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Preparation of ribavirin analogues by copper- and ruthenium-catalyzed azide-alkyne 1,3-dipolar cycloaddition

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Abstract

In this study, we described the synthesis of 1,4- and 1,5-disubstituted-1,2,3-triazolo-nucleosides from various alkynes with 1′-azido-2′,3′,5′-tri-*O*-acetylribose using either copper-catalyzed azide-alkyne cycloaddition (CuAAC) or ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC), respectively. Optimized RuAAC conditions were realized with the commercially available [Cp*RuCl(PPh_3)$_2$] under microwave heating, which allows a significant acceleration of the reaction times (from 6 h to 5 min). This reaction can work under water-containing system. RuAAC and CuAAC are useful tools for the synthesis of 1,2,3-triazolyl-nucleosides small libraries.

1. Introduction

In recent years, many nucleoside analogues have been successfully developed into DNA virus and retrovirus therapeutic agents,[1] against different human immunodeficiency virus (HIV) strains and viruses with related-polymerases such as hepatitis B (HBV) or C (HCV). In the case of HCV, the template and substrate specificity of HCV RNA-dependent RNA polymerase differs from the host DNA-dependent polymerase, increasing thus the probability of developing potent HCV-specific nucleoside chain terminator. Figure 1 shows some examples of anti-HCV nucleosides and some triazolo derivatives (Fig. 1). The first nucleoside to show a therapeutic effect in HCV infection was ribavirin[2] (**1**) whose mechanism of action is a subject of debate.

Stuyver et al.[3] reported the activity of a N^4-hydroxycytidine (NHC) analogue (**2**), meanwhile several reports[4] describe the anti-HCV replicon activity of nucleosides modified at the 2′-position (**3**). Another approach to discover a potent anti-HCV compounds was reported by Smith et al.[5] in which analogues of triciribine (**4**), a cyclic sangivamycin analog with anti-cancer and anti-viral activity was reported. The synthesis of various triazolo compounds has been reported by Schinazi et al. (for **5**),[6] Benhida et al. (for **6**),[7] and by our team (for **7**).[8] As

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part of our drug discovery program, we report herein the synthesis of new 1,4-disubstituted-1,2,3-triazolonucleosides through well established Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). We have then investigated the Ru(II)-catalyzed azide-alkyne cycloaddition (RuAAC) under microwave conditions for the synthesis of 1,5-regiomers. All obtained compounds were evaluated for their anti-HCV activity in vitro.

2. Results and discussion

The Huisgen 1,3-dipolar cycloaddition of alkynes and azides (AAC)[9] to give substituted-1,2,3-triazoles has emerged as a powerful linking reaction in both uncatalyzed[10] and copper (I)-catalyzed leading to the sole 1,4-regioisomers.[11] The copper-catalyzed version of the reaction (CuAAC) has proven to be popular in many conditions, ranging from drug discovery to surface science, where rapid and reliable bond formation is required. Such 1,4 selectivity has been already reported in a very similar system under microwave conditions by Benhida et al.[7] Nevertheless, we have synthesized new compounds and evaluated them against HCV. Starting with the protected β-azido-ribose (**8**),[12] the synthesis of various protected 1,4-disubstituted-1,2,3-triazolyl-nucleosides (Scheme 1) was performed regioselectively with Cu(0)/$CuSO_4$ as catalyst precursor. The desired new compounds **9a**–**h** were obtained in yields ranging from 83 to 93% (Table 1, entries 1–7) except for ethoxy-ethyne (Table 1, entry 8). This system has the advantage of being simple and the products can be obtained from the reaction mixture by simple extraction.

We then turn our attention to the ruthenium-catalyzed version of the reaction (RuAAC), which is less extensively described and led mainly to 1,5-regioisomers.[13] Generally, the common approaches to 1,5-regioisomers were based on Grignard reagents,[14] or 1-trimethylsilylalkynes;[15] nevertheless, these approaches suffer from some limitations including the number of steps and the chemical behavior of some functional groups toward those conditions. Thus, under classical heating, the azido-ribose (**8**) was reacted with various alkynes and 5 mol % Cp*RuCl(PPh_3)$_2$ catalyst[16] (**11**) in THF at 50 °C. After 6 h, the desired triazolo compounds **10a**–**h** were obtained in moderate to good yield (54–83%), after purification by column chromatography. Except for the ethyl ethynyl ether derivative (54%), the yields of all other alynes are almost identical (from 71 to 83%) for the RuAAc reaction showing that the influence of the steric hindrance of alkyne is low.

During the RuAAC, 3 to 7% of the 1,4-regioisomers, separable by column chromatography on silica gel, were obtained. Their structures were unambiguously confirmed by NMR (e.g., δ_{H1}=6.44 ppm (for 1,4-isomer) and δ_{H1}=6.15 ppm (for 1,5-isomer)) and TLC comparison with those obtained under CuAAC conditions. It should be noted that some catalyst deactivation has been encountered during long heating times. Thus, to circumvent this limitation, we decided to work under microwave activation[17] (Table 1). Microwave heating is known as powerful tool to promote a variety of chemical reactions.[18] While yields and purities of the coupling products were comparable to heating conditions, microwave heating allows a significant acceleration of the reaction from 6 h to 5 min (Table 1).

Working in THF at 100 °C, we first investigated the optimal conditions for the cycloaddition of azido-ribose **8** and hexyne with different concentration of catalyst **11** (Table 2). A 95%

conversion was obtained after only 3 min of reaction with 5% catalyst. The total conversion of starting azido-ribose was obtained after 10 min with 3.5% catalyst loading and in 5 min for 5% catalyst loading. For lower catalyst loading, conversion was not complete, even after 10 min reaction.

Thus, 5 mol % catalyst and 1.5 equiv of alkyne in THF at 100 °C for 5 min under microwave irradiation allowed the isolation of the desired compound **10e**. It is interesting to note that anhydrous conditions are not necessary (e.g., undistilled THF, or THF-containing 2 equiv of water can be used to run this RuAAC). With this optimized conditions in hand, we probed the scope of the reaction on protected azido-ribose (**8**) with various alkynes. The desired 1,5-disubstituted-1,2,3-triazolyl-nucleosides **10a**–**h** were obtained in good yields (Table 1). In most examples (Table 1, entries 1–7), microwave irradiation had evident beneficial effects in terms of reaction time and yield. For example, using classical heating, sluggish reactions with ethyl ethynyl ether were observed (54% after 6 h), meanwhile under microwave irradiation, complete conversion was achieved with [Cp*RuCl(PPh_3)$_2$] after short reaction time (5 min). The deacylation of 1,4-regioisomers (**9a**–**h**) and 1,5-regioisomers (**10a**–**h**) was carried out using a 7 N solution of ammonia in methanol at 0 °C over 12 h and led quantitatively to the final 1,4-disubstituted-1,2,3-triazolo-nucleosides (**12a**–**h**) and 1,5-disubstituted-1,2,3-triazolo-nucleosides (**13a**–**h**), respectively (Scheme 2).

Finally, the scope of this reaction with respect to unprotected azido-ribose (**14**) was next investigated on the hexyne and after 5 min of irradiation with 5 mol % RuAAC catalyst, the desired product (**13e**) was obtained in 95% yield (Scheme 3). This result confirms the robustness of the RuACC reaction conditions.

3. Biological results

The biological activity and toxicity of the synthesized triazoles against HCV were investigated in a replicon system in Huh-7 cells, and these compounds did not exhibit any marked activity or toxicity. The anti-viral[19] and cytotoxicity[20] assays were done as previously described.

4. Conclusion

In summary, we have used either the Cu(0)/$CuSO_4$ catalytic system for CuAAC or the Cp*RuCl(PPh_3)$_2$ (**11**) under microwave conditions for RuAAC to reach *hitherto unknown* 1,4- and 1,5-di-substituted-1,2,3-triazolyl-nucleosides. The cooperative effect of the catalyst **11** and the microwave activation afforded the desired compounds in a few minutes in high yields. This approach allows an easy access to a small library of 1,5-disubstituted-triazolo derivatives under RuAAC and 1,4-regioisomers under CuAAC.

5. Experimental

5.1. General

Commercially available chemicals were of reagent grade and used as received. THF was distilled from sodium/benzophenone ketyl; CH_2Cl_2 from CaH_2 immediately prior use and

benzene over Na. The microwave was a Biotage AB Initiator EXP EU with a maximum power of 300 W. The vials used in the microwave were Emrys™ process vials 0.5–2 mL. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel plates (Kieselgel $60F_{254}$, E. Merck). Column chromatography was performed on Silica Gel 60M (0.040–0.063 mm, E. Merck). Melting points are uncorrected and were measured on a Kofler apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX 250 and Varian $Inova_{Unity}$ 400 spectrometer (^{1}H: 250 MHz, ^{13}C: 100 MHz) in (d_4) methanol and $CDCl_3$, shift values in parts per million relative to $SiMe_4$ as internal reference, the ^{31}P spectra were reported using aqueous phosphoric acid as external reference (^{31}P: 161.97 MHz) in CD_3OD, unless otherwise stated; J in hertz. Evidence of purity has been done from a proton-decoupled ^{13}C NMR spectrum with a signal-to-noise ratio sufficient to permit seeing peak with 5% of the intensity of the strongest peak.

5.2. General procedure under CuAAC condition

To a solution of selected alkyne (1.1 mmol) and azido-ribose (**8**) (1 mmol) in H_2O/^{t}BuOH (1 mL) were added Cu powder (4 mmol) and $CuSO_4$ (0.2 mmol). The resulting suspension was stirred overnight at room temperature, then the mixture was extracted twice with ethyl acetate (50 mL), and dried over $MgSO_4$. The solvents were removed under reduced pressure and the obtained residue was purified on silica gel (petroleum ether/ethyl acetate, 8:2, v/v) to give the desired compound.

5.2.1. 2′,3′,5′-Tri-O-benzoyl-1′-[4-phenyl-[1,2,3]triazol-1yl]ribofuranose (9a)—

Prepared from compound **8** with the typical procedure described before to give **9a** (86%) as an oil. IR: 1717, 1451, 1316, 1124, 1093,1040, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, J=7.2 Hz, 2H, H^{Ar}), 8.00–7.95 (m, 5H, H^{Ar} and H^{5}), 7.65 (d, J=7.5 Hz, 2H, H^{Ar}), 7.58–7.50 (m, 3H, H^{Ar}), 7.41–7.30 (m, 9H, H^{Ar}), 6.53 (d, J=3.8 Hz, 1H, $H^{1'}$), 6.30 (dd, J=5.3, 3.8 Hz, 1H, $H^{2'}$), 6.18 (t, J=5.3 Hz, 1H, $H^{3'}$), 4.86–4.92 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.62 (dd, J=12.0, 3.6 Hz, 1H, $H^{5'}$); ^{13}C NMR ($CDCl_3$): δ 166.0 (C(O)), 165.1 (C(O)), 165.0 (C(O)), 148.2 (C^{4}), 133.8 (C^{Ar}), 133.6 (C^{Ar}), 133.3 (C^{Ar}), 129.8 (2C, C^{Ar}), 129.7 (C^{Ar}), 129.6 (C^{Ar}), 129.2 (C^{Ar}), 128.6 (2C, C^{Ar}), 128.5 (2C, C^{Ar}), 128.4 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 125.7 (C^{Ar}), 118.4 (C^{5}), 90.3 ($C^{1'}$), 81.1 ($C^{4'}$), 75.2 ($C^{2'}$), 71.5 ($C^{3'}$), 63.5 ($C^{5'}$); CAS: 26295-47-6; MS (ESI): m/z $[M+Na]^{+}$ calcd for $C_{34}H_{27}N_3NaO_7$: 612.6, found: 612.5.

5.2.2. 2′,3′,5′-Tri-O-benzoyl-1′-[4–4-fluoro-3-methylphenyl-[1,2,3]triazol-1-yl]ribofuranose (9b)—

Prepared from compound **8** with the typical procedure described before to give **9b** (88%) as a slight yellow oil. IR: 1720, 1602, 1493, 1451, 1259, 1091, 1069, 1024, 799, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J=8.3 Hz, 2H, H^{Ar}), 8.00 (d, J=8.3 Hz, 2H, H^{Ar}), 7.97 (d, J=8.3 Hz, 2H, H^{Ar}), 7.89 (s, 1H, H^{5}), 7.61–7.50 (m, 4H, H^{Ar}), 7.44–7.37 (m, 7H, H^{Ar}), 6.98 (t, J=9.0 Hz, 1H, H^{Ar}), 6.53 (d, J=3.9 Hz, 1H, $H^{1'}$), 6.28 (dd, J=5.2, 3.9 Hz, 1H, $H^{2'}$), 6.15 (t, J=5.2 Hz, 1H, $H^{3'}$), 4.93–4.87 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.62 (dd, J=13.2, 4.8 Hz, 1H, $H^{5'}$), 2.28 (d, J=1.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 166.1 (C(O)), 165.2 (C(O)), 165.1 (C(O)), 147.7 (C^{4}), 133.9 (C^{Ar}), 133.8 (C^{Ar}), 133.5 (C^{Ar}), 129.9 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 129.2 (C^{Ar}), 129.0 (C^{Ar}), 128.9 (C^{Ar}), 128.7 (C^{Ar}), 128.6 (3C, C^{Ar}), 128.5 (C^{Ar}), 125.8 (2C, C^{Ar}), 125.4 (C^{Ar}), 125.2 (C^{Ar}), 124.9 (C^{Ar}), 124.8 (C^{Ar}), 118.0 (C^{5}), 115.5 (C^{Ar}), 115.2 (C^{Ar}), 90.4 ($C^{1'}$), 81.3 ($C^{4'}$), 75.3 ($C^{2'}$), 71.6 ($C^{3'}$), 63.6

($C^{5'}$), 14.6, 14.5 (CH_3); MS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{35}H_{28}FN_3NaO_7$: 644.6, found: 644.5.

5.2.3. 2′,3′,5′-Tri-O-benzoyl-1′-[4-benzyl-[1,2,3]triazol-1-yl]ribofuranose (9c)—Prepared from compound **8** with the typical procedure described before to give **9c** (93%) as white solid. Mp: 158 °C ($CHCl_3$); IR: 1727, 1708, 1601, 1450, 1270, 1123, 1095, 1068, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.09–7.96 (m, 6H, H^{Ar}), 7.64–7.56 (m, 3H, H^{Ar}), 7.50–7.38 (m, 7H, H^{Ar} and H^5), 7.33–7.21 (m, 5H, H^{Ar}), 6.43 (d, *J*=3.1 Hz, $H^{1'}$), 6.28–6.25 (m, 1H, $H^{2'}$), 6.19 (t, *J*=5.5 Hz, 1H, $H^{3'}$), 4.95–4.88 (m, 1H, $H^{4'}$), 4.83 (dd, *J*=12.2, 3.3 Hz, 1H, $H^{5'}$), 4.63 (dd, *J*=12.2, 4.5 Hz, 1H, $H^{5'}$), 4.02–3.88 (m, 1H, CH_2Ph); ^{13}C NMR ($CDCl_3$): δ 166.0 (C(O)), 165.6 (C(O)), 165.0 (C(O)), 138.4 (C^4), 133.8 (C^{Ar}), 133.6 (C^{Ar}), 133.3 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (2C, C^{Ar}), 129.2 (C^{Ar}), 128.7 (C^{Ar}), 128.6 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 126.5 (C^5), 90.1 ($C^{1'}$), 81.0 ($C^{4'}$), 75.2 ($C^{2'}$), 71.6 ($C^{3'}$), 63.7 ($C^{5'}$), 32.1 (CH_2Ph); MS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{35}H_{29}N_3NaO_7$: 626.6, found: 626.5.

5.2.4. 2′,3′,5′-Tri-O-benzoyl-1′-[4-methylcyclopentyl-[1,2,3]triazol-1-yl]ribofuranose (9d)—Prepared from compound **8** with the typical procedure described before to give **9d** (87%) as white solid. Mp: 121 °C ($CHCl_3$); IR: 1716, 1601, 1451, 1261, 1093, 1068, 1023, 803, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J*=8.2 Hz, 2H, H^{Ar}), 7.97 (d, *J*=8.2 Hz, 2H, H^{Ar}), 7.94 (d, *J*=8.2 Hz, 2H, H^{Ar}), 7.57–7.49 (m, 4H, H^{Ar} and H^5), 7.44–7.31 (m, 6H, H^{Ar}), 6.46 (d, *J*=3.6 Hz, 1H, $H^{1'}$), 6.23 (dd, *J*=5.2, 3.6 Hz, 1H, $H^{2'}$), 6.15 (t, *J*=5.4 Hz, 1H, $H^{3'}$), 4.89–4.79 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.59 (dd, *J*=12.1, 4.2 Hz, 1H, $H^{5'}$), 2.63 (d, *J*=6.9 Hz, 2H, CH_2–CHCH_2CH_2), 2.11–2.01 (m, 1H, CH_2–C*H*CH_2CH_2), 1.73–1.62 (m, 2H, CH_2–CHCH_2CH_2), 1.60–1.52 (m, 2H, CH_2–CHCH_2CH_2), 1.50–1.42 (m, 2H, CH_2–CHCH_2CH_2), 1.17–1.07 (m, 2H, CH_2–CHCH_2CH_2); ^{13}C NMR ($CDCl_3$): δ 166.1 (C(O)), 165.2 (C(O)), 165.1 (C(O)), 148.6 (C^4), 133.8 (C^{Ar}), 133.7 (C^{Ar}), 133.4 (C^{Ar}), 130.1 (C^{Ar}), 129.9 (C^{Ar}), 129.8 (2C, C^{Ar}), 129.3 (C^{Ar}), 128.7 (C^{Ar}), 128.6 (2C, C^{Ar}), 128.5 (C^{Ar}), 128.3 (C^{Ar}), 112.0 (C^5), 90.2 ($C^{1'}$), 81.0 ($C^{4'}$), 75.2 ($C^{2'}$), 71.7 ($C^{3'}$), 63.8 ($C^{5'}$), 39.7 (CH_2–*C*HCH_2CH_2), 32.5 (2C, CH_2–CH*C*H_2CH_2), 31.6 (CH_2–CHCH_2CH_2), 25.1 (CH_2–CHCH_2*C*H_2); MS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{34}H_{33}N_3NaO_7$: 618.7, found: 618.5.

5.2.5. 2′,3′,5′-Tri-O-benzoyl-1′-[4-butyl-[1,2,3]triazol-1-yl]ribofuranose (9e)—Prepared from compound **8** with the typical procedure described before to give **9e** (89%) as white solid. Mp: 98 °C ($CHCl_3$); IR: 1726, 1601, 1451, 1254, 1124, 1090, 1068, 1045, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J*=8.5 Hz, 2H, H^{Ar}), 7.99 (d, *J*=8.5 Hz, 2H, H^{Ar}), 7.95 (d, *J*=8.5 Hz, 2H, H^{Ar}), 7.58–7.52 (m, 3H, H^{Ar}), 7.49 (s, 1H, H^5), 7.46–7.34 (m, 6H, H^{Ar}), 6.45 (d, *J*=3.6 Hz, 1H, $H^{1'}$), 6.23 (dd, *J*=5.3, 3.6 Hz, 1H, $H^{2'}$), 6.15 (t, *J*=5.3 Hz, 1H, $H^{3'}$), 4.90–4.80 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.60 (dd, *J*=12.1, 4.2 Hz, 1H, $H^{5'}$), 2.64 (td, *J*=7.6, 2.3 Hz, 2H, CH_2CH_2CH_2CH_3), 1.59–1.50 (m, 2H, CH_2CH_2CH_2CH_3), 1.39–1.28 (m, 2H, CH_2CH_2CH_2CH_3), 0.89 (t, *J*=7.3 Hz, 3H, $CH_2CH_2CH_2$CH_3); ^{13}C NMR ($CDCl_3$): δ 166.0 (C(O)), 165.0 (C(O)), 164.9 (C(O)), 148.9 (C^4), 133.7 (C^{Ar}), 133.6 (C^{Ar}), 133.3 (C^{Ar}), 129.7 (2C, C^{Ar}), 129.6 (C^{Ar}), 129.2 (C^{Ar}), 128.6 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (2C, C^{Ar}), 119.5 (C^5), 90.0 ($C^{1'}$), 80.9 ($C^{4'}$), 75.1 ($C^{2'}$), 71.6 ($C^{3'}$), 63.6 ($C^{5'}$), 31.0 (CH_2*C*$H_2CH_2CH_3$), 25.1 (*C*$H_2CH_2CH_2CH_3$), 22.2 (CH_2*C*H_2*C*H_2CH_3), 13.7 ($CH_2CH_2CH_2$*C*H_3); MS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{32}H_{31}N_3NaO_7$: 592.6, found: 592.5.

5.2.6. 2′,3′,5′-Tri-O-benzoyl-1′-[4-(3-chloropropyl)-[1,2,3]triazol-1-yl]ribofuranose (9f)—

Prepared from compound **8** with the typical procedure described before to give **9f** (83%) as white solid. Mp: 132 °C ($CHCl_3$); IR: 1716, 1601, 1451, 1264, 1124, 1099, 1070, 1047, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.03 (d, J=8.5 Hz, 2H, H^{Ar}), 7.98 (d, J=8.4 Hz, 2H, H^{Ar}), 7.94 (d, J=8.4 Hz, 2H, H^{Ar}), 7.58–7.52 (m, 4H, H^{Ar} and H^5), 7.45–7.33 (m, 6H, H^{Ar}), 6.44 (d, J=3.5 Hz, 1H, $H^{1'}$), 6.24 (dd, J=5.4, 3.5 Hz, 1H, $H^{2'}$), 6.14 (t, J=5.4 Hz, 1H, $H^{3'}$), 4.90–4.79 (m, 2H, H4′ and $H^{5'}$), 4.58 (dd, J=12.2, 4.3 Hz, 1H, $H^{5'}$), 3.51 (t, J=6.4 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.79 (t, J=6.4 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.07–2.00 (m, 2H, $CH_2CH_2CH_2Cl$); ^{13}C NMR ($CDCl_3$): δ 165.9 (C(O)), 165.0 (C(O)), 164.9 (C(O)), 146.7 (C^4), 133.7 (C^{Ar}), 133.6 (C^{Ar}), 133.3 (C^{Ar}), 129.7 (C^{Ar}), 129.6 (2C, C^{Ar}), 129.2 (C^{Ar}), 128.5 (2C, C^{Ar}), 128.4 (2C, C^{Ar}), 128.3 (C^{Ar}), 120.1 (C^5), 90.0 ($C^{1'}$), 80.9 ($C^{4'}$), 75.1 ($C^{2'}$), 71.5 ($C^{3'}$), 63.5 ($C^{5'}$), 44.0 ($CH_2CH_2CH_2Cl$), 31.4 ($CH_2CH_2CH_2Cl$), 22.5 ($CH_2CH_2CH_2Cl$); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{31}H_{28}ClN_3NaO_7$: 612.6, found: 612.5.

5.2.7. 2′,3′,5′-Tri-O-benzoyl-1′-[4-terbutyl-[1,2,3]triazol-1-yl]ribofuranose (9g)—

Prepared from compound **8** with the typical procedure described before to give **9g** (92%) as white solid. Mp: 129 °C ($CHCl_3$); IR: 1718, 1600, 1450, 1265, 1094, 1069, 1037, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.07 (d, J=8.0 Hz, 2H, H^{Ar}), 7.99 (d, J=8.3 Hz, 2H, H^{Ar}), 7.94 (d, J=8.3 Hz, 2H, H^{Ar}), 7.59–7.51 (m, 3H, H^{Ar}), 7.46–7.33 (m, 7H, H^{Ar} and H^5), 6.46 (d, J=3.1 Hz, 1H, $H^{1'}$), 6.20–6.14 (m, 2H, $H^{2'}$ and $H^{3'}$), 4.90–4.80 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.61 (dd, J=11.9, 4.1 Hz, 1H, $H^{5'}$), 1.27 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 166.1 (2C, C(O)), 165.1 (2C, C(O)), 158.2 (C^4), 133.8 (C^{Ar}), 133.7 (C^{Ar}), 133.4 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (2C, C^{Ar}), 129.3 (C^{Ar}), 128.6 (2C, C^{Ar}), 128.5 (3C, C^{Ar}), 117.4 (C^5), 90.1 ($C^{1'}$), 81.0 ($C^{4'}$), 75.2 ($C^{2'}$), 71.8 ($C^{3'}$), 63.8 ($C^{5'}$), 30.7 ($CHCH_3$), 30.1 ($CHCH_3$); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{32}H_{31}N_3NaO_7$: 592.6, found: 592.0.

5.2.8. 2′,3′,5′-Tri-O-benzoyl-1′-[4-O-ethoxy-[1,2,3]triazol-1-yl]ribofuranose (9h)—

Prepared from compound **8** with the typical procedure described before to give **9h** (63%) as yellow solid. Mp: 117 °C ($CHCl_3$); IR: 1715, 1568, 1451, 1282, 1265, 1127, 1092, 1024, 701 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06 (d, J=8.4 Hz, 2H, H^{Ar}), 7.98 (d, J=8.4 Hz, 2H, H^{Ar}), 7.95 (d, J=8.4 Hz, 2H, H^{Ar}), 7.60–7.53 (m, 3H, H^{Ar}), 7.48–7.34 (m, 6H, H^{Ar}), 7.16 (s, 1H, H^5), 6.36 (d, J=3.8 Hz, 1H, $H^{1'}$), 6.22 (dd, J=5.3, 3.8 Hz, 1H, $H^{2'}$), 6.10 (t, J=5.3 Hz, 1H, $H^{3'}$), 4.88–4.79 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.69 (dd, J=12.1, 4.2 Hz, 1H, $H^{5'}$), 4.12 (q, J=7.1 Hz, 2H, OCH_2CH_3), 1.35 (t, J=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 166.0 (C(O)), 165.1 (C(O)), 165.0 (C(O)), 161.2 (C^4), 133.8 (C^{Ar}), 133.7 (C^{Ar}), 133.4 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 128.6 (2C, C^{Ar}), 128.5 (2C, C^{Ar}), 104.5 (C^5), 90.7 ($C^{1'}$), 81.1 ($C^{4'}$), 74.9 ($C^{2'}$), 71.6 ($C^{3'}$), 66.3 (OCH_2CH_3), 63.7 ($C^{5'}$), 14.7 (OCH_2CH_3); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{30}H_{27}N_3NaO_8$: 580.6, found: 580.5.

5.3. General procedure for the RuAAC reaction

In a microwave sealed reactor, a mixture of azido-ribose (**8**) (1 mmol), the selected alkyne (1.5 mmol), and $Cp^*RuCl(PPh_3)_2$ (0.05 mmol) in THF (10 mL) was irradiated for 5 min at 100 °C (200 W, normal mode). The mixture was then evaporated under reduced pressure and

the residue purified on silica gel (petroleum ether/ethyl acetate; 7:3) to give the desired product.

5.3.1. 2′,3′,5′-Tri-O-benzoyl-1′-[5-phenyl-[1,2,3]triazol-1-yl]ribofuranose (10a)—Prepared from compound **8** with the typical procedure described before to give **10a** (see Table 1) as a slightly brown oil. IR: 1721, 1601, 1451, 1261, 1090, 1069, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.05–7.90 (m, 6H, H^{Ar}), 7.74 (s, 1H, H^4), 7.59–7.47 (m, 8H, H^{Ar}), 7.43–7.30 (m, 6H, H^{Ar}), 6.54–6.47 (m, 2H, $H^{2'}$ and $H^{3'}$), 6.15 (d, J=1.6 Hz, 1H, $H^{1'}$), 4.91 (m, 1H, $H^{4'}$), 4.78 (dd, J=12.12, 3.96 Hz, 1H, $H^{5'}$), 4.61 (dd, J=12.12, 5.13 Hz, 1H, $H^{5'}$); ^{13}C NMR ($CDCl_3$): δ 166.2 (C(O)), 165.0 (2C, C(O)), 139.1 (C^5), 133.7 (C^{Ar}), 133.5 (C^{Ar}), 133.1 (C^{Ar}), 133.0 (C^5), 129.9 (C^{Ar}), 129.8 (2C, C^{Ar}), 129.4 (C^{Ar}), 129.2 (2C, C^{Ar}), 128.8 (C^{Ar}), 128.7 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 126.0 (C^4), 88.2 ($C^{1'}$), 80.9 ($C^{4'}$), 75.6 ($C^{2'}$), 72.2 ($C^{3'}$), 63.7 ($C^{5'}$); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{34}H_{27}N_3NaO_7$: 612.6, found: 612.5.

5.3.2. 2′,3′,5′-Tri-O-benzoyl-1′-[5–4-fluoro-3-methylphenyl-[1,2,3]triazol-1-yl]ribofuranose (10b)—Prepared from compound **8** with the typical procedure described before to give **10b** (see Table 1) as a slight brown oil. IR: 1720, 1602, 1492, 1451, 1253, 1084, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.05–7.91 (m, 6H, H^{Ar}), 7.70 (s, 1H, H^4), 7.60–7.48 (m, 3H, H^{Ar}), 7.44–7.30 (m, 9H, H^{Ar}), 7.16–7.08 (t, J=8.0 Hz, 1H, H^{Ar}), 6.51–6.45 (m, 2H, $H^{2'}$ and $H^{3'}$), 6.10 (d, J=1.2 Hz, 1H, $H^{1'}$), 4.93–4.89 (m, 1H, $H^{4'}$), 4.78 (dd, J=12.1, 3.9 Hz, 1H, $H^{5'}$), 4.61 (dd, J=12.1, 5.2 Hz, 1H, $H^{5'}$), 2.32 (d, J=1.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 166.2 (C(O)), 165.1 (C(O)), 165.0 (C^{Ar}), 163.5 (C^{Ar}), 161.0 (C^{Ar}), 138.4 (C^{Ar}), 133.8 (C^{Ar}), 133.5 (C^{Ar}), 133.2 (C^{Ar}), 132.9 (C^{Ar}), 132.6 (2C, C^{Ar}), 129.8 (3C, C^{Ar}), 129.4 (C^{Ar}), 128.7 (2C, C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 126.3 (C^4), 126.1 (C^4), 121.7 (C^{Ar}), 121.6 (C^{Ar}), 116.0 (C^{Ar}), 115.8 (C^{Ar}), 88.1 ($C^{1'}$), 80.8 ($C^{4'}$), 75.7 ($C^{2'}$), 72.1 ($C^{3'}$), 63.7 ($C^{5'}$), 14.5 (2C, CH_3); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{35}H_{28}FN_3NaO_7$: 644.6, found: 644.5.

5.3.3. 2′,3′,5′-Tri-O-benzoyl-1′-[5-methylbenzyl-[1,2,3]triazol-1-yl]ribofuranose (10c)—Prepared from compound **8** with the typical procedure described before to give **10c** (see Table 1) as a slight brown oil. IR: 1720, 1577, 1451, 1261, 1091, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.93–7.80 (m, 6H, H^{Ar}), 7.51–7.40 (m, 3H, H^{Ar}), 7.34–7.22 (m, 7H, H^{Ar} and H^4), 7.21–7.09 (m, 3H, H^{Ar}), 7.09–7.04 (m, 2H, H^{Ar}), 6.35 (dd, J=5.2, 2.1 Hz, 1H, $H^{2'}$), 6.21 (dd, J=7.0, 5.2 Hz, 1H, $H^{3'}$), 6.07 (d, J=2.1 Hz, 1H, $H^{1'}$), 4.80–4.74 (m, 1H, $H^{4'}$), 4.65 (dd, J=12.1, 3.8 Hz, 1H, $H^{5'}$), 4.46 (dd, J=12.1, 5.1 Hz, 1H, $H^{5'}$), 4.03 (q, J=16.6 Hz, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$): δ 166.1 (C(O)), 165.0 (2C, C(O)), 137.0, 135.6 (C^{Ar} and C^5), 133.8 (C^{Ar}), 133.7 (C^{Ar}), 133.5 (C^{Ar}), 133.1 (C^{Ar}), 129.7 (2C, C^{Ar}), 129.3 (C^{Ar}), 128.9, 128.7, 128.6, 128.5, 128.4 (2C), 128.3 (C^{Ar} and C^4), 127.2 (C^{Ar}), 88.0 ($C^{1'}$), 80.8 ($C^{4'}$), 75.1 ($C^{2'}$), 71.8 ($C^{3'}$), 63.6 ($C^{5'}$), 29.0 (CH_2Ph); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{35}H_{29}N_3NaO_7$: 626.6, found: 626.5.

5.3.4. 2′,3′,5′-Tri-O-benzoyl-1′-[5-methylcyclopentyl-[1,2,3]triazol-1-yl]ribofuranose (10d)—Prepared from compound **8** with the typical procedure described before to give **10d** (see Table 1) as a slight brown oil. IR: 1721, 1601, 1580, 1451, 1262,

1091, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06–7.92 (m, 6H, H^{Ar}), 7.62–7.49 (m, 3H, H^{Ar}), 7.47 (s, 1H, H^4), 7.46–7.32 (m, 6H, H^{Ar}), 6.48 (dd, J=5.2, 1.8 Hz, 1H, $H^{2'}$), 6.36 (dd, J=7.1, 5.2 Hz, 1H, $H^{3'}$), 6.20 (d, J=1.8Hz, 1H, $H^{1'}$), 4.93–4.87 (m, 1H, $H^{4'}$), 4.73 (dd, J=12.1, 3.9 Hz, 1H, $H^{5'}$), 4.53 (dd, J=12.1, 5.3 Hz, 1H, $H^{5'}$), 2.73 (d, J=7.4 Hz, 2H, CH_2–$CHCH_2CH_2$), 2.25–2.12 (m, 1H, CH_2–$CHCH_2CH_2$), 1.85–1.73 (m, 2H, CH_2–$CHCH_2CH_2$), 1.68–1.47 (m, 4H, CH_2–$CHCH_2CH_2$), 1.24–1.12 (m, 2H, CH_2–$CHCH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ 166.1 (C(O)), 165.1 (C(O)), 165.0 (C(O)), 138.0 (C^5), 133.7 (C^{Ar}), 133.5 (C^{Ar}), 133.1 (C^{Ar}), 132.8 (C^4), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 129.3 (C^{Ar}), 128.8 (C^{Ar}), 128.7 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 87.8 ($C^{1'}$), 80.8 ($C^{4'}$), 75.4 ($C^{2'}$), 72.1 ($C^{3'}$), 63.8 ($C^{5'}$), 38.7 (CH_2–$CHCH_2CH_2$), 32.5 (2C, CH_2–$CHCH_2CH_2$), 28.9 (CH_2–$CHCH_2CH_2$), 25.0 (CH_2–$CHCH_2CH_2$); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{34}H_{33}N_3NaO_7$: 618.7, found: 618.5.

5.3.5. 2′,3′,5′-Tri-O-benzoyl-1′-[5-butyl-[1,2,3]triazol-1-yl]ribofuranose (10e)— Prepared from compound **8** with the typical procedure described before to give **10e** (see Table 1) as a brown oil. IR: 1721, 1602, 1451, 1261, 1092, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05–7.93 (m, 6H, H^{Ar}), 7.62–7.50 (m, 3H, H^{Ar}), 7.46 (s, 1H, H^4), 7.45–7.33 (m, 6H, H^{Ar}), 6.46 (dd, J=5.2, 1.8 Hz, 1H, $H^{2'}$), 6.35 (dd, J=7.2, 5.2 Hz, 1H, $H^{3'}$), 6.19 (d, J=1.8 Hz, 1H, $H^{1'}$), 4.92–4.88 (m, 1H, $H^{4'}$), 4.73 (dd, J=12.1, 3.9 Hz, 1H, $H^{5'}$), 4.54 (dd, J=12.1, 5.5 Hz, 1H, $H^{5'}$), 2.73 (t, J= 7.8 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.71–1.62 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.44–1.33 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.96–0.89 (t, J=7.4 Hz, 3H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 166.1 (C(O)), 165.2 (C(O)), 165.0 (C(O)), 138.4 (C^5), 133.8 (C^{Ar}), 133.5 (C^{Ar}), 133.2 (C^{Ar}), 132.4 (C^4), 129.8 (2C, C^{Ar}), 129.4 (C^{Ar}), 128.8 (2C, C^{Ar}), 128.6 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 87.9 ($C^{1'}$), 80.8 ($C^{4'}$), 75.4 ($C^{2'}$), 72.0 ($C^{3'}$), 63.8 ($C^{5'}$), 30.2 ($CH_2CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_3$), 22.2 ($CH_2CH_2CH_2CH_3$), 13.6 ($CH_2CH_2CH_2CH_3$); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{32}H_{31}N_3NaO_7$: 592.6, found: 592.5.

5.3.6. 2′,3′,5′-Tri-O-benzoyl-1′-[5-(3-chloropropyl)-[1,2,3]triazol-1-yl]ribofuranose (10f)— Prepared from compound **8** with the typical procedure described before to give **10f** (see Table 1) as a brown oil. IR: 1719, 1602, 1451, 1260, 1092, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05–7.94 (m, 6H, H^{Ar}), 7.61–7.50 (m, 3H, H^{Ar}), 7.50 (s, 1H, H^4), 7.39 (m, 6H, H^{Ar}), 6.50 (dd, J=5.2, 1.8 Hz, 1H, $H^{2'}$), 6.34 (dd, J=7.2, 5.2 Hz, 1H, $H^{3'}$), 6.25 (d, J=1.8 Hz, 1H, $H^{1'}$), 4.94–4.90 (m, 1H, $H^{4'}$), 4.74 (dd, J=12.2, 3.8 Hz, 1H, $H^{5'}$), 4.53 (dd, J=12.2, 5.1 Hz, 1H, $H^{5'}$), 3.60–3.48 (m, 2H, $CH_2CH_2CH_2Cl$), 3.03–2.88 (m, 2H, $CH_2CH_2CH_2Cl$), 2.20–2.09 (m, 2H, $CH_2CH_2CH_2Cl$); ^{13}C NMR ($CDCl_3$): δ 166.0 (C(O)), 165.1 (C(O)), 165.0 (C(O)), 136.7 (C^5), 133.7 (C^{Ar}), 133.5 (C^{Ar}), 133.1 (C^{Ar}), 132.6 (C^4), 129.7 (C^{Ar}), 129.6 (C^{Ar}), 129.2 (C^{Ar}), 128.6 (2C, C^{Ar}), 128.5 (C^{Ar}), 128.3 (2C, C^{Ar}), 87.8 ($C^{1'}$), 80.8 ($C^{4'}$), 75.2 ($C^{2'}$), 71.8 ($C^{3'}$), 63.5 ($C^{5'}$), 43.4 ($CH_2CH_2CH_2Cl$), 30.7 ($CH_2CH_2CH_2Cl$), 19.9 ($CH_2CH_2CH_2Cl$); MS (ESI): m/z $[M+Na]^+$ calcd for $C_{31}H_{28}ClN_3NaO_7$: 612.6, found: 612.5.

5.3.7. 2′,3′,5′-Tri-O-benzoyl-1′-[5-tert-butyl-[1,2,3]triazol-1-yl]ribofuranose (10g)— Prepared from compound **8** with the typical procedure described before to give **10g** (see Table 1) as a brown oil. IR: 1721, 1602, 1451, 1250, 1092, 1069, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.09 (d, J=8.5 Hz, 2H, H^{Ar}), 8.01 (d, J=8.5 Hz, 2H, H^{Ar}), 7.97 (d, J=8.5 Hz, 2H,

H^{Ar}), 7.61–7.54 (m, 3H, H^{Ar}), 7.47–7.36 (m, 7H, H^{Ar} and H^4), 6.45 (d, J=3.1 Hz, 1H, $H^{2'}$), 6.19–6.15 (m, 2H, $H^{3'}$ and $H^{1'}$), 4.89–4.80 (m, 2H, $H^{4'}$ and $H^{5'}$), 4.61 (dd, J=11.9, 4.1 Hz, 1H, $H^{5'}$), 1.27 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 166.1 (C(O)), 165.1 (C(O)), 165.0 (C(O)), 146.5 (C^5), 133.7 (C^{Ar}), 133.4 (C^{Ar}), 133.0 (C^{Ar}), 131.2 (C^4), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 129.4 (C^{Ar}), 128.8 (2C, C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 117.4 (C^4), 89.2 ($C^{1'}$), 80.7 ($C^{4'}$), 72.4 ($C^{2'}$), 63.8 ($C^{5'}$), 30.3 (C(CH_3)$_3$), 30.1 (C(CH$_3$)$_3$); MS (ESI): m/z [M +Na]$^+$ calcd for $C_{32}H_{31}N_3NaO_7$: 592.6, found: 592.0.

5.3.8. 2′,3′,5′-Tri-O-benzoyl-1′-[5-O-ethoxy-[1,2,3]triazol-1-yl]ribofuranose (10h)—Prepared from compound **8** with the typical procedure described before to give **10h** (see Table 1) as a brown oil. IR: 1720, 1577, 1451, 1261, 1091, 1026, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.07–7.98 (m, 4H, H^{Ar}), 7.96–7.90 (m, 2H, H^{Ar}), 7.55 (m, 3H, H^{Ar}), 7.44–7.31 (m, 6H, H^{Ar}), 7.07 (s, 1H, H^4), 6.34 (dd, J=5.3, 2.4 Hz, 1H, $H^{2'}$), 6.30–6.25 (m, 2H, $H^{3'}$ and $H^{1'}$), 4.88–4.82 (m, 1H, $H^{4'}$), 4.72 (dd, J=12.0, 4.1 Hz, 1H, $H^{5'}$), 4.60 (dd, J=12.0, 5.4 Hz, 1H, $H^{5'}$), 4.23–4.16 (dq, J=7.1, 1.4 Hz, 2H, OCH_2CH$_3$), 1.46 (t, J=7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$): δ 166.2 (C(O)), 165.0 (2C, C(O)), 152.0 (C^5), 133.7 (C^{Ar}), 133.5 (C^{Ar}), 133.1 (C^{Ar}), 129.8 (C^{Ar}), 129.7 (C^{Ar}), 129.4 (C^{Ar}), 128.7 (2C, C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 113.8 (C^4), 86.7, 80.2, 74.5, 71.8, 69.3, 63.9, 14.4; MS (ESI): m/z [M +Na]$^+$ calcd for $C_{30}H_{27}N_3NaO_8$: 580.6, found: 580.5.

5.4. General procedure for sugar deprotection

To the protected compounds (**9a**–**h** and **10a**–**h**) was added a solution of 7 N NH_3/MeOH. The reaction was followed by TLC. After evaporation of the solvent under reduced pressure, the crude product was purified by liquid chromatography on silica gel (methanol/ethyl acetate, 1:9, v/v) to give the desired pure product.

5.4.1. 1′-[4-Phenyl-[1,2,3]triazol-1-yl]ribofuranose (12a)—Prepared from compound **9a** with the typical procedure described above to give **12a** (>98%) as an oil. IR: 3368, 1661, 1447, 1191, 1135, 799, 723 cm^{-1}; ^{1}H NMR (CD_3OD): δ 8.58 (s, 1H, H^5), 7.82 (d, J=8.3 Hz, 2H, H^{Ar}), 7.43 (t, J=7.5 Hz, 2H, H^{Ar}), 7.35 (t, J=7.4 Hz, 1H, H^{Ar}), 6.09 (d, J=4.0 Hz, 1H, $H^{1'}$), 4.57 (t, J=4.5 Hz, 1H, $H^{2'}$), 4.37 (t, J=5.1 Hz, 1H, $H^{3'}$), 4.17 (m, 1H, $H^{4'}$), 3.86 (dd, J=12.3, 3.2 Hz, 1H, $H^{5'}$), 3.73 (dd, J=12.3, 4.2 Hz, 1H, $H^{5'}$); ^{13}C NMR (CD_3OD): δ 149.0 (C^4), 131.6 (C^{Ar}), 130.0 (C^{Ar}), 129.5 (C^{Ar}), 126.7 (C^{Ar}), 120.9 (C^5), 94.5 ($C^{1'}$), 87.2 ($C^{4'}$), 77.1 ($C^{2'}$), 71.9 ($C^{3'}$), 62.8 ($C^{5'}$); HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{13}H_{16}N_3NO_4$: 278.1141, found: 278.1148. Known product CAS: 26295-54-5.

5.4.2. 1′-[4–4-Fluoro-3-methylphenyl-[1,2,3]triazol-1-yl]ribofuranose (12b)—Prepared from compound **9b** with the typical procedure described above to give **121b** (>98%) as white solid. Mp: 158 °C (MeOH); IR: 3344, 2929, 1493, 1233, 1082, 1043, 817 cm^{-1}; UV (MeOH) λ_{max}: 241 nm; $[\alpha]_D^{20}$ −76.4 (c 1.45, MeOH); ^{1}H NMR (CD_3OD): δ 8.53 (s, 1H, H^5), 7.71 (d, J=7.3 Hz, 1H, H^{Ar}), 7.67–7.62 (m, 1H, H^{Ar}), 7.10 (t, J=9.1 Hz, 1H, H^{Ar}), 6.08 (d, J=4.0 Hz, 1H, $H^{1'}$), 4.55 (t, J=4.5 Hz, 1H, $H^{2'}$), 4.35 (t, J=5.0 Hz, 1H, $H^{3'}$), 4.18–4.13 (m, 1H, $H^{4'}$), 3.85 (dd, J=12.2, 3.2 Hz, 1H, $H^{5'}$), 3.71 (dd, J=12.2, 4.2 Hz, 1H, $H^{5'}$), 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 148.3 (C^4), 130.0 (C^{Ar}), 126.1 (C^{Ar}), 120.7

(C^5), 116.6 (C^{Ar}), 116.4 (C^{Ar}), 94.6 ($C^{1'}$), 87.3 ($C^{4'}$), 77.2 ($C^{2'}$), 71.9 ($C^{3'}$), 62.9 ($C^{5'}$), 14.6 (CH_3); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}FN_3O_4$: 310.1203, found: 310.1218.

5.4.3. 1′-[4-Methylbenzen-[1,2,3]triazol-1-yl]ribofuranose (12c)—Prepared from compound **9c** with the typical procedure described above to give **12c** (>98%) as white solid. Mp: 100 °C (MeOH); IR: 3355, 2928, 2360, 1454, 1230, 1047, 725 cm^{-1}; UV (MeOH) λ_{max}: 212 nm; $[\alpha]_D^{20}$ −58.0 (c 0.59, MeOH); ^1H NMR (CD_3OD): δ 7.97 (s, 1H, H^5), 7.30–7.16 (m, 5H, H^{Ar}), 6.00 (d, J=4.1 Hz, 1H, $H^{1'}$), 4.48 (t, J=4.6 Hz, 1H, $H^{2'}$), 4.30 (t, J=5.0 Hz, 1H, $H^{3'}$), 4.14–4.09 (m, 1H, $H^{4'}$), 4.04 (s, 2H, CH_2Ph), 3.79 (dd, J=12.2, 3.2 Hz, 1H, $H^{5'}$), 3.67 (dd, J=12.2, 4.3 Hz, 1H, $H^{5'}$); ^{13}C NMR (CD_3OD): δ 148.6 (C^4), 140.3 (C^{Ar}), 129.6 (2C, C^{Ar}), 127.5 (C^{Ar}), 122.6 (C^5), 94.8 ($C^{1'}$), 87.1 ($C^{4'}$), 77.0 ($C^{2'}$), 71.9 ($C^{3'}$), 62.9 ($C^{5'}$), 32.6 (CH_2Ph); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_3O_4$: 292.1297, found: 292.1283.

5.4.4. 1′-[4-Methylcyclopentyl-[1,2,3]triazol-1-yl]ribofuranose (12d)—Prepared from compound **9d** with the typical procedure described above to give **12d** (>98%) as a white solid. Mp: 87 °C (MeOH); IR: 3349, 1298, 2868, 1452, 1228, 1048 cm^{-1}; UV (MeOH) λ_{max}: 223 nm; $[\alpha]_D^{20}$ −51.5 (c 1.37, MeOH); ^1H NMR (CD_3OD): δ 8.00 (s, 1H, H^5), 6.00 (d, J=4.0 Hz, 1H, $H^{1'}$), 4.47 (t, J=4.5 Hz, 1H, $H^{2'}$), 4.30 (t, J=5.1 Hz, 1H, $H^{3'}$), 4.15–4.09 (m, 1H, $H^{4'}$), 3.81 (dd, J=12.2, 3.2 Hz, 1H, $H^{5'}$), 3.69 (dd, J=12.2, 4.3 Hz, 1H, $H^{5'}$), 2.70 (d, J=7.4 Hz, 2H, CH_2–$CHCH_2CH_2$), 2.24–2.12 (m, 1H, CH_2–$CHCH_2CH_2$), 1.82–1.72 (m, 2H, CH_2–$CHCH_2CH_2$), 1.71–1.62 (m, 2H, CH_2–$CHCH_2CH_2$), 1.61–1.51 (m, 2H, CH_2–$CHCH_2CH_2$), 1.31–1.18 (m, 2H, CH_2–$CHCH_2CH_2$); ^{13}C NMR (CD_3OD): δ 148.9 (C^4), 122.2 (C^5), 94.3 ($C^{1'}$), 87.1 ($C^{4'}$), 77.1 ($C^{2'}$), 71.9 ($C^{3'}$), 62.9 ($C^{5'}$), 41.3 (CH_2–$CHCH_2CH_2$), 33.4 (CH_2–$CHCH_2CH_2$), 32.4 (CH_2–$CHCH_2CH_2$), 26.1 (CH_2–$CHCH_2CH_2$); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{22}N_3O_4$: 284.1610, found: 284.1608.

5.4.5. 1′-[4-Butyl-[1,2,3]triazol-1-yl]ribofuranose (12e)—Prepared from compound **9e** with the typical procedure described above to give **12e** (>98%) as a white solid. Mp: 105 °C (MeOH); IR: 3316, 2930, 2870, 1456, 1043, 826 cm^{-1}; UV (MeOH) λ_{max}: 223 nm; $[\alpha]_D^{20}$ −50.7 (c 0.56, MeOH); ^1H NMR (CD_3OD): δ 8.00 (s, 1H, H^5), 6.00 (d, J=4.1 Hz, 1H, $H^{1'}$), 4.48 (t, J=4.5 Hz, 1H, $H^{2'}$), 4.32 (t, J=5.0 Hz, 1H, $H^{3'}$), 4.15–4.11 (m, 1H, $H^{4'}$), 3.82 (dd, J=12.2, 3.2 Hz, 1H, $H^{5'}$), 3.70 (dd, J=12.2, 4.3 Hz, 1H, $H^{5'}$), 2.71 (t, J=7.6 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.70–1.61 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.45–1.34 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.95 (t, J=7.4 Hz, 3H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (CD_3OD): δ 149.4 (C^4), 121.8 (C^5), 94.3 ($C^{1'}$), 87.1 ($C^{4'}$), 77.0 ($C^{2'}$), 71.9 ($C^{3'}$), 62.9 ($C^{5'}$), 32.7 ($CH_2CH_2CH_2CH_3$), 26.0 ($CH_2CH_2CH_2CH_3$), 23.3 ($CH_2CH_2CH_2CH_3$), 14.2 ($CH_2CH_2CH_2CH_3$); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{19}N_3NaO_4$: 280.1273, found: 280.1269.

5.4.6. 1′-[4-(3-Chloropropyl)-[1,2,3]triazol-1-yl]ribofuranose (12f)—Prepared from compound **9f** with the typical procedure described above to give **12f** (>98%) as colorless crystals. Mp: 91 °C (MeOH); IR: 3316, 2928, 2361, 1546, 1229, 1048 cm^{-1}; UV (MeOH) λ_{max}: 223 nm; $[\alpha]_D^{20}$ −46.7 (c 0.89, MeOH); ^1H NMR (CD_3OD): δ 8.05 (s, 1H, H^5),

6.01 (d, J=4.1 Hz, 1H, $H^{1'}$), 4.49 (t, J=4.5 Hz, 1H, $H^{2'}$), 4.31 (t, J=5.0 Hz, 1H, $H^{3'}$), 4.15–4.11 (m, 1H, $H^{4'}$), 3.81 (dd, J=12.2, 3.2 Hz, 1H, $H^{5'}$), 3.69 (dd, J=12.2, 4.3 Hz, 1H, $H^{5'}$), 3.61 (t, J=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.87 (t, J=7.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.17–2.08 (m, 2H, $CH_2CH_2CH_2Cl$); ^{13}C NMR (CD_3OD): δ 147.9 (C^4), 122.2 (C^5), 94.3 ($C^{1'}$), 87.1 ($C^{4'}$), 77.0 ($C^{2'}$), 71.9 ($C^{3'}$), 62.9 ($C^{5'}$), 44.8 ($CH_2CH_2CH_2Cl$), 33.3 ($CH_2CH_2CH_2Cl$), 23.6 ($CH_2CH_2CH_2Cl$); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{17}ClN_3O_4$: 278.0908, found: 278.0902.

5.4.7. 1′-[4-tert-Butyl-[1,2,3]triazol-1-yl]ribofuranose (12g)—Prepared from compound **9g** with the typical procedure described above to give **12g** (>98%) as a white solid. Mp: 114 °C (MeOH); IR: 3355, 2964, 2361, 1461, 1365, 1232, 1104, 1047 cm^{-1}; UV (MeOH) λ_{max}: 221 nm; $[\alpha]_D^{20}$ −55.7 (c 0.88, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 8.01 (s, 1H, H^5), 6.00 (d, J=4.2 Hz, 1H, $H^{1'}$), 4.49 (t, J=4.6 Hz, 1H, $H^{2'}$), 4.30 (t, J=5.0 Hz, 1H, H3′), 4.14–4.09 (m, 1H, $H^{4'}$), 3.82 (dd, J=12.2, 3.2 1H, Hz, $H^{5'}$), 3.69 (dd, J=12.2, 4.3 Hz, 1H, $H^{5'}$), 1.34 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, CD_3OD): δ 158.7 (C^4), 119.9 (C^5), 94.2 ($C^{1'}$), 87.1 ($C^{4'}$), 77.0 ($C^{2'}$), 71.9 ($C^{3'}$), 62.9 ($C^{5'}$), 31.7 ($C(CH_3)_3$), 30.7 ($C(CH_3)_3$); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{20}N_3O_4$: 258.1454, found: 258.1457.

5.4.8. 1′-[4-O-Ethoxy-[1,2,3]triazol-1-yl]ribofuranose (12h)—Prepared from compound **9h** with the typical procedure described above to give **12h** (>98%) as colorless crystals. Mp: 127 °C (MeOH); IR: 3348, 2927, 2361, 1667, 1571, 1381, 1340, 1045 cm^{-1}; UV (MeOH) λ_{max}: 233 nm; $[\alpha]_D^{20}$ −63.1 (c 1.12, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (s, 1H, H^5), 5.91 (d, J=4.1 Hz, 1H, $H^{1'}$), 4.46 (t, J=4.6 Hz, 1H, $H^{2'}$), 4.29 (t, J=5.0 Hz, 1H, H3′), 4.17 (q, J=7.1 Hz, 2H, OCH_2CH_3), 4.13–4.09 (m, 1H, $H^{4'}$), 3.81 (dd, J=12.2, 3.2 Hz, 1H, $H^{5'}$), 3.69 (dd, J=12.2, 4.2 Hz, 1H, $H^{5'}$), 1.38 (t, 3H, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (101 MHz, CD_3OD): δ 162.4 (C^4), 106.4 (C^5), 95.0 ($C^{1'}$), 87.2 ($C^{4'}$), 76.9 ($C^{2'}$), 71.9 ($C^{3'}$), 67.9 (OCH_2CH_3), 62.8 ($C^{5'}$), 15.1 (OCH_2CH_3); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_9H_{15}N_3NaO_5$: 268.0909, found: 268.0915.

5.4.9. 1′-[5-Phenyl-[1,2,3]triazol-1-yl]ribofuranose (13a)—Prepared from compound **10a** with the typical procedure described above to give **13a** (>98%) as a white solid. Mp: 151 °C (MeOH); IR: 3332, 2930, 1486, 1454, 1243, 1058, 765, 699 cm^{-1}; UV (MeOH) λ_{max}: 242 nm; $[\alpha]_D^{20}$ −116.5 (c 0.83, MeOH); ^{1}H NMR (CD_3OD): δ 7.84 (s, 1H, H^4), 7.64–7.60 (m, 2H, H^{Ar}), 7.58–7.52 (m, 3H, H^{Ar}), 5.81 (d, J=3.7 Hz, 1H, $H^{1'}$), 4.91 (dd, J=5.1, 3.7 Hz, 1H, $H^{2'}$), 4.51 (t, J=5.1 Hz, 1H, $H^{3'}$), 4.16–4.12 (m, 1H, $H^{4'}$), 3.80 (dd, J=12.1, 3.9 Hz, 1H, $H^{5'}$), 3.66 (dd, J=12.1, 5.8 Hz, 1H, $H^{5'}$); ^{13}C NMR (CD_3OD): δ 141.2 (C^5), 133.4 (C^{Ar}), 131.0 (C^{Ar}), 130.3 (2C, C^{Ar}), 127.4 (C^4), 91.4 ($C^{1'}$), 87.3 ($C^{4'}$), 75.9 ($C^{2'}$), 72.6 ($C^{3'}$), 63.7 ($C^{5'}$); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_3O_4$: 278.1141, found: 278.1142.

5.4.10. 1′-[5–4-Fluoro-3-methylphenyl-[1,2,3]triazol-1-yl]ribofuranose (13b)—Prepared from compound **10b** with the typical procedure described above to give **13b** (>98%) as yellow crystals. Mp: 69 °C (MeOH); IR: 3332, 2929, 1493, 1243, 1124, 1059, 824 cm^{-1}; UV (MeOH) λ_{max}: 243 nm; $[\alpha]_D^{20}$ −91.3 (c 0.67, MeOH); ^{1}H NMR (CD_3OD): δ

7.86 (s, 1H, H^4), 7.57–7.49 (m, 2H, H^{Ar}), 7.30–7.23 (t, *J*=9.0 Hz, 1H, H^{Ar}), 5.83 (d, *J*=3.7 Hz, 1H, $H^{1'}$), 4.95 (dd, *J*=4.9, 3.8 Hz, 1H, $H^{2'}$), 4.55 (t, *J*=5.2 Hz, 1H, $H^{3'}$), 4.22–4.17 (m, 1H, H4′), 3.84 (dd, *J*=12.1, 3.8 Hz, 1H, $H^{5'}$), 3.70 (dd, *J*=12.1, 5.9 Hz, 1H, $H^{5'}$), 2.40 (d, *J*=1.8 Hz, 3H, C*H*$_3$); ^{13}C NMR (CD_3OD): δ 164.8 (C^{Ar}), 162.4 (C^{Ar}), 140.4 (C^5), 133.7 (2C, C^{Ar}), 133.5 (C^{Ar}), 129.9 (C^{Ar}), 129.8 (C^{Ar}), 127.4 (C^4), 127.2 (C^4), 123.4 (2C, C^{Ar}), 116.9 (C^{Ar}), 116.7 (C^{Ar}), 91.3 ($C^{1'}$), 87.4 ($C^{4'}$), 75.9 ($C^{2'}$), 72.6 ($C^{3'}$), 63.7 ($C^{5'}$), 14.4 (2C, *C*H$_3$); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{14}H_{17}FN_3O_4$: 310.1203, found: 310.1216.

5.4.11. 1′-[5-Benzyl-[1,2,3]triazol-1-yl]ribofuranose (13c)—Prepared from compound **10c** with the typical procedure described above to give **13c** (>98%) as an yellow oil. IR: 3341, 2928, 2361, 1455, 1242, 1058, 720. UV (MeOH) λ_{max}: 214 nm; $[\alpha]_D^{20}$ −50.6 (*c* 0.51, MeOH); ^{1}H NMR (CD_3OD): δ 7.38 (s, 1H, H^4), 7.36–7.31 (m, 2H, H^{Ar}), 7.29–7.21 (m, 3H, H^{Ar}), 5.88 (d, *J*=3.6 Hz, 1H, $H^{1'}$), 4.82 (dd, *J*=5.0, 3.6 Hz, 1H, $H^{2'}$), 4.42 (t, *J*=5.2 Hz, 1H, $H^{3'}$), 4.18 (d, *J*=2.7 Hz, 2H, C*H*$_2$Ph), 4.13–4.08 (m, 1H, $H^{4'}$), 3.74 (dd, *J*=12.1, 3.7 Hz, 1H, $H^{5'}$), 3.58 (dd, *J*=12.1, 5.6 Hz, 1H, $H^{5'}$); ^{13}C NMR (CD_3OD): δ 139.8 (C^5), 137.8 (C^{Ar}), 134.1 (C^4), 129.9 (C^{Ar}), 129.7 (C^{Ar}), 128.2 (C^{Ar}), 91.5 ($C^{1'}$), 87.2 ($C^{4'}$), 75.7 ($C^{2'}$), 72.3 ($C^{3'}$), 63.6 ($C^{5'}$), 29.6 (*C*H$_2$Ph); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{14}H_{18}N_3O_4$: 292.1297, found: 292.1298.

5.4.12. 1′-[5-Methylcyclopentyl-[1,2,3]triazol-1-yl]ribofuranose (13d)—Prepared from compound **10d** with the typical procedure described above to give **13d** (>98%) as an yellow oil. IR: 3315, 2946, 2867, 1449, 1241, 1050, 830 cm^{-1}; UV (MeOH) λ_{max}: 221 nm; $[\alpha]_D^{20}$ −62.1 (*c* 1.04, MeOH); ^{1}H NMR (CD_3OD): δ 7.55 (s, 1H, H^4), 5.89 (d, *J*=4.0 Hz, 1H, $H^{1'}$), 4.83 (dd, *J*=5.0, 4.0 Hz, 1H, $H^{2'}$), 4.43 (t, *J*=5.0 Hz, 1H, $H^{3'}$), 4.14–4.10 (m, 1H, $H^{4'}$), 3.74 (dd, *J*=12.0, 3.9 Hz, 1H, $H^{5'}$), 3.60 (dd, *J*=12.0, 5.6 Hz, 1H, $H^{5'}$), 2.79 (d, *J*=7.5 Hz, 2H, CH_2–$CHCH_2CH_2$), 2.29–2.16 (m, 1H, CH_2–C*H*CH_2CH_2), 1.88–1.77 (m, 2H, CH_2–$CHCH_2CH_2$), 1.75–1.64 (m, 2H, CH_2–$CHCH_2CH_2$), 1.64–1.53 (m, 2H, CH_2–$CHCH_2CH_2$), 1.31–1.19 (m, 2H, CH_2–$CHCH_2CH_2$); ^{13}C NMR (CD_3OD): δ 140.4 (C^5), 133.3 (C^4), 91.1 ($C^{1'}$), 87.4 ($C^{4'}$), 75.9 ($C^{2'}$), 72.5 ($C^{3'}$), 63.6 ($C^{5'}$), 40.3 (CH_2–*C*HCH_2CH_2), 33.5 (CH_2–$CHCH_2CH_2$), 29.7 (CH_2–$CHCH_2CH_2$), 26.0 (CH_2–$CHCH_2CH_2$); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{13}H_{22}N_3O_4$: 284.1610, found: 284.1600.

5.4.13. 1′-[5-Butyl-[1,2,3]triazol-1-yl]ribofuranose (13e)—Prepared from compound **10e** with the typical procedure described above to give **13e** (>98%) as an yellow oil. IR: 3331, 2932, 2871, 1428, 1243, 1056, 832 cm^{-1}; UV (MeOH) λ_{max}: 221 nm; $[\alpha]_D^{20}$ −64.4 (*c* 0.70, MeOH); ^{1}H NMR (CD_3OD): δ 7.53 (s, 1H, H^4), 5.88 (d, *J*=3.9 Hz, 1H, $H^{1'}$), 4.84 (dd, *J*=5.0, 3.9 Hz, 1H, $H^{2'}$), 4.33 (t, *J*=5.0 Hz, 1H, $H^{3'}$), 4.14–4.11 (m, 1H, $H^{4'}$), 3.74 (dd, *J*=12.1, 3.8 Hz, 1H, $H^{5'}$), 3.59 (dd, *J*=12.1, 5.6 Hz, 1H, $H^{5'}$), 2.79 (t, *J*=7.8 Hz, 2H, C*H*$_2$$CH_2CH_2CH_3$), 1.73–1.64 (m, 2H, CH_2C*H*$_2$$CH_2CH_3$), 1.48–1.39 (m, 2H, CH_2CH_2C*H*$_2$$CH_3$), 0.98 (t, *J*=7.4 Hz, 3H, $CH_2CH_2CH_2$C*H*$_3$); ^{13}C NMR (CD_3OD): δ 140.9 (C^5), 132.9 (C^4), 91.1 ($C^{1'}$), 87.3 ($C^{4'}$), 75.8 ($C^{2'}$), 72.5 ($C^{3'}$), 63.7 ($C^{5'}$), 31.7 (CH_2*C*H$_2$$CH_2CH_3$), 23.3 (2C, *C*H$_2$$CH_2CH_2CH_3$ and CH_2CH_2*C*H$_2$$CH_3$), 14.0 ($CH_2CH_2CH_2$*C*H$_3$); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{11}H_{20}N_3O_4$: 258.1454, found: 2258.1448.

5.4.14. 1′-[5-(3-Chloropropyl)-[1,2,3]triazol-1-yl]ribofuranose (13f)—Prepared from compound **10f** with the typical procedure described above to give **13f** (>98%) as an yellow oil. IR: 3315, 2927, 2360, 1717, 1446, 1276, 1242, 1058, 833 cm^{-1}; UV (MeOH) λ_{max}: 220 nm; $[\alpha]_D^{20}$ −50.5 (*c* 0.39, MeOH); ^1H NMR (CD_3OD): δ 7.59 (s, 1H, H^4), 5.91 (d, *J*=3.9 Hz, 1H, $H^{1'}$), 4.88 (dd, *J*=5.0, 3.9 Hz, 1H, $H^{2'}$), 4.43 (t, *J*=5.0 Hz, 1H, $H^{3'}$), 4.15–4.10 (m, 1H, $H^{4'}$), 3.73 (dd, *J*=12.1, 3.8 Hz, 1H, $H^{5'}$), 3.67–3.60 (m, 2H, $CH_2CH_2CH_2Cl$), 3.58 (dd, *J*=12.1, 5.6 Hz, 1H, $H^{5'}$), 3.01–2.95 (t, *J*=7.6 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.20–2.11 (m, 2H, $CH_2CH_2CH_2Cl$); ^{13}C NMR (CD_3OD): δ 139.5 (C^5), 133.2 (C^4), 91.2 ($C^{1'}$), 87.3 ($C^{4'}$), 75.7 ($C^{2'}$), 72.4 ($C^{3'}$), 63.6 ($C^{5'}$), 44.6 ($CH_2CH_2CH_2Cl$), 32.4 ($CH_2CH_2CH_2Cl$), 21.0 ($CH_2CH_2CH_2Cl$); HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{17}ClN_3O_4$: 278.0908, found: 278.0892.

5.4.15. 1′-[5-tert-Butyl-[1,2,3]triazol-1-yl]ribofuranose (13g)—Prepared from compound **10g** with the typical procedure described above to give **13g** (>98%) as an yellow oil. IR: 3346, 2969, 2360, 1371, 1057 cm^{-1}; UV (MeOH) λ_{max}: 221 nm; $[\alpha]_D^{20}$ −70.9 (*c* 1.21, MeOH); ^1H NMR (CD_3OD): δ 7.49 (s, 1H, H^4), 6.20 (d, *J*=3.8 Hz, 1H, $H^{1'}$), 4.85 (dd, *J*=5.0, 3.8 Hz, 1H, $H^{2'}$), 4.47 (t, *J*=5.1 Hz, 1H, $H^{3'}$), 4.16–4.08 (m, 1H, $H^{4'}$), 3.76 (dd, *J*=12.0, 4.0 Hz, 1H, $H^{5'}$), 3.64 (dd, *J*=12.0, 5.7 Hz, 1H, $H^{5'}$), 1.44 (d, *J*=6.2 Hz, 9H, $C(CH_3)3$); ^{13}C NMR (CD_3OD): δ 148.7 (C^5), 131.5 (C^4), 92.4 ($C^{1'}$), 87.4 ($C^{4'}$), 76.5 ($C^{2'}$), 72.6 ($C^{3'}$), 63.8 ($C^{5'}$), 31.4 ($C(CH_3)_3$), 30.5 ($C(CH_3)_3$); HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{11}H_{20}N_3O_4$: 258.1454, found: 258.1451.

5.4.16. 1′-[5-O-Ethoxy-[1,2,3]triazol-1-yl]ribofuranose (13h)—Prepared from compound **10h** with the typical procedure described above to give **13h** (>98%) as a white solid (MeOH). Mp: 149 °C; IR: 3357, 2936, 1579, 1458, 1325, 1056, 982 cm^{-1}; UV (MeOH) λ_{max}: 231 nm; $[\alpha]_D^{20}$ −56.2 (*c* 0.55, MeOH); ^1H NMR (CD_3OD): δ 7.24 (s, 1H, H^4), 5.83 (d, *J*=3.9 Hz, 1H, $H^{1'}$), 4.68 (dd, *J*=5.0, 3.9 Hz, 1H, $H^{2'}$), 4.39 (t, *J*=5.0 Hz, 1H, $H^{3'}$), 4.25 (q, *J*=7.5 Hz, 2H, OCH_2CH_3), 4.10–4.05 (m, 1H, $H^{4'}$), 3.75 (dd, *J*=12.0, 3.9 Hz, 1H, $H^{5'}$), 3.62 (dd, *J*=12.0, 5.8 Hz, 1H, $H^{5'}$), 1.45 (t, *J*=7.5 Hz, 3H, OCH_2CH_3); ^{13}C NMR (CD_3OD): δ 153.9 (C^5), 114.8 (C^4), 90.9 ($C^{1'}$), 86.9 ($C^{4'}$), 75.2 ($C^{2'}$), 72.3 ($C^{3'}$), 70.6 (OCH_2CH_3), 63.7 ($C^{5'}$), 14.8 (OCH_2CH_3); HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_9H_{15}N_3NaO_5$: 268.0909, found: 268.0909.

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References and notes

1. (a)Simons C Nucleoside Mimetics: their Chemistry and Biological Properties; Gordon and Breach Science: Amsterdam, 2001; Vol. 3, p 192;(b)Agrofoglio LA; Challand SR Acyclic, Carbocyclic and l-Nucleosides; Kluwer Academic: Dordrecht, 1998;(c)Agrofoglio LA; Amblard F; Broggi J; Garnier E In Modern Approaches to the Synthesis of O- and N-Heterocyles; Kaufman TS, Larghi EL, Eds.; Research Signpost: Trivandrum, India, 2007; Vol. 2, pp 195–246;(e)De Clercq E. Biochem. Pharmacol 2007, 73, 911. [PubMed: 17045247]

2. (a)Lau JY; Tam RC; Liang TJ; Hong Z Hepatology 2002, 35, 1002; [PubMed: 11981750] (b)Borowski P; Lang M; Niebuhr A; Haag A; Schmitz H; Schulze zur Wiesch J; Choe J; Siwecka MA; Kulikowski T Acta Biochim. Pol 2001, 48, 739; [PubMed: 11833782] (c)Contreras AM; Hiasa Y; He W; Terella A; Schmidt EV; Chung RT J. Virol 2002, 76, 8505; [PubMed: 12163570] (d)Crotty S; Cameron CE; Andino R Proc. Natl. Acad. Sci. U.S.A 2001, 98, 6895. [PubMed: 11371613]
3. (a)Hollecker L; Choo H; Chong Y; Chu CK; Lostia S; McBrayer TR; Stuyver LJ; Mason JC; Du J; Rachakonda S; Shi J; Schinazi RF; Watanabe KA Antiviral Chem. Chemother 2004, 15, 43; (b)Stuyver LJ; Whitaker T; McBrayer TR; Hernandez-Santiago BI; Liosta S; Tharnish PM; Ramesh M; Chu CK; Jordan R; Shi J; Rachakonda S; Watanabe KA; Otto MJ; Schinazi RF Antimicrob. Agents Chemother 2003, 47, 244. [PubMed: 12499198]
4. (a)Carroll SS; Tomassini JE; Bosserman M; Getty K; Stahlhut MW; Eldrup AB; Bhat B; Hall D; Simcoe AL; LaFemina R; Rutkowski CA; Wolanski B; Yang Z; Migliaccio G; De Francesco R; Kuo LC; MacCoss M; Olsen DB J. Biol. Chem 2003, 278, 11979; [PubMed: 12554735] (b)Eldrup AB; Allerson CR; Bennett CF; Bera S; Bhat B; Bhat N; Bosserman MR; Brooks J; Burlein C; Carroll SS; Cook PD; Getty KL; MacCoss M; McMasters DR; Olsen DB; Prakash TP; Prhavc M; Song Q; Tomassini JE; Xia JJ Med. Chem 2004, 47, 2283.
5. Smith KL; Lai VCH; Prigaro BJ; Ding Y; Gunic E; Girardet J-L; Zhong W; Hong Z; Lang S; An H Bioorg. Med. Chem. Lett 2004, 14, 3517. [PubMed: 15177464]
6. Wang P; Hollecker L; Pankiewicz KW; Patterson SE; Whitaker T; McBrayer TR; Tharnish PM; Sidwell RW; Stuyver LJ; Otto MJ; Schinazi RF; Watanabe KA J. Med. Chem 2004, 47, 6100. [PubMed: 15537363]
7. (a)El Akri K; Bougrin K; Balzarini J; Faraj A; Benhida R Bioorg. Med. Chem. Lett 2007, 17, 6656; [PubMed: 17931862] (b)Guezguez R; Bougrin K; El Akri K; Benhida R Tetrahedron Lett. 2006, 47, 4807.
8. Saito Y; Escuret V; Durantel D; Zoulim F; Schinazi RF; Agrofoglio LA Bioorg. Med. Chem 2003, 11, 3633. [PubMed: 12901908]
9. (a)Huisgen R Angew. Chem., Int. Ed. Engl 1963, 2, 565;(b)Huisgen R In 1,3-Di-polar Cycloaddition Chemistry; Padwa A, Ed.; Wiley: New York, NY, 1984; Vol. 1.
10. (a)Mock WL; Irra TA; Wepsiec JP; Manimaran TL J. Org. Chem 1983, 48, 3619;(b)Lewis WG; Green LG; Grynszpan F; Radic Z; Carlier PR; Taylor P; Finn MG; Sharpless KB Angew. Chem., Int. Ed 2002, 41, 1053.
11. (a)Gilchrist TL; Gymer GE Adv. Heterocycl. Chem 1974, 16, 33;(b)Finley T; Montgomery JA The Chemistry of Heterocyclic Compounds. Triazoles 1,2,3; Wiley: New York, NY, 1981; Vol. 39; (c)Katritzky AR; Zhang Y; Singh SK Heterocycles 2003, 60, 1225;(d)Rostovtsev VV; Green LG; Fokin VV; Sharpless KB Angew. Chem., Int. Ed 2002, 41, 2596;(e)Wu P; Feldman AK; Nugent AK; Hawker CJ; Scheel A; Voit B; Pyun J; Frechet JM; Sharpless KB; Fokin VV Angew. Chem., Int. Ed 2004, 43, 3928;(f)Broggi J; Díez-González S; Petersen JL; Berteina-Raboin S; Nolan SP; Agrofoglio LA Synthesis 2008, 1, 141.
12. (a)Stimac A; Kobe J Carbohydr. Res 2000, 324, 149; [PubMed: 10724529] (b)Camarasa MJ; Alonso R; De Las Heras FG Carbohydr. Res 1980, 83, 152.
13. (a)Zhang L; Chen X; Xue P; Sun HHY; Williams ID; Sharpless KB; Fokin VV; Jia GJ Am. Chem. Soc 2005, 127, 15998;(b)Majireck MM; Weinreb SM J. Org. Chem 2006, 71, 8680; [PubMed: 17064059] (c)Oppilliart S; Mousseau G; Zhang L; Jia G; Thuéry P; Rousseau B; Cintrat J-C Tetrahedron 2007, 63, 8094;(d)Tam A; Arnold U; Soellner MB; Raines RT J. Am. Chem. Soc 2007, 129, 12670; [PubMed: 17914828] (e)Imperio D; Pirali T; Galli U; Pagliai F; Cafici L; Canonico PL; Sorba G; Genazzani AA; Tron GC Bioorg. Med. Chem 2007, 15, 6748. [PubMed: 17765552]
14. Krasinski A; Fokin VV; Sharpless KB Org. Lett 2004, 6, 1237. [PubMed: 15070306]
15. Coats SJ; Link JS; Gauthier D; Hlasta DJ Org. Lett 2005, 7, 1469. [PubMed: 15816729]
16. Fokin V; Jia G; Sharpless KB Patent WO 2007041451; CAN 146:401986.
17. During the course of our investigations, Kokin et al. reported a RuAAC of aryl azides under microwave irradiation with [Cp*RuCl]4 but under drastic anhydrous conditions and in DMF Rasmussen LK; Boren BC; Fokin VV Org. Lett 2007, 9, 5337. [PubMed: 18052070]

18. For reviews on microwave-assisted reactions see:(a)Caddick STetrahedron 1995, 51, 10403; (b)Perreux L; Loupy A Tetrahedron 2001, 57, 9199;(c)Loupy A Microwaves in Organic Synthesis; Wiley-VCH: Weinheim, 2002;(d)Kappe CO Angew. Chem., Int. Ed 2004, 43, 6250.

19. Schinazi RF; Peters J; Williams CC; Chance D; Nahmias AJ Antimicrob. Agents Chemother 1982, 22, 499. [PubMed: 6182836]

20. Schinazi RF; Chou TC; Scott RJ; Yao X; Nahmias AJ Antimicrob. Agents Chemother 1986, 30, 491. [PubMed: 3777913]

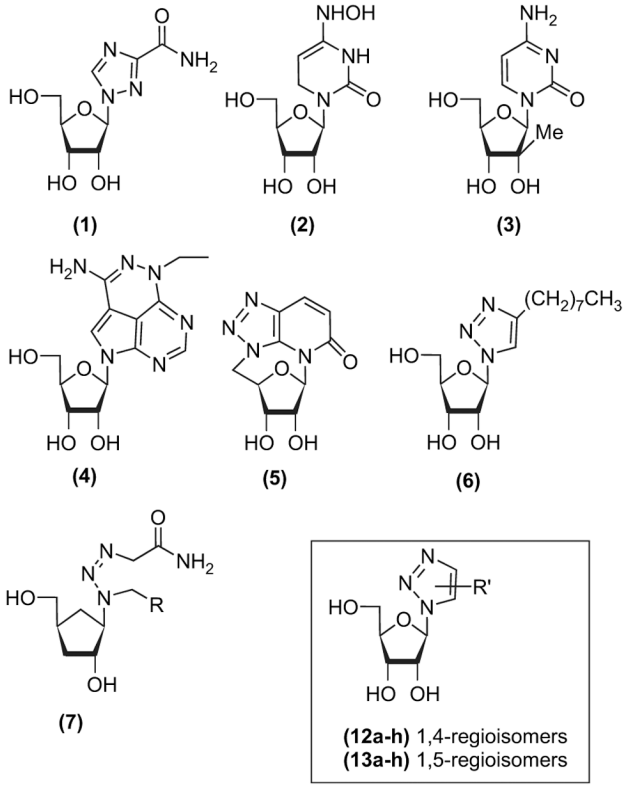
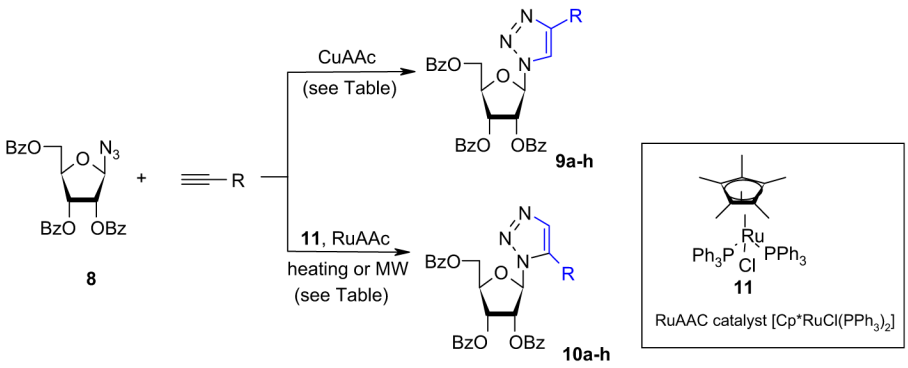
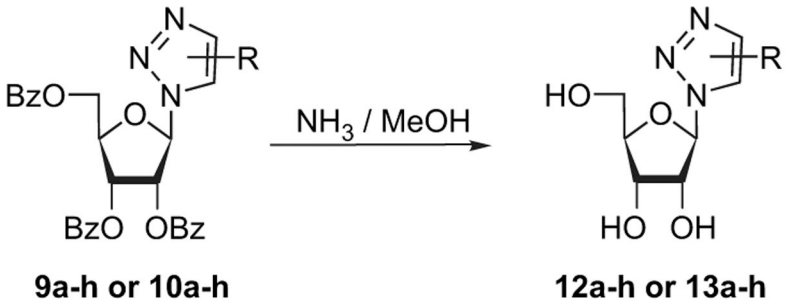


Figure 1.
Some anti-HCV triazolo-nucleosides and target compounds (**12** and **13**).

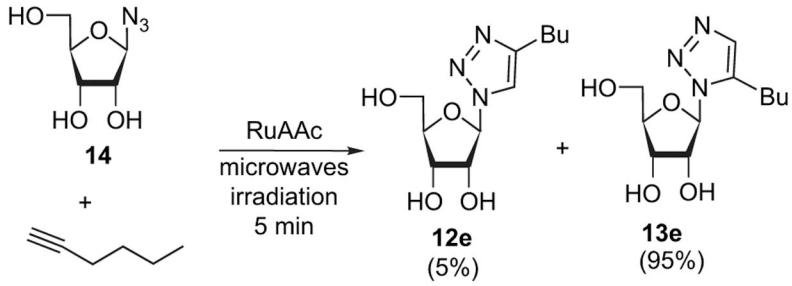


Scheme 1.



9a-h or 10a-h **12a-h or 13a-h**

Scheme 2.
Cleavage of benzoyl protective group.

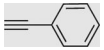
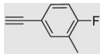
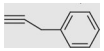
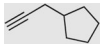
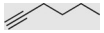
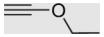


Scheme 3.

RuAAC on deprotected azido-ribose under thermal heating.

Table 1

Survey of CuAAC and RuAAC reaction[a,b]

Entry	Alkyne	R	1,4-Regioisomers (CuAAC) (%)		1,5-Regioisomers (RuAAC)[b]		Ratio 1,4/1,5
			Δ		Δ	MW yield % (Conv. %)	
1		**a**	86		79	88 (93)	4:96
2		**b**	88		83	92 (100)	3:93
3		**c**	93		71	92 (100)	4:96
4		**d**	87		79	87 (100)	5:95
5		**e**	89		82	91 (96)	4:96
6		**f**	83		68	87 (100)	5:95
7		**g**	92		77	95 (100)	5:95
8		**h**	63		54	93 (100)	3:97

[a]Conditions: azide **1** (1 equiv), alkyne (1.1 equiv), Cu powder (4 equiv), $CuSO_4 \cdot 5H_2O$ (0.2 equiv), $^tBuOH/H_2O$.

[b]Conditions: azide **1** (1 equiv, 0.1 M in THF), alkyne (1.5 equiv), $Cp^*RuCl(PPh_3)_2$ (0.05 equiv), THF, thermal heating (Δ): 6 h, T=50 °C or microwave conditions (MW): 5 min, T=100 °C.

Table 2

Optimization of RuAAC under microwave conditions for **11e**

Catalyst loading (mol %)	Irradiation time		
	3 min	**5 min**	**10 min**
1	—	—	36%
2	—	—	57%
3.5	—	84%	**100**%
5	94%	**100**%	—