol) was dissolved in IL (1 ml) at 50°C and the mixture was then cooled down to room temperature followed by addition of CAN and lithium halides. The reaction mixture was then stirred at the desired temperature. To check the reaction progress, a small amount of reaction mixture was taken out by capillary tube and dissolved in methanol, and this solution was used to check the TLC for reactions of **1a**, **1b (**20% $MeOH/CH_2Cl_2$), and **2a, 2b** (5% $MeOH/CH_2Cl_2$). After completion, the reaction mixture was diluted by CH_2Cl_2 (5 ml), loaded on silica gel column which was eluted with $MeOH/CH_2Cl_2$ in increasing order of polarity. The fractions containing the pure product were mixed together and concentrated under vacuum to get the desired products. The reaction temperature, different ionic liquids used, and amount of CAN and lithium halides used (with respect to the substrate) for different reactions alongwith the isolated yields are given in Tables 2, 4, and 5.

General procedure for deacetylation reactions: The deacetylation was carried out by base-catalyzed de-esterification. Compounds **3a-d** (0.25 mmol) were dissolved in the 0.5 M solution of NaOMe in methanol (2 ml) and the reaction mixture was stirred at room temperature. The reaction was completed in one h and checked by TLC (10% $MeOH/CH_2Cl_2$). The reaction mixture was then concentrated under vacuum and the residue was purified by silica gel flash chromatography using $MeOH/CH_2Cl_2$ as solvent system in increasing order of polarity to get the products **4a-d**. The overall yields of **4a-d** from **2a-b** are given in Table 5.

3′,5′-Di-*O*-acetyl-2′-deoxyuridine (2a):[18] Obtained as white solid with m.p. 106–107°C (lit m.p. 104–108°C[18]); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.82 (s, 1H, NH), 7.51 (d, 1H, J = 8.2 Hz, H^6), 6.29 (dd, 1H, J = 5.9 and 7.9 Hz, $H^{1'}$), 5.80 (d, 1H, J = 8.1 Hz, H^5), 5.22 (d, 1H, J = 6.4 Hz, $H^{3'}$), 4.42–4.22 (m, 3H, $H^{5'}$ and $H^{4'}$), 2.54 (dd, 1H, J = 4.3 and 14.2 Hz, $_bH_{2'}$), 2.26–1.97 (m, 7H, $_aH^{2'}$ and 2 × C*H*$_3$CO); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.53 (CH_3CO), 170.37 (CH_3CO), 163.50 (C4), 150.49 (C2), 139.02 (C6), 103.10 (C5), 85.45 (C1′), 82.49 (C3′), 74.22 (C4′), 63.95 (C5′), 37.97 (C2′), 21.03 (CH_3CO), 20.94 (CH_3CO); LC-MS (ESI-TOF): m/z 313.12259 ($[M+H]^+$, $C_{13}H_{17}N_2O_7Na$ calcd. 313.10303).

2′,3′,5′-Tri-*O*-acetyluridine (2b):[19] Obtained as white solid with m.p. 127–128°C (lit. m.p. 128.3–129.7°C[19]); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.75 (s, 1H, NH), 7.42 (d, 1H, J = 8.2 Hz, H^6), 6.06 (d, 1H, J = 4.9 Hz, $H^{1'}$), 5.81 (d, 1H, J = 8.1 Hz, H^5), 5.41–5.30 (m, 2H, $H^{2'}$ and $H^{3'}$), 4.42–4.30 (m, 3H, $H^{5'}$ and $H^{4'}$), 2.15 (s, 3H, C*H*$_3$CO), 2.14 (s, 3H, C*H*$_3$CO), 2.11 (s, 3H, C*H*$_3$CO).^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.19 (CH_3CO), 169.68 (CH_3CO), 169.67 (CH_3CO), 163.10 (C4), 150.40 (C2), 139.39 (C6), 103.45 (C5), 87.45 (C1′), 79.92 (C3′), 72.72 (C2′), 70.21 (C4′), 63.20 (C5′), 20.79 (CH_3CO), 20.53 (CH_3CO), 20.43 (CH_3CO); LC-MS (ESI-TOF): m/z 371.13206 ($[M+H]^+$, $C_{15}H_{19}N_2O_9$ calcd. 371.10851).

5-Iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (3a):[11] Obtained as white solid with m.p. 156–158°C (lit. m.p. 157–158°C[11]); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.76 (s, 1H, NH), 7.98 (s, 1H, H^6), 6.30 (dd, 1H, J = 5.8 and 8.1 Hz, $H^{1'}$), 5.25 (dt, 1H, J = 1.9 and 6.3 Hz, $H^{3'}$), 4.45–4.28 (m, 3H, $H^{5'}$ and $H^{4'}$), 2.61–2.52 (m, 1H, $_bH^{2'}$), 2.26–2.19 (m, 4H, $_aH^{2'}$ and C*H*$_3$CO), 2.13 (s, 3H, C*H*$_3$CO). ^{13}C NMR (101 MHz,) 170.43 (CH_3CO), 170.21 (CH_3CO), 159.94 (C4), 150.08 (C2), 143.81 (C6), 85.50 (C1′), 82.66 (C3′), 74.13 (C4′), 69.10 (C5), 63.88 (C5′), 38.26 (C2′), 21.14 (CH_3CO), 20.92 (CH_3CO); LC-MS (ESI-TOF): m/z 439.02593 ($[M+H]^+$, $C_{13}H_{16}IN_2O_7$ calcd. 438.99967).

5-Bromo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (3b):[11] Obtained as white solid with m.p. 153–154°C (lit. m.p. 15205–153°C[11]); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.37 (s, 1H, NH), 7.91 (s, 1H, H^6), 6.31 (dd, 1H, J = 5.8 and 8.0 Hz, $H^{1'}$), 5.24 (d, 1H, J = 6.6 Hz, $H^{3'}$), 4.47–4.27 (m, 3H, $H^{5'}$ and $H^{4'}$), 2.56 (ddd, 1H, J = 2.2, 5.8 and 14.3 Hz, $_bH^{2'}$), 2.27–2.16 (m, 4H, $_aH^{2'}$ and C*H*$_3$CO), 2.13 (s, 3H, C*H*$_3$CO). ^{13}C NMR (101 MHz,) 170.39 (CH_3CO), 170.13 (CH_3CO), 158.70 (C4), 149.54 (C2), 138.58 (C6), 97.46 (C5), 85.56 (C1′), 82.69 (C-3′), 73.98 (C4′), 63.81 (C5′), 38.26 (C2′), 20.93(CH_3CO), 20.89 (CH_3CO); LC-MS (ESI-TOF): m/z 391.04328 ($[M+H]^+$, $C_{13}H_{16}BrN_2O_7$ calcd. 391.01345).

5-Chloro-3′,5′-di-*O*-acetyl-2′-deoxyuridine (3c):[11] Obtained as white solid with m.p. 174–175°C (lit. m.p. 174.5–175°C[11]); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.07 (s, 1H, NH), 7.81 (s, 1H, H^6), 6.31 (dd, 1H, J = 5.7 and 8.0 Hz, $H^{1'}$), 5.24 (dt, 1H, J = 2.4 and 6.4 Hz, $H^{3'}$), 4.45–4.27 (m, 3H, $H^{5'}$ and

$H^{4'}$), 2.56 (ddd, 1H, J = 2.3, 5.8 and 14.3 Hz, $_bH^{2'}$), 2.25–2.15 (m, 4H, $_aH^{2'}$ and CH_3CO), 2.13 (s, 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.36 (CH_3CO), 170.08 (CH_3CO), 158.47 (C4), 149.16 (C2), 135.92 (C6), 109.67 (C5), 85.52 (C1′), 82.65 (C-3′), 73.88 (C4′), 63.76 (C5′), 38.20 (C2′), 20.87 (CH_3CO), 20.84 (CH_3CO); LC-MS (ESI-TOF): m/z 347.07952 ($[M+H]^+$, $C_{13}H_{16}ClN_2O_7$ calcd. 347.06406).

5-Iodo-2′,3′,5′-tri-*O*-acetyluridine (3d): [19] Obtained as white solid with m.p. 177–178°C (lit. m.p. 177.8–179.3°C[19]); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.90 (s, 1H, H^6), 6.08 (d, 1H, J = 5.0 Hz, $H^{1'}$), 5.31– 5.35 (m, 2H, $H^{2'}$ and $H^{3'}$), 4.43–4.32 (m, 3H, $H^{4'}$ and $H^{5'}$), 2.25 (s, 3H, CH_3CO), 2.14 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.30 (CH_3CO), 169.86 (CH_3CO), 169.83 (CH_3CO), 159.68 (C4), 150.06 (C2), 143.92 (C6), 87.37 (C1′), 80.54 (C3′), 73.30 (C2′), 70.41 (C4′), 69.83 (C5), 63.25 (C5′), 21.35 (CH_3CO), 20.74 (CH_3CO), 20.64 (CH_3CO); LC-MS (ESI-TOF): m/z 497.03674 ($[M+H]^+$, $C_{15}H_{18}IN_2O_9$ calcd. 497.00515).

5-Bromo-2′,3′,5′-tri-*O*-acetyluridine (3e):[12b] Obtained as colorless highly viscous material that solidify on scratching to give a white solid with m.p. 50–55°C (m.p not reported in lit.); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.24 (brs, 1H, NH), 7.85 (s, 1H, H^6), 6.10 (d, 1H, J = 4.1 Hz, $H^{1'}$), 5.37–5.29 (m, 2H, $H^{2'}$ and $H^{3'}$), 4.46–4.31 (m, 3H, $H^{4'}$ and $H^{5'}$), 2.23 (s, 3H, CH_3CO), 2.14 (s, 3H, CH_3CO), 2.12 (s, 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.08 (CH_3CO), 169.66 (CH_3CO), 169.61 (CH_3CO), 158.49 (C4), 149.55 (C2), 138.54 (C6), 97.97 (C5), 87.29 (C1′), 80.28 (C3′), 73.10 (C2′), 70.07 (C4′), 62.96 (C5′), 20.94 (CH_3CO), 20.53 (CH_3CO), 20.41 (CH_3CO); LC-MS (ESI-TOF): m/z 449.04934 ($[M+H]^+$, $C_{15}H_{18}BrN_2O_9$ calcd. 449.01902).

5-Chloro-2′,3′,5′-tri-*O*-acetyluridine (3f):[12b] Obtained as colorless highly viscous material that solidify on scratching to give a white solid with m.p. 46–50°C (m.p not reported in lit.); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.98 (s, 1H, NH), 7.75 (s, 1H, H^6), 6.09 (d, 1H, J = 3.9 Hz, $H^{1'}$), 5.37–5.30 (m, 2H, $H^{2'}$ and $H^{3'}$), 4.45–4.31 (m, 3H, $H^{4'}$ and $H^{5'}$), 2.21 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 2.12 (s, 3H, CH_3CO). ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.01 (CH_3CO), 169.62 (CH_3CO), 169.57 (CH_3CO), 158.27 (C4), 149.20 (C2), 135.87 (C6), 110.12 (C5), 87.30 (C1′), 80.26 (C3′), 73.06 (C2′), 70.02 (C4′), 62.91 (C5′), 20.83 (CH_3CO), 20.50 (CH_3CO), 20.41 (CH_3CO); LC-MS (ESI-TOF): m/z 405.09464 ($[M+H]^+$, $C_{15}H_{18}ClN_2O_9$ calcd. 405.06953).

5-Iodo-2′-deoxyuridine (4a):[11] Obtained as white solid with m.p. 172–180°C (dec) (lit. m.p. 170–180°C (dec)[11]); ^{1}H NMR (400 MHz, DMSO-d_6, δ) 11.66 (s, 1H, NH), 8.40 (s, 1H, H^6), 6.10 (t, 1H, J = 6.5 Hz, $H^{1'}$), 5.24 (d, 1H, J = 4.2 Hz, $OH^{3'}$), 5.14 (t, 1H, J = 4.8 Hz, $OH^{5'}$), 4.21–4.26 (m, 1H, $H^{3'}$), 3.79 (dd, 1H, J = 3.2 and 6.4 Hz, $H^{4'}$), 3.67–3.51 (m, 2H, $H^{5'}$), 2.20–2.04 (m, 2H, $H^{2'}$). ^{13}C NMR (101 MHz, DMSO-d_6, δ) 160.48 (C4), 150.09 (C2), 145.03 (C6), 87.50 (C1′), 84.63 (C3′), 69.99 (C5),

69.25 (C4′), 60.80 (C5′), 40.13 (C2′); LC-MS (ESI-TOF): m/z 354.995241 ($[M+H]^+$, $C_9H_{12}IN_2O_5$ calcd. 354.97854).

5-Bromo-2′-deoxyuridine (4b):[11] Obtained as white solid with m.p. 174–176°C (dec) (lit. m.p. 175–179°C (dec)[11]); ^{1}H NMR (400 MHz, DMSO-d_6, δ) δ 11.76 (s, 1H, NH), 8.36 (s, 1H, H^6), 6.07 (t, 1H, J = 6.5 Hz, $H^{1\prime}$), 5.22 (brs, 1H, $OH^{3\prime}$), 5.14 (brs, 1H, $OH^{5\prime}$), 4.21 (d, 1H, J = 3.3 Hz, $H^{3\prime}$), 3.77 (q, 1H, J = 3.2 Hz, $H^{4\prime}$), 3.57 (dd, 2H, J = 11.7 and 25.3 Hz, $H^{5\prime}$), 2.19–2.01 (m, 2H, $H^{2\prime}$). ^{13}C NMR (101 MHz, DMSO-d_6, δ) 159.17 (C4), 149.74 (C2), 140.27 (C6), 95.66 (C5), 87.57 (C1′), 84.86 (C3′), 69.96 (C4′), 60.79 (C5′), 40.13 (C2′); LC-MS (ESI-TOF): m/z 307.00631 ($[M+H]^+$, $C_9H_{12}BrN_2O_5$ calcd. 306.99241).

5-Chloro-2′-deoxyuridine (4c):[11] Obtained as white solid with m.p. 174–178°C (dec) (lit. m.p. 173–176°C (dec)[11]); ^{1}H NMR (400 MHz, DMSO-d_6, δ) 11.80 (brs, 1H, NH), 8.28 (s, 1H, H^6), 6.08 (t, 1H, J = 6.5 Hz, $H^{1\prime}$), 5.22 (d, 1H, J = 3.8 Hz, $OH^{3\prime}$), 5.14 (brs, 1H, $OH^{5\prime}$), 4.21 (brs, 1H, $H^{3\prime}$), 3.77 (q, 1H, J = 3.2 Hz, $H^{4\prime}$), 3.52–3.62 (m, 2H, $H^{5\prime}$), 2.15–2.03 (m, 2H, $H^{2\prime}$). ^{13}C NMR (101 MHz, DMSO-d_6, δ) 160.09 (C4), 150.40 (C2), 137.39 (C6), 107.27 (C5), 87.45 (C1′), 84.76 (C3′), 70.02 (C4′), 60.89 (C5′), 40.09 (C2′); LC-MS (ESI-TOF): m/z 263.05489 ($[M+H]^+$, $C_9H_{12}ClN_2O_6$ calcd. 263.04293).

5-Iodouridine (4d):[11] Obtained as white solid with m.p. 205–210°C (dec) (lit. m.p. 207–209°C (dec)[11]); ^{1}H NMR (400 MHz, DMSO-d_6, δ) 11.68 (s, 1H, NH), 8.48 (s, 1H, H^6), 5.72 (d, 1H, J = 4.6 Hz, $H^{1\prime}$), 5.41 (d, 1H, J = 5.0 Hz, $OH^{3\prime}$), 5.26 (t, 1H, J = 4.5 Hz, $OH^{5\prime}$), 5.07 (d, 1H, J = 5.0 Hz, $OH^{2\prime}$), 4.01 (dq, 2H, J = 4.6 and 21.6 Hz, $H^{3\prime}$ and $H^{2\prime}$), 3.87 (dt, 1H, J = 2.6 and 4.9 Hz, $H^{4\prime}$), 3.73–3.64 (m, 1H,$_a$ $H^{5\prime}$), 3.62–3.53 (m, 1H,$_b$ $H^{5\prime}$). ^{13}C NMR (101 MHz, DMSO-d_6, δ) 160.48 (C4), 150.35 (C2), 145.11 (C6), 96.17 (C5), 88.27 (C1′), 84.73 (C3′), 73.95 (C2′), 69.31 (C4′), 60.18 (C5′); LC-MS (ESI-TOF): m/z 370.99221 ($[M+H]^+$, $C_9H_{12}IN_2O_6$ calcd. 370.97346).

5-Bromouridine (4e):[11] Obtained as white solid with m.p. 190–95°C (dec) (lit. m.p. 190–198°C (dec)[11]); ^{1}H NMR (400 MHz, DMSO-d_6, δ) δ11.78 (s, 1H, NH), 8.45 (s, 1H, H^6), 5.70 (d, 1H, J = 4.5 Hz, $H^{1\prime}$), 5.40 (d, 1H, J = 5.2 Hz, $OH^{3\prime}$), 5.25 (t, 1H, J = 4.7 Hz, $OH^{5\prime}$), 5.04 (d, 1H, J = 4.6 Hz, $OH^{2\prime}$), 4.01 (dd, 1H, J = 4.7 and 9.4 Hz, $H^{3\prime}$), 3.96 (d, 1H, J = 4.2 Hz, $H^{2\prime}$), 3.84 (dt, 1H, J = 2.7 and 4.9 Hz), 3.67 (dd, 1H, J = 6.7 and 9.8 Hz), 3.59–3.50 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, δ)159.14 (C4), 149.97 (C2), 140.35 (C6), 95.69 (C5), 88.49 (C1′), 84.67 (C3′), 73.94 (C2′), 69.25 (C4′), 60.11 (C5′); LC-MS (ESI-TOF): m/z 323.0019 ($[M+H]^+$, $C_9H_{12}BrN_2O_6$ calcd. 322.98733).

5-Chlorouridine (4f):[11] Obtained as white solid with m.p. 210–216°C (dec) (lit. m.p. 215–220°C (dec)[11]); ^{1}H NMR (400 MHz, DMSO-d_6, δ) 11.85 (s, 1H, NH), 8.41 (s, 1H, H^6), 5.73 (d, 1H, J = 4.5 Hz, $H^{1\prime}$), 5.43 (d, 1H, J = 5.3 Hz, $OH^{3\prime}$), 5.28 (t, 1H, J = 4.7 Hz, $OH^{5\prime}$), 5.08 (d, 1H, J =

5.4 Hz, $OH^{2'}$), 4.05 (dd, 1H, $J = 4.8$ and 9.6 Hz, $H^{3'}$), 3.99 (dd, 1H, $J = 4.9$ and 9.8 Hz, $H^{2'}$), 3.87 (dt, 1H, $J = 2.7$ and 5.0 Hz, $H^{4'}$), 3.74–3.64 (m, 1H, $_bH^{5'}$), 3.64–3.54 (m, 1H, $_aH^{5'}$). ^{13}C NMR (101 MHz, DMSO-d_6, δ) 160.49 (C4), 150.99 (C2), 137.43 (C6), 107.35 (C5), 88.56 (C1′), 84.55 (C3′), 73.88 (C2′), 69.30 (C4′), 60.24 (C5′); LC-MS (ESI-TOF): m/z 279.04976 ($[M+H]^+$, $C_9H_{12}ClN_2O_6$ calcd. 279.03784).

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