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SYNTHESIS OF 2′-*O*-METHYL-5-ALKYNYL AND ALKENYL SUBSTITUTED URIDINE DERIVATIVES TO SCREEN FOR INHIBITORS OF HCV

Yili Ding,* Jean-Luc Girardet, Zhi Hong, Stephanie Z. Shaw, and Nanhua Yao

Valeant Pharmaceuticals International, 3300 Hyland Avenue Costa Mesa, CA 92626, USA.
yding@valeant.com

Abstract – Using Sonogashira and Heck coupling reactions, a series of 5-alkynyl and 5-alkenyl substituted 2′-*O*-methyluridine derivatives were synthesized in high yields. These compounds were used to screen for inhibitors of HCV, however none of them showed significant HCV inhibitory activity under 300 μM.

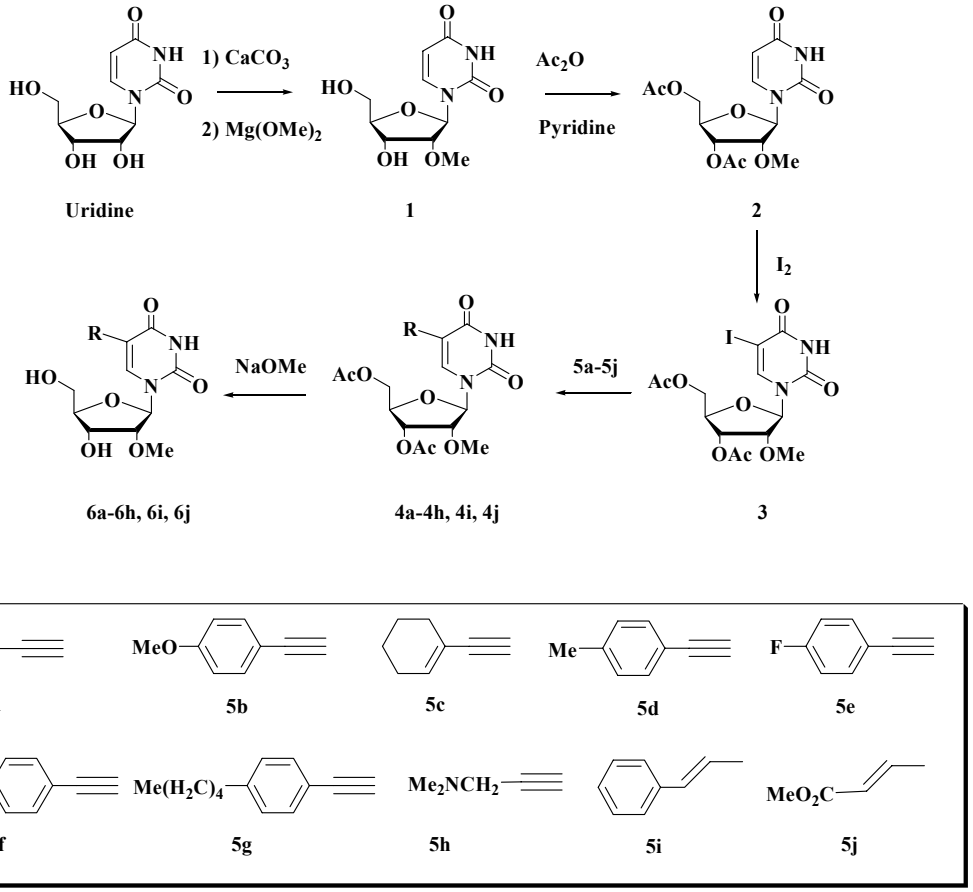
INTRODUCTION

Modified nucleosides have been of interest, due primarily to the medicinal value of these molecules.[1] From the screening of available nucleosides as inhibitors in the cell-based bicistronic replicon assay, 2′-*O*-methylcytidine was identified as specific inhibitor for HCV RNA replication with 14 μM activity without cytotoxicity.[2] The antiviral activities of 5-substituted uridines and 5-alkynyluracilnucleosides,[3] clinical application of *N*-substituted cytidines,[4] stimulated our interest to synthesize 2′-*O*-methyl-5-alkynyl and alkenyluridine derivatives and their *N*-substituted cytidine derivatives in order to find more efficient inhibitors of HCV.

Earlier, we reported the synthesis of 2′-*O*-methyl-5-alkynyl and alkenyl *N*-substituted cytidine derivatives on solid phase.[5] In this paper, we would like to report the synthesis of 5-alkynyl- and 5-alkenyl-2′-*O*-methyluridine derivatives using Sonogashira and Heck coupling reactions and their anti-HCV activity.

RESULTS AND DISCUSSION

5-Substituted pyrimidine nucleosides have been typically prepared by palladium catalyzed coupling of a suitable protected 5-iodo derivatives with alkenes and terminal alkynes.[3] Therefore, 5-alkynyl- and 5-alkenyl-2′-*O*-methyluridine derivatives could also be synthesized through Sonogashira and Heck coupling reactions, and the synthetic route is summarized in Scheme **1**.



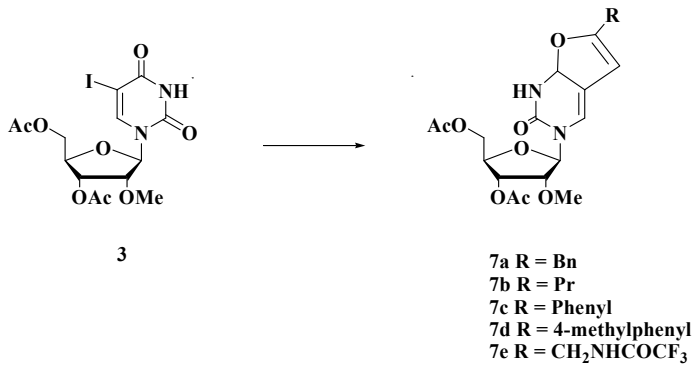
Scheme 1 Synthesis of 2-*O*'-methyl-5-alkynyl and 5-alkenyl substituted uridines

By using the established procedure, compound (**1**) was synthesized from uridine in large scale (100 g) in two steps.[6] Treatment of **1** with acetic anhydride and pyridine gave the compound (**2**)**,** which was then converted to 5-iodo derivative (**3**) using I_2/ceric ammonium nitrate reagents.[7] As an alterative synthetic method, we tried to obtain compound (**3**) from 5-iodouridine in a two-step methylation procedure,[6] however, due to the instability of the 5-iodouridine, we could not isolate any desired product from the reaction mixture.

The conventional synthesis of 2′-*O*-methyl-5-alkynyluridines (**4a-4h**) involves the Pd-catalyzed coupling of terminal alkynes (**5a-5h**) with compound (**3**). However, under Sonogashira conditions, a generally by-product, fluorescent furanopyrimidine, was formed.[8] Reaction conditions were optimized by varying solvents, temperature and catalysts. Each reaction was monitored by LC-MS spectral analysis, and the

suitable condition was found. Among to catalysts studied, $Pd(PPh_3)_4$ and $Pd_2(dba)_4$ were found to be best. The reaction should be performed in dry and deoxygenated DMF at room temperature over-night. Under these conditions, higher yields for the desired compounds were observed. However, for benzylalkyne and 1-pentyne, only the cyclic by-product**s**, were isolated from the reaction mixtures.

Cyclic fused furopyrimidine nucleosides were also formed as by-products under our reaction conditions as well. In fact, cyclic fused furopyrimidine nucleoside analogues exhibited excellent antiviral activity against VZV,[9] and the preparation for these compounds was not optimized in the literature and the yields were very lower (11-16%).[10] We found that high temperature (80 ^{Po}C), and longer reaction time (24 hours) gave higher yields (more than 50% yields) for the cyclic fused furopyrimidine nucleosides. Under these conditions, compounds (**7a-7e**) were obtained in high yields (Scheme **2**).



3

7a R = Bn
7b R = Pr
7c R = Phenyl
7d R = 4-methylphenyl
7e R = $CH_2NHCOCF_3$

Scheme 2 Synthesis of 2-*O*'-methyl cyclic furofused pyrimidine nucleoside derivatives

Reaction of compounds (**4a-4h**) with sodium methoxide in methanol offered the expected products (**6a-6h**). Using the modified Heck reaction conditions, the *C*-5 alkenyl substituted 2′-*O*-methyluridine derivatives (**6i-6j**) were then synthesized from a Pd catalyzed coupling of compound (**3**). Thus, reaction of 5-iodo derivative (**3**) with styrene (**5i**) and methyl acrylate (**5j**) in dry and deoxygenated dioxane in the presence of palladium(II) acetate, triphenylphosphine, and triethylamine afforded the products (**4i**) and (**4j**) in 47% and 69% yields. The *trans* stereochemistry for the nucleosides was indicated by the large vinylic coupling constants (>15 Hz) respectively for olefin protons, and no cyclic by-products were isolated. After deacetylation with NaOMe/MeOH, compounds (**4i-4j**) were converted to products (**6i-6j**).

Structure of the final compounds including 5-alkynyl substituted 2′-*O*-methyl uridine derivatives **6a-6h**, 5-alkenyl substituted 2′-*O*-methyluridine derivatives (**6i**) and (**6j**), and 2′-*O*-methyl related cyclic fused furopyrimidine nucleosides (**7a-7e)** was confirmed by ESMS and ^{1}H NMR spectra, and the purity of each compound was determined by LC-MS spectra. All of these compounds showed more than 90% purity. Compounds (**6a-6j**) were then used to screen the activity in a cell-based HCV subgenomic replicon assay.

Unfortunately, none of them showed significant inhibitory activity for HCV RNA replication.

In conclusion, the 5-alkynyl and 5-alkenyl substituted of 2′-*O*-methyluridine derivatives and 2′-*O*-methyl related cyclic fused furopyrimidine nucleosides were synthesized in high yields by using Sonogashira and Heck coupling reactions. It was found that lower reaction temperature and short reaction time favor the formation of the desired products, and high reaction temperature and long reaction time favor the formation of cyclic fused furopyrimidine nucleosides. The 5-alkynyl and 5-alkenyl substituted of 2′-*O*-methyluridine derivatives (**6a-6j**) did not show anti-HCV activity under 300 μM, indicated that any substitution at 5 position of the ring is not tolerated for anti-HCV activity.

EXPERIMENTAL

Experimental

1H NMR spectra were recorded at 300 MHz and the chemical shifts are expressed related to the added tetramethylsilane. The MS spectra were acquired using electrospray ionization with both positive and negative ion detections. The LC-MS spectral system consist of Water 2790 HPLC, Water 996 photodiode array (PDA) detector, and Micromass/Water ZQ mass spectrometer. Merck silica gel 60 was used for chromoatography (70-230 mesh) and flash chromatography (230-400) columns. Extracts were dried over Na_2SO_4 and evaporated under reduced pressure with a rotary evaporator.

3′, 5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(2-pyridine-ethynyl)uridine (**4a**): 5-Iodouridine derivative (**3**) (5.4 g, 11.5 mmol), triethylamine (11.5 mL), triphenylphosphine (91.0 mg, 3.5 mmol), copper iodide (44 mg, 0.23 mmol) and 2-ethynylpyridine (**5a**) (3.5 mL, 35 mmol) was added to degassed anhydrous DMF (60 mL). The resultant solution was degassed for an additional 30 min under argon and placed in a glove bag where $Pd(dba)_2$ (105 mg, 0.12 mmol) was added. The reaction mixture was stirred at rt for 10 h. After the reaction was completed, the solvent was concentrated and filtered through silica gel with ethyl acetate. The residue was purified by silica gel column chromatography using 1:1 toluene-ethyl acetate as eluent to yield 3.96 g (78%) of the desired product (**4a**): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 8.87 (br s, 1H), 8.59-8.56 (m, 1H), 7.66 (ddd, 1H, J = 2.1, 7.8, 9.6 Hz), 8.13 (s, 1H), 7.54 (ddd, 1H, J = 1.2, 2.1, 7.5 Hz), 7.23 (ddd, 1H, J = 1.2, 2.7, 4.8 Hz), 5.93 (d, 1H, J = 2.7 Hz,), 4.97 (dd, 1H, J = 5.1, 7.5 Hz), 4.46-4.42 (m, 1H), 4.39 (d, 2H, J = 2.7 Hz), 4.09 (dd, 1H, J = 2.7, 5.1 Hz), 3.52 (s, 3H), 2.21 (s, 3H), 2.13 (s, 3H); ESMS: m/z 444 $[M+1]^+$.

2′-*O*-Methoxy-5-(2-pyridine-ethynyl)uridine (**6a**): To a solution of compound (**4a**) (3.0 g, 6.6 mmol) in MeOH (100 mL) was added 25% wt NaOMe/MeOH (5 mL). The resulting mixture was stirred at

ambient temperature for 4 h. After completed, the reaction mixture was neutralized with acetic acid followed by the addition of dichloromethane where solution became turbid. The suspension was filtered through silica gel to provide product (**6a**) as green solid (1.6 g, 66%): ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.79 (br s, 1H), 8.58 (s, 1H) 7.82 (ddd, 1H, J = 1.8, 7.8, 9.3 Hz), 7.52 (d, 1H, J = 8.1 Hz), 7.38 (dddd, 1H, J = 4.8, 6.0, 7.5, 8.7 Hz), 5.82 (d, 1H, J = 3.6 Hz), 4.13 (dd, 1H, J = 5.4, 11.1 Hz), 3.88-3.82 (m, 4H), 3.72 (dd, 1H, J =2.4, 12.0 Hz), 3.59 (dd, 1H, J = 2.1, 12.3 Hz), 3.38 (s, 3H); ESMS: m/z 358 $[M-1]^-$; LC-MS spectrum showed 93% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(4-methoxyphenylethynyl)uridine (**4b**): Prepared from 1-ethynyl-4-methoxybenzene (**5b**) and compound (**3**) by the procedure described in the preparation of **4a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to offer the desired product (**4b**) in 67% yield: ^{1}H NMR ($CDCl_3$, 300 MHz); δ 9.20 (br s, 1H), 7.96 (s, 1H), 7.11 (AB quartet, 1H, J = 8.7, 3.8 Hz), 5.97 (d, 1H, J=2.7 Hz), 4.98 (dd, 1H, J = 5.4, 7.2 Hz), 5.93 (d, 1H, J = 2.7 Hz), 4.97 (dd, 1H, J = 5.1, 7.5 Hz), 4.44-4.35 (m, 3H), 3.75 (dd, 1H, J = 2.4, 5.1 Hz), 3.81 (s, 3H), 3.52 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H); ESMS: m/z 473 $[M+1]^+$.

2′-*O*-Methoxy-5-(4-methoxyphenylethynyl)uridine (**6b**): Prepared from compound (**4b**) by the procedure described in the preparation of **6a**. The product (**6b**) was obtained as solid in 78.4% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.7 (br s, 1H), 8.44 (s, 1H), 7.11 (AB quartet, 1H, J = 9.0, 10.7 Hz), 5.82 (d, 1H, J = 4.2 Hz), 5.31 (dd, 1H, J = 4.8, 9.3 Hz), 5.14 (d, 1H, J = 6.3 Hz), 4.13 (ddd, 1H, J =5.4, 9.9, 16.8 Hz), 3.86-3.80 (m, 2H), 3.76 (s, 3H), 3.74-3.54 (m, 2H), 3.38 (s, 3H), 3.31 (s, 3H); ESMS: m/z 387 $[M-1]^-$; LC-MS spectrum showed 94% purity.

3′, 5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(2-cyclohexene-ethynyl)uridine (**4c**): Prepared from 1-ethynylcyclohexene (**5c**) and compound (**3**) by the procedure described in the preparation of **4a**. The residue was purified by silica gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4c**) in 75% yield: ^{1}H NMR ($CDCl_3$, 300 MHz); δ 9.34 (br s, 1H, NH), 7.84 (s, 1H), 6.18-6.16 (m, 1H), 5.96 (d, 1H, J = 2.7 Hz), 4.96 (dd, 1H, J = 5.1, 7.2 Hz), 4.42-4.31 (m, 3H), 4.03 (dd, 1H, J = 2.7, 5.1 Hz), 3.49 (s, 3H), 2.21 (s, 3H), 2.15 (s, 3H), 2.13-2.07 (m, 4H), 1.66-1.54 (m, 4H); ESMS: m/z 447 $[M+1]^+$.

2′-*O*-Methoxy-5-(2-cyclohexene-ethynyl)uridine (**6c**): Prepared from compound (**4c**) by the procedure described in the preparation of **6a**. The product (**6c**) was obtained as solid in 94.1% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.6 (br s, 1H, NH), 8.31 (s, 1H), 6.09-6.07 (m, 1H), 5.80 (d, 1H, J = 4.2 Hz), 5.27 (dd, 1H, J = 4.2, 8.4 Hz), 5.13 (d, 1H, J = 6.3 Hz), 4.10 (dd, 1H, J = 5.4, 10.8 Hz), 3.85-3.82 (m, 1H), 3.78 (dd, 1H, J = 4.2, 8.7 Hz), 3.71-3.52 (m, 2H), 2.10-2.00 (m, 4H), 1.59-1.50 (m, 4H); ESMS: m/z 361 $[M-1]^-$; LC-MS spectrum showed 91% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(4-methylphenylethynyl)uridine (**4d**): Prepared from

1-ethynyl-*p*-methylbenzene (**5d**) and compound (**3**) by the procedure described in the preparation of **4a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4d**) in 67% yield: ^{1}H NMR (CD_3OD, 300 MHz); δ 7.87 (s, 1H), 7.33 (d, 2H, J = 7.8 Hz), 7.09 (d, 2H, J = 7.8 Hz), 5.96 (d, 1H, J = 2.4 Hz), 4.99 (dd, 1H, J = 5.4, 7.5 Hz), 4.39 (m, 3H), 4.09 (dd, 1H, J = 2.7, 5.1 Hz), 3.51 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H); ESMS: m/z 457 $[M+1]^+$.

2′-*O*-Methoxy-5-(4-methylphenylethynyl)uridine (**6d**): Prepared from compound (**4d**) by the procedure described in the preparation of **6a**. The product (**6d**) was obtained as solid in 74.1% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.72 (br s, 1H, NH), 8.48 (s, 1H), 7.33 (d, 2H, J = 7.8 Hz), 7.19 (d, 2H, J = 7.8 Hz), 5.81 (d, 1H, J = 3.9 Hz), 5.33 (t, 1H, J = 4.5 Hz), 5.14 (d, 1H, J = 6.3 Hz), 4.12 (m, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.57 (m, 1H), 3.40 (s, 3H), 2.31 (s, 3H); ESMS: m/z 371 $[M-1]^-$; LC-MS spectrum showed 95% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(4-fluorophenylethynyl)uridine (**4e**): Prepared from 1-ethynyl-*p*-fluorobenzene (**5e**) and compound (**3**) by the procedure described in the preparation of **4a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4e**) in 72% yield: ^{1}H NMR ($CDCl_3$, 300 MHz); δ 10.21 (s, 1H, NH), 7.98 (s, 1H), 7.20 (m, 2H), 6.98 (m, 2H), 5.90 (d, 1H, J = 2.4 Hz), 4.93 (dd, 1H, J = 5.4, 7.5 Hz), 4.34 (m, 4H), 3.45 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H); ESMS: m/z 461 $[M+1]^+$.

2′-*O*-Methoxy-5-(4-fluorophenylethynyl)uridine (**6e**): Prepared from compound (**4e)** by the procedure described in the preparation of **6a**. The product (**6e)** was obtained as solid in 64.1% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.75 (br s, 1H, NH), 8.51 (s, 1H), 7.50 (m, 2H), 7.23 (m, 2H), 5.80 (d, 1H, J = 3.6 Hz), 5.34 (t, 1H, J = 4.5 Hz, OH), 5.23 (d, 1H, J = 6.3 Hz, OH), 4.12 (m, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.57 (m, 1H), 3.44 (s, 3H); ESMS: m/z 375 $[M-1]^-$; LC-MS spectrum showed 91% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(4-trifluoromethylphenylethynyl)uridine (**4f**): Prepared from 1-ethynyl-*p*-trifluoromethylbenzene (**5f)** and compound (**3)** by the procedure described in the preparation of **4a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4f)** in 78% yield: ^{1}H NMR (CD_3OD, 300 MHz); δ 7.93 (s, 1H), 7.37 (d, 2H, J = 7.8 Hz), 7.09 (d, 2H, J = 7.8 Hz), 5.94 (d, 1H, J = 2.3 Hz), 4.97 (dd, 1H, J = 5.4, 7.5 Hz), 4.39 (m, 3H), 4.09 (dd, 1H, J = 2.7, 5.1 Hz), 3.51 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H); ESMS: m/z 511 $[M+1]^+$.

2′-*O*-Methoxy-5-(4-trifluoromethylphenylethynyl)uridine (**6f**): Prepared from compound (**4f**) by the procedure described in the preparation of **6a**. The product (**6f**) was obtained as solid in 54.1% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.72 (br s, 1H, NH), 8.52 (s, 1H), 7.15 (d, 2H, J =7.8 Hz), 7.25 (d, 2H, J = 7.8 Hz), 5.82 (d, 1H, J = 3.6 Hz), 5.30 (1H, OH), 5.10 (1H, OH), 4.12 (m, 1H), 3.92 (m, 2H), 3.75 (m, 12H), 3.60 (m, 1H), 3.40 (s, 3H); ESMS: m/z 425 $[M-1]^-$; LC-MS spectrum showed 92% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(4-pentylphenylethynyl)uridine (**4g**): Prepared from 1-ethynyl-*p*-pentylbenzene (**5g**) and compound (**3**) by the procedure described in the preparation of **4a**. The residue was purified by silica gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4g)** in 75% yield: ^{1}H NMR ($CDCl_3$, 300 MHz); δ 8.70 (s, 1H, NH), 7.97 (s, 1H), 7.37 (d, 2H, J = 7.8 Hz), 7.13 (d, 2H, J = 7.8 Hz), 5.97 (d, 1H, J = 2.7 Hz), 4.98 (dd, 1H, J = 5.4, 7.5 Hz), 4.41 (m, 4H), 4.07 (q, 1H, J = 2.4 Hz), 3.52 (s, 3H), 2.59 (t, 2H, J =8.1 Hz), 2.20 (s, 3H), 2.16 (s, 3H), 1.60 (m, 3H), 1.13 (m, 5H); ESMS: m/z 513 $[M+1]^+$.

2′-*O*-Methoxy-5-(4-pentylphenylethynyl)-uridine (**6g**): Prepared from compound **4g** by the procedure described in the preparation of **6a**. The product (**6g)** was obtained as solid in 87.1% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 11.72 (br s, 1H, NH), 8.48 (s, 1H), 7.36 (d, 2H, J =8.4 Hz), 7.20 (d, 2H, J = 8.4 Hz), 5.80 (d, 1H, J = 3.9 Hz), 5.33 (t, 1H, J = 6.0 Hz, OH), 5.15 (d, 1H, J = 6.6 Hz, OH), 4.12 (m, 1H), 3.83 (m, 2H), 3.72 (m, 1H), 3.59 (m, 1H), 3.38 (s, 3H), 2.57 (t, 2H, J = 8.4 Hz), 1.55 (m, 3H), 1.27 (m, 5H), 0.84 (t, 3H, J = 8.4 Hz); ESMS: m/z 427 $[M-1]^-$; LC-MS showed 95% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(2-dimethylaminoethynyl)uridine (**4h**): Prepared from 1-dimethylamino-2-propyne (**5h**) and compound (**3**) by the procedure described in the preparation of **4a**. The residue was purified by silica gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4h**) in 61% yield: ^{1}H NMR (CD_3OD, 300 MHz); δ 7.98 (s, 1H), 5.91 (d, 1H, J = 2.7 Hz), 4.96 (t, 1H, J = 5.1 Hz), 4.40 (m, 3H), 4.10 (dd, 1H), 3.83 (s, 2H), 3.50 (s, 3H), 2.62 (s, 6H), 2.21 (s, 3H), 2.16 (s, 3H); ESMS: m/z 424 $[M+1]^+$.

2′-*O*-Methoxy-5-(2-dimethylaminoethynyl)uridine (6h): Prepared from compound (**4h**) by the procedure described in the preparation of **6a**. The product (**6h**) was obtained as solid in 87.1% yield: ^{1}H NMR (CD_3OD, 300 MHz); δ 8.61 (s, 1H), 5.95 (d, 1H, J = 2.7 Hz), 3.90 (m, 32H), 3.80 (m, 2H), 3.60 (s, 3H), 3.59 (s, 2H), 2.78 (s, 6H); ESMS: m/z 338 $[M-1]^-$; LC-MS spectrum showed 92% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-styryluridine (**4i**): Palladium acetate (96.0 mg, 0.43 mmol), triphenylphosphine (300 mg, 1.10 mmol) and triethylamine (5.1 mL, mmol) were combined in deoxygenated 1,4-dioxane (10 mL) and the mixture was stirred at 60 ^{o}C under an argon atmosphere until a deep red coloration developed. Compound (**3**) (4 g, 8.5 mmol) and styrene (**5i**) (3 mL, 31.7 mmol) were added, and the mixture was stirred at 80 ^{o}C for 44 h. The hot reaction mixture was filtered through celite, washed with hot 1,4-dioxane and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 2:1 toluene:ethyl acetate as eluent to yield 1.76 g of compound (**4i**) (47%): ^{1}H NMR ($CDCl_3$, 300 MHz); δ 8.78 (br s, 1H), 7.62 (s, 1H), 7.46-7.19 (m, 6H), 6.81 (d, 1H, J = 16.2 Hz), 5.98 (d, 1H, J = 3.3 Hz), 5.04 (dd, 1H, J = 5.7, 11.4 Hz), 4.48-4.38 (m, 3H), 4.10 (dd, 1H, J = 3.6, 5.1 Hz), 3.50 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H); ESMS: m/z 445 $[M+1]^+$.

2′-*O*-Methoxy-5-styryluridine (**6i**): To a solution of compound (**4i**) (2.4 g, 5.3 mmol) in MeOH (100

mL) was added 25% wt NaOMe/MeOH (1 mL) dropwise over a period of 1.5 h. Follow the completion of the reaction, the reaction mixture was neutralized with acetic acid. The suspension was filtered through silica gel, after evaporation of the solvent, 1.9 g of desired compound (**6i)** (100%) was obtained as white solid: ^{1}H NMR (DMSO, 300 MHz); δ 8.39 (s, 1H), 7.46-7.20 (m, 7H), 6.84 (d, 1H, J = 16.2 Hz), 5.84 (d, 1H, J = 3.6 Hz), 4.19 (dd, 1H, J = 5.7, 11.2 Hz), 3.85-3.61 (m, 6H), 3.27 (s, 3H); ESMS: m/z 359 $[M-1]^-$; LC-MS spectrum showed 90% purity.

3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-5-(2-methoxycarbonyl-vinyl)uridine (**4j**): Prepared from methyl acrylate (**5j**) and compound (**3**) by the procedure described in the preparation of **4i**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**4j)** in 69% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.42 (br s, 1H), 7.83(s, 1H), 7.28 (d, 1H, J = 15.9 Hz), 7.00 (d, 1H, J = 15.6 Hz), 5.93 (d, 1H, J = 2.4 Hz), 4.94 (dd, 1H, J = 5.4, 7.2 Hz), 4.50-4.35 (m, 3H), 4.08 (dd, 1H, J = 3.0, 5.4 Hz), 3.76 (s, 3H), 3.51 (m, 3H), 2.19 (s, 3H), 2.16 (s, 3H); ESMS: m/z 427 $[M+1]^+$.

2′-*O*-Methoxy-5-(2-methoxycarbonylvinyl)uridine (**6j**): Prepared from compound (**4j**) by the procedure described in the preparation of **6i**. The product (**6j**) was obtained as solid in 95% yield: ^{1}H NMR (DMSO-D_6, 300 MHz); δ 8.51 (s, 1H), 7.29 (d, 1H, J = 15.6 Hz), 6.82 (d, 1H, J = 15.6 Hz), 5.80 (d, 1H, J = 3.3 Hz), 4.13 (dd, 1H, J = 6.0, 11.4 Hz), 3.83-3.77 (m, 2H), 3.74-3.57 (m, 2H), 3.65 (s, 3H), 3.38 (s, 3H); ESMS: m/z 343 $[M-1]^-$; LC-MS spectrum showed 93% purity.

3-(3′,5′-Di-*O*-acetyl-2′-*O*-Methoxy-*β*-D-ribofuranosyl)-6-benzyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one (7a): Compound (**3**) (5.4 g, 11.5 mmol), triethylamine (11.5 mL, mmol), triphenylphosphine (91.0 mg, 3.5 mmol), copper iodide (44 mg, 0.23 mmol) and 3-phenyl-1-propyne (3.5 mL, 35 mmol) were added to degassed dry DMF (60 mL). The resultant solution was degassed for an additional 30 min under argon and placed in a glove bag where $Pd(dba)_2$ (105 mg, 0.12 mmol) was added. The reaction mixture was heated at 80 °C for 24 h. After the reaction was completed, the solvent was concentrated and filtered through silica gel with ethyl acetate. The residue was purified by silica gel column chromatography using 1:1 toluene-ethyl acetate as eluent to yield **7a** (3.60 g, 70%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 7.26 (m, 5H), 6.03 (s, 1H), 6.03 (s, 1H), 4.77 (dd, 1H, J = 2.4, 5.8 Hz), 4.49 (m, 1H), 4.40 (dd, 1H, J = 3.6, 14.4 Hz), 4.35 (m, 1H), 4.12 (m, 1H), 3.96 (s, 2H), 3.60 (s, 3H), 2.12 (s, 1H), 2.09 (s, 3H); ESMS: m/z 459 $[M+1]^+$.

3-(3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-*β*-D-ribofuranosyl)-6-propyl-2,3-dihydrofuro[2,3-*d*]-pyrimidin-2-one (7b): Prepared from 1-pentyne and compound (**3**) by the procedure described in the preparation of **7a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**7b**) in 65% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H), 6.19 (s, 1H), 6.17 (s, 1H), 4.90 (dd, 1H, J = 2.4, 5.7 Hz), 4.65 (dd, 1H, J = 1.5, 4.2 Hz), 4.53 (dq, 2H, J = 1.5 Hz, 7.8 Hz),

4.24 (d, 1H, *J* = 3.0 Hz), 3.76 (s, 3H), 2.74 (t, 2H, *J* = 4.2 Hz), 2.27 (s, 3H), 2.24 (s, 3H), 1.83 (q, 2H, *J* =5.2 Hz), 1.09 (t, 3H, *J* = 5.2 Hz); ESMS: m/z 411 $[M+1]^+$.

3-(3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-*β*-D-ribofuranosyl)-6-phenyl-2,3-dihydrofuro[2,3-*d*]-pyrimidin-2-one (7c): Prepared from phenylacetylene and compound (**3**) by the procedure described in the preparation of **7a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**7b**) in 60% yield: ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 8.48 (s, 1H), 7.77 (m, 2H), 7.43 (m, 3H), 6.68 (s, 1H), 6.08 (s, 1H), 4.81 (dd, 1H, *J* = 2.4, 5.7 Hz), 4.50 (m, 3H) 4.19 (d, 1H, *J* = 5.2 Hz), 3.67 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H); ESMS: m/z 445 $[M+1]^+$.

3-(3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-*β*-D-ribofuranosyl)-6-(4-methylphenyl)-2,3-dihydrofuro[2,3-*d*]-pyrimidin-2-one (7d): Prepared from 4-methylphenylacetylene and compound (**3**) by the procedure described in the preparation of **7a**. The residue was purified by silica gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**7d**) in 65% yield: ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 8.43 (s, 1H), 7.63 (d, 2H, *J* = 8.1 Hz), 7.22 (d, 2H, *J* = 8.1 Hz), 6.60 (s, 1H), 6.07 (s, 1H), 4.81 (dd, 1H, *J* = 2.4, 5.7 Hz), 4.47 (m, 3H) 4.17 (d, 1H, *J* = 5.1 Hz), 3.65 (s, 3H), 2.37 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H); ESMS: m/z 459 $\{M+1\}^+$.

3-(3′,5′-Di-*O*-acetyl-2′-*O*-methoxy-*β*-D-ribofuranosyl)-6-trifluoroacetylamidomethylene-2,3-dihydro-furo[2,3-*d*]pyrimidin-2-one (7e): Prepared from trifluoroacetyl-propargyl amind and compound (**3**) by the procedure described in the preparation of **7a**. The residue was purified by silica-gel column chromatography using 1:1 toluene-ethyl acetate as eluent to give the desired product (**7f**) in 55% yield: ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 8.81 (t, 1H, NH), 8.50 (s, 1H), 6.46 (s, 1H), 6.03 (s, 1H), 4.77 (dd, 1H, *J* = 2.4, 5.7 Hz), 4.54 (d, 2H, *J* =5.7 Hz), 4.45 (m, 2H), 4.12 (d, 1H, *J* = 5.1 Hz), 3.60 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H); ESMS: m/z 494 $[M+1]^+$.

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