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Synthesis of novel *NH*-1,2,3-triazolo-nucleosides by the Banert cascade reaction

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ABSTRACT

Nucleoside analogs with the 4,5-dimethyl-*NH*-1,2,3-triazolo-linker between thymine and a carbohydrate, or a hydroxyalkoxyl, or phosphonomethoxyl residue, were obtained by the Bannert cascade reaction from 1-(4-azidobut-2-yn-1-yl)thymine and the carbohydrate or acyclic alcohol. The reaction conditions were developed on the basis of a thermal analysis of the starting azide and by the optimization of the reaction components ratio. The best results were obtained when the reaction cascade employed the azide/nucleophile molar ratio of 1/14, at 55 °C, with no solvent addition. The reaction showed good discrimination between the pentofuranose hydroxyls, yielding triazoles linked at the carbohydrate 5′-oxygen atom.

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1. Introduction

The identification of tenofovir and cidofovir (Fig. 1a) as antiviral agents active against a broad spectrum of DNA and RNA viruses[1] has stimulated research on nucleoside analogs featuring a high degree of structural flexibility.[2] Modifications of the sugar–nucleobase linkage resulted in the development of a unique class of nucleoside analogs termed 'shape-modified nucleosides' or 'fleximers' (Fig. 1b and c). The first group of fleximers (Fig. 1b) contains an aglycone derived from 5-(pyrimidin-6-yl)-1*H*-imidazole (compounds **1**[3]), 4-(pyrimidin-5-yl)-1*H*-imidazole (compounds **2**[4]) or 4-(pyrimidin-5-yl)-1*H*-1,2,3-triazole (compounds **3**[5]). Formally, structures of the compounds **1** and **2** were derived from purine nucleosides (adenosine, guanosine, inosine or isoguanosine) by splitting of their purine systems into imidazole and pyrimidine components and then reconnecting of the resulting heterocycles with the C(5)–C(6′) bond (compounds **1**) or with the C(4)–C(5′) bond (compounds **2**). Derivatives **3** are analogs of nucleosides **2**, resulting from replacement of the 1*H*-imidazole ring with the 1*H*-1,2,3-triazole one. Among analogs **1**–**3**, the guanosine-derived analog **1a** was identified as inhibitor of *S*-adenosyl-L-homocysteine hydrolase.[6] The activity of nucleoside **1a** was suggested to be a consequence of its high conformational adaptability to the target enzyme active site, resulting from a rotation of the pyrimidine ring about the C(5)–C(6′) bond.[6,7] The second series of fleximers comprises compounds **4**–**6** (Fig. 1c). The parent compounds of the series, nucleosides **4**, were formally derived from insertion of the 4-methyl-1*H*-1,2,3-triazole linker between a sugar and a nucleobase.[8] Their analogs **5** originated from translocation of the nucleobase-bearing 1,2,3-triazole residue from the C-1′ to the *exo*-cyclic carbon of the sugar moiety.[9] In contrast to analogs **5**, compound **6** possess the 4-methyl-2*H*-1,2,3-triazole linker between the nucleobase and the sugar residue.[9a] This compound was recently synthesized in our laboratory. To the best of our knowledge, it is the only example of a 1,2,3-triazole fleximer with a modified substitution pattern of the 1,2,3-triazole core. Among compounds **4**–**6**, some of fleximers **4** and **5** were reported to show antitumor[8a] or anti-HBV[9b,c] activity.

Herein, we describe the synthesis of 4,5-disubstituted-*NH*-1,2,3-triazoles **7**, **8** and their *O*- or *N*-substituted-derivatives, *NH*-1,2,3-triazolo-nucleosides **9** and **10** (Fig. 2). Derivatives **10** represent a novel series of fleximers bearing the 4,5-dimethyl-*NH*-1,2,3-triazole linker between the sugar and the nucleobase.

It is worth noting that although the pharmacological significance of the 4,5-disubstituted-*NH*-1,2,3-triazole system is well documented,[10] nucleoside analogs bearing this functionality have not been extensively explored.[11] Biochemical properties of the compounds were not reported.

2. Results and discussion

2.1. Synthesis

A literature survey of the synthetic approaches to 4,5-disubstituted-*NH*-1,2,3-triazoles[12] revealed that one of the most

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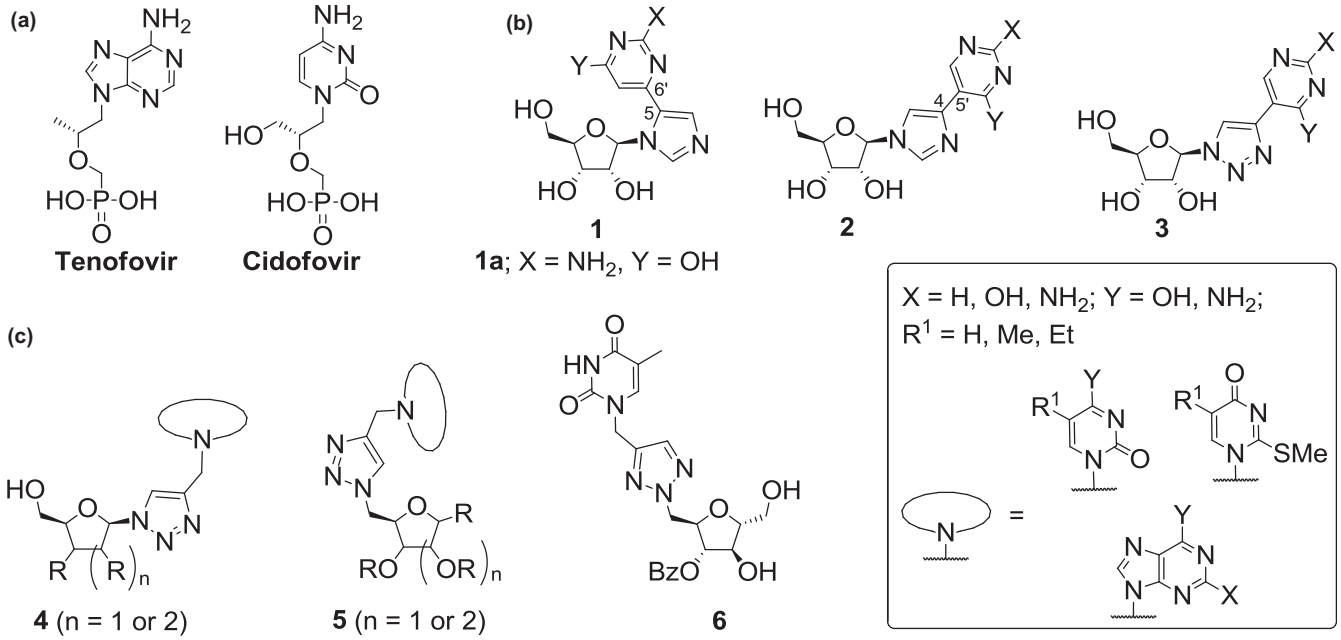


Fig. 1. (a) Structures of tenofovir and cidofovir; (b) nucleoside fleximers bearing an aglycone derived from 5-(pyrimidin-6-yl)-1*H*-imidazole, 4-(pyrimidin-5-yl)-1*H*-imidazole or 4-(pyrimidin-5-yl)-1*H*-1,2,3-triazole; (c) nucleoside fleximers bearing 4-methyl-1*H*- or 4-methyl-2*H*-1,2,3-triazole linker between a sugar and a nucleobase.

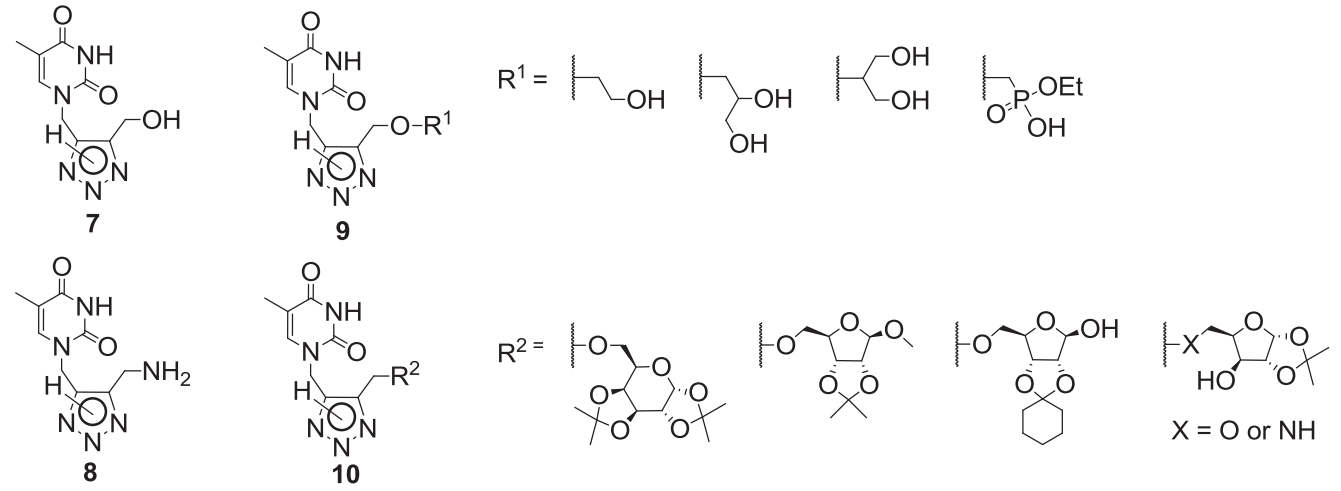
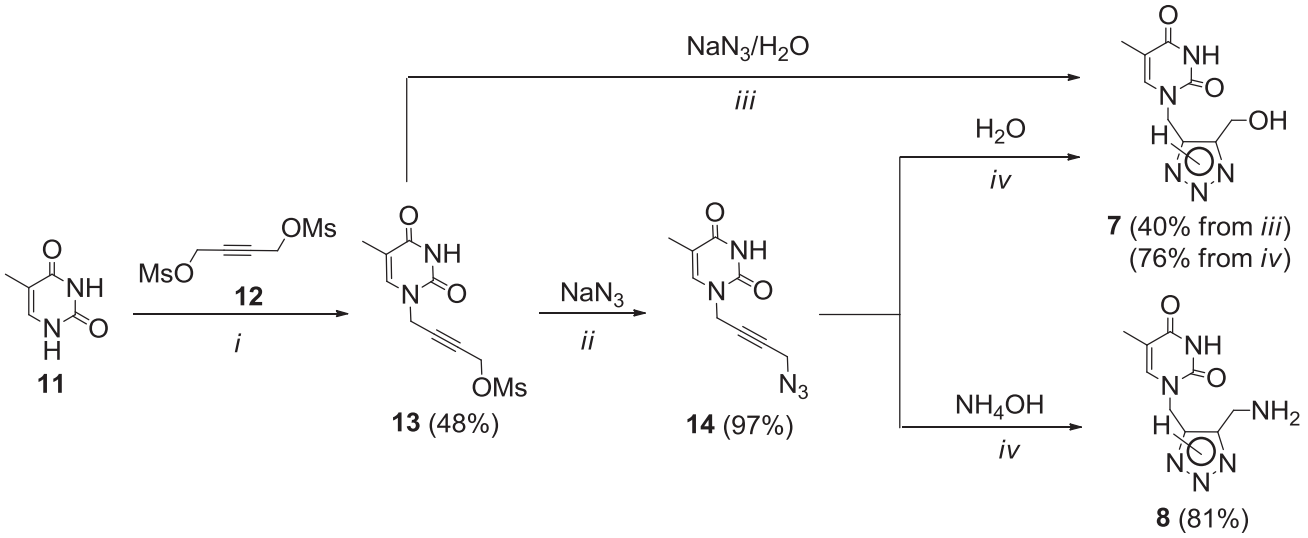


Fig. 2. Target 4,5-disubstituted-*NH*-1,2,3-triazoles **7**, **8** and their *O*- or *N*-substituted-derivatives, *NH*-1,2,3-triazolo-nucleosides **9** and **10**.

common methods used, i.e., the 1,3-dipolar cycloaddition of trimethylsilyl azide (or its equivalent, such as benzyl azide) to internal alkynes, required harsh reaction conditions (e.g., 105 °C/48 h for trimethylsilyl azide,[11a] or 70 °C/3 days for benzyl azide[11b]). Moreover, the cycloaddition of benzyl azide yielded a mixture of two regioisomeric *N*-benzyl-1,2,3-triazoles. Their de-benzylation needed an additional reaction step. Owing to these inconveniences, we presumed that the Banert cascade reaction[13] would be useful to synthesize the target compounds **7**–**10**. The number of publications on the synthetic applications of the Banert cascade reaction is limited.[10,13,14] The reaction involves a thermal rearrangement of a propargyl azide into the corresponding triazafulvene, which is trapped in situ by a nucleophilic reagent to give a 4,5-disubstituted-*NH*-1,2,3-triazole. A survey of the reported examples revealed that, the reaction has not been applied in the nucleoside or carbohydrate chemistry. Moreover, in contrast to the azides used, the reported nucleophilic reagents were limited to low-molecular weight, mostly monofunctional alcohols, amines, thiols, or electron-rich aromatics (including heteroaromatics). From a preparative point of view, two variants of the Banert cascade reaction have been reported. One-step variant[15] involved the preparation of a propargyl azide from the corresponding halide (or sulfonate) and sodium azide, followed by its in situ-treatment with a nucleophilic reagent at an elevated temperature.[13a,15] In the two-step variant, the propargyl azide was isolated prior to its subsequent treatment with the nucleophilic reagent.[10a–h]

In order to revise an applicability of these two preparative protocols to the synthesis of the target compounds **7**–**10**, mesylate **13**, and azide **14** were prepared and then their reactivity was examined (Scheme 1). Our experiment with mesylate **13** was based on the report from Sharpless and Loren[14] and involved treatment of **13** with 1 equiv of sodium azide in a 1,4-dioxane–water mixture at 75 °C. The target hydroxymethyl-triazole **7** was obtained in 40% yield.

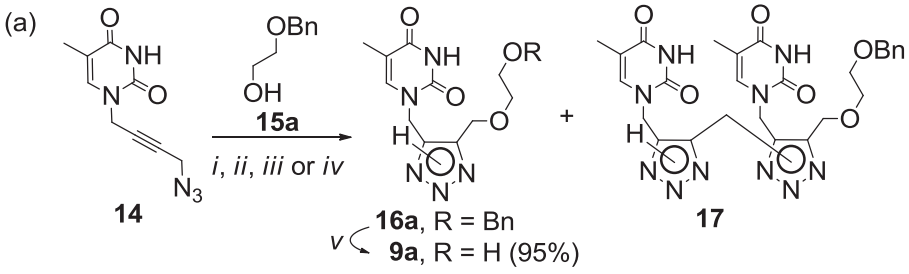
The reaction involving azide **14** and water was performed at 55 °C. The reaction temperature was chosen on the basis of the DSC



Scheme 1. Reagents and conditions: (i) BSA, acetonitrile, 20 °C, 5 days; (ii) NaN_3, NH_4Cl, DMF, 20 °C, 1 h; (iii) 1,4-dioxane, 75 °C, 4.5 h; (iv) 55 °C, overnight.

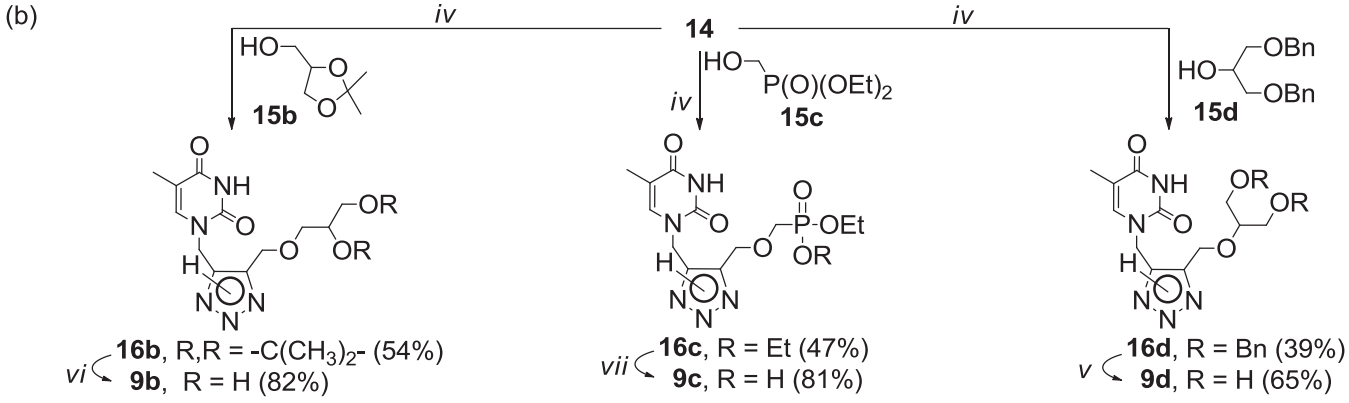
and TGA analyses of azide **14** (Section 2.2). This reaction gave product **7** in 76% yield. Under the same conditions, the reaction with ammonium hydroxide gave aminomethyl-triazole **8** in 81% yield. On the basis of these findings, azide **14** was chosen as the substrate in the synthesis of nucleosides **9** and **10** (Schemes 2 and 3).

best yield of triazole **16a** (64%) was obtained from run (iv) employing the **14**/**15a** molar ratio of 1/14, with no solvent addition. The Pd-catalyzed hydrogenolysis of compound **16a** under the hydrogen-transfer conditions gave the target nucleoside **9a** in 95% yield.



Run	**14**/**15a**/1,4-dioxane[a]	**16**[b]	**17**[c]
(i)	1/7/1	44%	53%
(ii)	1/14/1	52%	25%
(iii)	1/7/0	46%	25%
(iv)	1/14/0	64%	7%

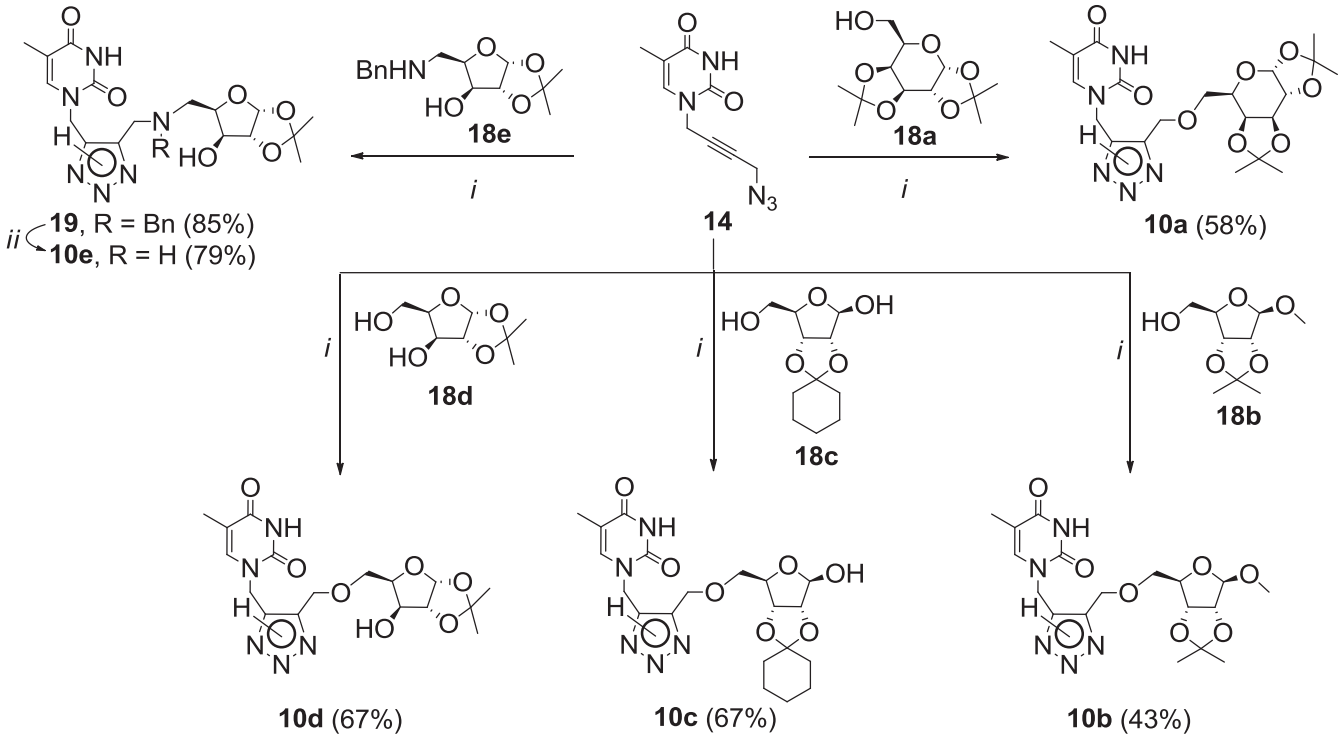
[a]A mmol/mmol/mL ratio. [b]Isolated yield.
[c]Isolated yield of a two-component mixture in a molar ratio of 4/6, by ^{1}H NMR analysis.



Scheme 2. Reagents and conditions: (i) or (ii) 1,4-dioxane, 55 °C, overnight; (iii) or (iv) 55 °C, overnight; (v) Pd/C, cyclohexene, EtOH, 50 °C, 2 days; (vi) trifluoroacetic acid, MeOH, 20 °C, 2 days; (vii) NH_4OH, MeOH, 70 °C, 4 days.

The optimization of the ratio of azide (**14**)/nucleophile/1,4-dioxane, with 2-(benzyloxy)ethanol (**15a**) as the nucleophile, is shown in Scheme 2a. The triazole **16a** and ditriazoles **17** were obtained from all the performed runs. The products were readily isolated from the reaction mixtures by column chromatography.[16] Ditriazoles **17**, obtained as an inseparable mixture of two isomers, were derived from the subsequent reaction between triazole **16a** and the triazafulvene intermediate formed from azide **14**.[17] The

The same two-step methodology was used for the preparation of nucleosides **9b**–**d** (Scheme 2b). The reactions involving azide **14** and alcohols **15b**–**d**, employing the previously established azide (**14**)/alcohol (**15**) molar ratio of 1/14 under the solvent-free conditions, gave the corresponding triazoles **16b**–**d** in the yields ranging from 39% to 54%. The final de-alkylation of the side chains in compounds **16b**–**d** were performed by: (a) trifluoroacetic acid-mediated de-acetalization (for **16b**); (b) ammonia-promoted de-alkylation



Scheme 3. Reagents and conditions: (i) 55 °C, overnight; (ii) H_2 (21 atm), Pd/C, EtOH, 25 °C, 6 days.

(for **16c**), or (c) hydrogenolysis under the Pd-catalyzed hydrogen-transfer conditions (for **16d**). The corresponding nucleosides **9b**–**d** were afforded in yields ranging from 65% to 82%.

The results from experiments performed with alcohols **15** were subsequently used in the synthesis of nucleosides **10a**–**e** from carbohydrates **18a**–**e**[18] (Scheme 3). The reaction products were obtained in the yields ranging from 43% to 85%. The reactions employing 2,3-*O*-cyclohexylidene-β-D-ribofuranose (**18c**) or 1,2-*O*-isopropylidene-α-D-xylofuranose (**18d**) yielded the corresponding product **10c** or **10d** with the triazole moiety located at the carbohydrate 5′-oxygen atom. Nucleoside **10e** was obtained from derivative **19** by the Pd-catalyzed hydrogenolysis in 79% yield.

2.2. Thermal analysis

The DSC analysis of azide **14** revealed two secondary transitions at 43.4 °C and at 49.6 °C, as well as an exothermic transition above 80 °C (Fig. 3). The TGA analysis showed no mass loss

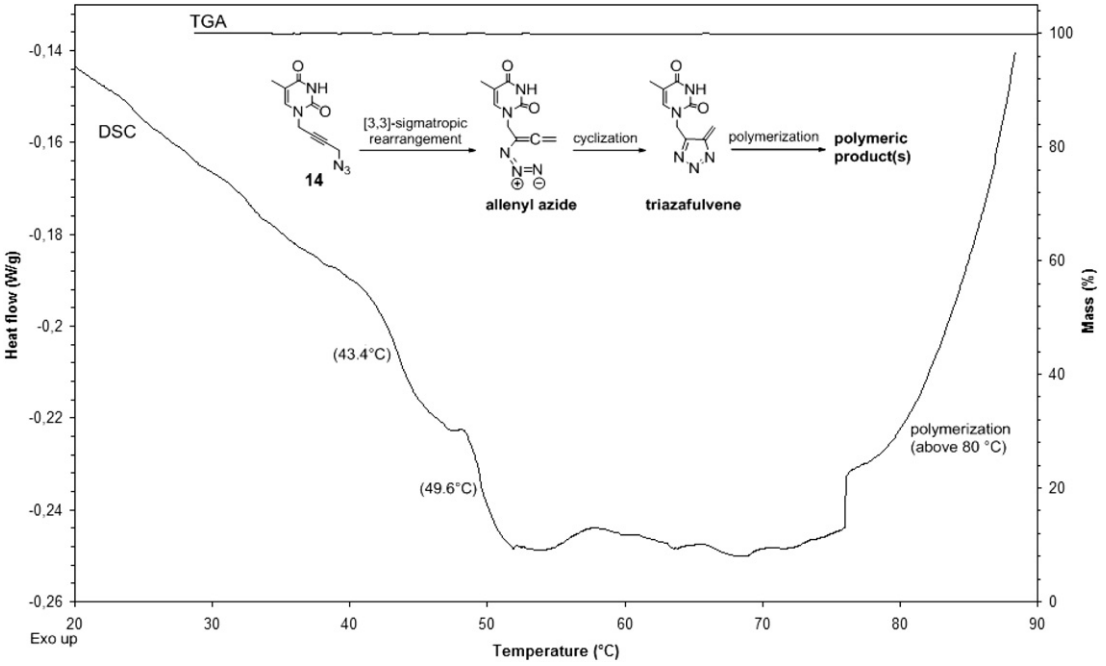


Fig. 3. DSC and TGA thermographs of azide **14**: DSC sample mass, 2.42 mg; TGA sample mass, 10 mg.

between 28 °C and 100 °C (Fig. 3). Therefore, taking into account the cascade course of the rearrangement of propargyl azides,[13a] we assumed that the transitions observed in the DSC thermogram might be correlated with: [3,3]-sigmatropic rearrangement of **14**, cyclization of the resulting allenyl azide to the corresponding triazafulvene, and polymerization of the triazafulvene in the absence of an external nucleophile.[13a,14] Following this assumption, temperature of 55 °C was anticipated as sufficient for the formation of the triazafulvene precursor of the target compounds.

2.3. Structure elucidation

The structures of the new compounds were determined using NMR spectroscopy. The ^{13}C resonances of the triazole carbon atoms of triazoles **7**–**10**, **16**, and **19** (from 134.82 to 145.12 ppm) were broadened, most probably due to a dynamic equilibrium between the tautomeric forms of the compounds and the influence of the adjacent quadrupolar nitrogen nuclei. In order to determine the location of these ^{13}C resonances, the ^{13}C NMR spectra of compounds **16a**, **9a**, **9b**, and **9d** were recorded in a DMSO-d_6/trifluoroacetic acid (TFA) mixture. The ^{13}C resonances for the triazole carbon atoms of compound **16d** were not determined. The ^{1}H and ^{13}C chemical shifts for nucleosides **10c**, **10d**, and **19** were assigned by $^{1}H-^{13}C$ HMBC NMR experiments (see Experimental). The numbering of atoms in these compounds, as well as the $^{1}H-^{13}C$ HMBC correlations crucial for the confirmation of their substitution pattern within the carbohydrate unit, are shown in Fig. 4.

4. Experimental

4.1. Materials and methods

Pre-coated Merck silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC, 0.2 mm); spots were detected under UV light (254 nm). Silica gel (200–400 mesh, Merck) was used for column chromatography. Optical rotations were measured with a PolAAr32 polarimeter. High Resolution Mass Spectra (Electrospray Ionization, ESI) were recorded on a Mariner® spectrometer. The NMR spectra were measured on a Varian Gemini-200BB spectrometer (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz) or a Varian VNMRS spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz) at 25 °C. ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent signals: $CDCl_3$, δ_H (residual $CHCl_3$) 7.26 ppm, δ_C 77.16 ppm; DMSO-d_6, δ_H (residual DMSO-d_5) 2.50 ppm, δ_C 39.52 ppm; signals are quoted as 's' (singlet), 'd' (doublet), 't' (triplet), 'm' (multiplet), 'br' (broad), and 't-like m' (triplet-like multiplet). Coupling constants (J) are reported in Hertz. The $^{1}H-^{13}C$ HMBC (Heteronuclear Multiple Bond Correlation) spectra were measured on a Varian VNMRS spectrometer. The IR spectrum of azide **14** was recorded on a Specord M80 (Carl-Zeiss Jena) spectrometer. DSC measurement was performed on a DSC Q200 V24.2 Build 107 instrument: 5.0 K/min, open Al pan, flow rate of nitrogen 25.0 mL/min, flow rate of helium 25.0 mL/min. TGA analysis was performed on a NETZSCH STA 449 C instrument: 5.0 K/min, Al_2O_3 pan, flow rate of argon 60 mL/min. Anhydrous $MgSO_4$ was employed as a drying agent. Volatiles were distilled off under reduced pressure on a rotating evaporator.

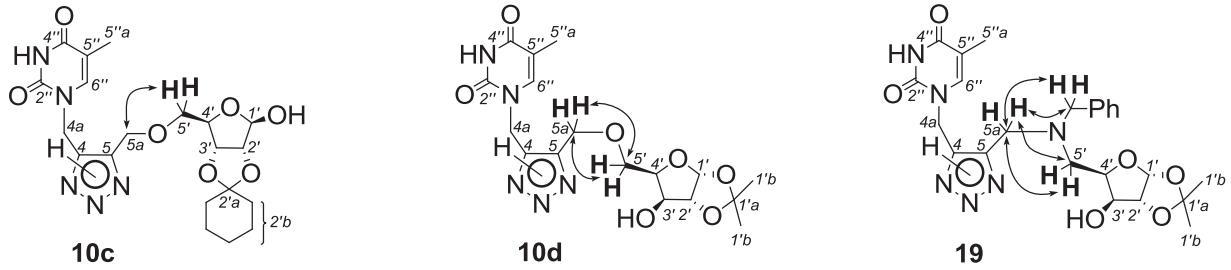


Fig. 4. Numbering of atoms and the selected $^{1}H-^{13}C$ HMBC correlations in nucleosides **10c**, **10d**, and **19**.

3. Conclusion

The Banert cascade reaction involving the nucleobase-bearing propargyl azide **14** and a variety of functionalized nucleophiles, including carbohydrate derivatives, was shown to serve as a convenient tool for the synthesis of 4,5-disubstituted-*NH*-1,2,3-triazolo-nucleosides. The applied solvent-free procedure was advantageous from both the preparative and ecological point of view. Although an appreciated molar excess of the organic nucleophilic reagent (the alcohol or the carbohydrate derivative) was used in the presented transformations, the target triazoles were routinely isolated by column chromatography, owing to a significant difference in polarity of the nucleophile and the corresponding triazole. The organic nucleophilic reagents recovered from the reaction mixtures did not need an additional purification prior to reuse in a subsequent reaction. We hope that the reported study will be of interest for research groups involved in the synthesis of both 1,2,3-triazolo-nucleosides and carbohydrate 1,2,3-triazolo-conjugates. A study on the improvement and extension of the presented methodology is now in progress. This study, including a SAR analysis of the obtained compounds, will be a subject of a forthcoming publication.

The concentration of ammonium hydroxide used was 25 wt %. 1,4-Dioxane, acetonitrile, and *N*,*N*-dimethylformamide were dried in accordance with known methods. *N*,*O*-Bis(trimethylsilyl)acetamide, thymine (**11**) 2-(benzyloxy)ethanol (**15a**), 2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane (**15b**), diethyl (hydroxymethyl) phosphonate (**15c**) or 1,3-bis(benzyloxy)propan-2-ol (**15d**) were used as purchased (Sigma–Aldrich).

4.2. 1-(4-Mesyloxybut-2-yn-1-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (13)

A mixture of thymine (**11**, 1.0 g, 7.9 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3.21 g, 15.8 mmol) in dry acetonitrile (80 mL) was stirred at 20 °C for 1 h under an argon atmosphere. Then, 1,4-bis(mesyloxy)but-2-yne[19] (**12**, 5.74 g, 23.7 mmol) was added. The reaction mixture was kept at room temperature for 5 days and then ethyl acetate (250 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL) were added. The mixture was stirred for 1 h and filtered through a Celite pad. The organic phase was separated from the filtrate, washed with brine (50 mL), and dried. Volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/MeOH, from 99/1 to 95/5,

v/v) gave **13** (1.04 g, 48%) as a white solid (mp 154–155 °C). δ_H (200 MHz, DMSO-d_6) 1.76 (br s, 3H), 3.24 (s, 3H), 4.60 (s, 2H), 5.00 (s, 2H), 7.58 (br d, $^4J_{HH}$ 1.2, 1H), 11.40 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6) 11.91, 35.69, 37.65, 57.96, 77.29, 83.99, 109.43, 140.15. 150.40, 164.13. HRMS *m*/*z* calcd for $C_{10}H_{12}N_2O_5SNa$ $(M+Na)^+$ 295.0365, found 295.0366.

4.3. 1-(4-Azidobut-2-yn-1-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (14)

A mixture of **13** (724 mg, 2.66 mmol), sodium azide (207 mg, 3.19 mmol), ammonium chloride (40 mg), and dry *N*,*N*-dimethylformamide (32 mL) was stirred at 20 °C for 1 h. Then, the solvent was distilled off under vacuum (water bath, 25–30 °C, 0.4 mmHg). The residue was sonicated with cold water (20 mL) for 3 min and filtered. The white solid was dried in a vacuum dessicator over phosphorus pentoxide to give **14** (564 mg, 97%). δ_H (500 MHz, DMSO-d_6) 1.76 (d, $^4J_{HH}$ 1.0, 3H), 4.19 (s, 2H), 4.58 (s, 2H), 7.58 (br d, $^4J_{HH}$ 1.0, 1H), 11.34 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 11.94, 36.50, 39.35, 77.50, 81.59, 109.45, 140.15, 150.38, 164.15. ν_{max} (−N_3)/KBr 2101 cm^{-1}. HRMS *m*/*z* calcd for $C_9H_9N_5O_2Na$ $(M+Na)^+$ 242.0654, found 242.0649.

4.4. 1-((5-(Hydroxymethyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (7)

*4.4.1. From mesylate (**13**).* A mixture of **13** (140 mg, 0.51 mmol), sodium azide (33 mg, 0.51 mmol), ammonium chloride (107 mg, 1.02 mmol), 1,4-dioxane (2.5 mL), and water (0.8 mL) was stirred at 75 °C for 4.5 h. The reaction mixture was cooled to 20 °C and volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v) gave **7** (49 mg, 40%) as a white solid (mp 187–198 °C dec). δ_H (200 MHz, DMSO-d_6) 1.74 (s, 3H), 4.58 (s, 2H), 4.94 (s, 2H), 7.55 (s, 1H), 11.28 (br s, 1H, NH), 14.62 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 12.07, 41.33, 54.13, 108.88, 140.86, 141.37, 145.12, 150.95, 164.42. HRMS *m*/*z* calcd for $C_9H_{11}N_5O_3Na$ $(M+Na)^+$ 260.0760, found 260.0760.

*4.4.2. From azide (**14**).* A mixture of **14** (100 mg, 0.46 mmol) and water (2 mL) was stirred at 55 °C overnight. The reaction mixture was cooled to 20 °C and volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v) gave **7** (84 mg, 76%). The spectroscopic data of **7** were in accordance with those reported in Section 4.4.1.

4.5. 1-((5-(Aminomethyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (8)

A mixture of azide **14** (100 mg, 0.46 mmol) and ammonium hydroxide (2 mL) was stirred at 55 °C overnight (sealed tube). The reaction mixture was cooled to 20 °C and volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/MeOH, 9/1, v/v) gave **8** (88 mg, 81%) as a white solid (mp >179 °C dec). δ_H (200 MHz, DMSO-d_6) 1.74 (br s, 3H), 3.88 (s, 2H), 4.92 (s, 2H), 7.46 (br s, 3H, NH), 7.59 (br d, $^4J_{HH}$ 0.8, 1H). δ_C (125 MHz, DMSO-d_6) 11.98, 34.80, 41.03, 108.32, 138.18, 141.26, 141.51, 150.92, 164.30. HRMS *m*/*z* calcd for $C_9H_{13}N_6O_2$ $(M+H)^+$ 237.1100, found 237.1096.

4.6. 1-((5-((2-Hydroxyethoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (9a)

*4.6.1. 1-((5-((2-(Benzyloxy)ethoxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**16a**) and ditriazoles (**17**)*

4.6.1.1. From runs (i) and (ii), Scheme 2a. The runs (i) and (ii) were performed from 100 mg (0.46 mmol) of azide **14**. A mixture of azide **14**, 2-(benzyloxy)ethanol (**15a**) and 1,4-dioxane was prepared in accordance with the **14**/**15a**/1,4-dioxane ratios given in Scheme 2a and stirred at 55 °C overnight. The reaction mixture was cooled to 20 °C and volatiles were distilled off. Column chromatography of the residue ($CHCl_3$/MeOH, from 99/1 to 95/5, v/v) gave **16a** (76 mg, 44% from run (i); or 88 mg, 52% from run (ii)) as a white solid (mp 129–131 °C) and ditriazoles **17** (76 mg, 53% from run (i); or 36 mg, 25% from run (ii)) as a colorless oil. **16a**: δ_H (200 MHz, DMSO-d_6) 1.72 (d, $^4J_{HH}$ 1.0, 3H), 3.42–3.71 (m, 4H), 4.46 (br s, 2H), 4.61 (s, 2H), 4.93 (s, 2H), 7.15–7.32 (m, 5H), 7.50 (br d, $^4J_{HH}$ 1.0, 1H). δ_C (50 MHz, DMSO-d_6/TFA) 12.00, 41.02, 62.34, 69.05, 69.21, 72.16, 108.84, 127.46, 127.59, 128.28, 138.44, 140.04, 140.36, 141.15, 150.86, 164.34. HRMS *m*/*z* calcd for $C_{18}H_{21}N_5O_4Na$ $(M+Na)^+$ 394.1491, found 394.1482. *Ditriazoles* (**17**), a mixture in a molar ratio of 4/6: δ_H (500 MHz, DMSO-d_6) 1.65 (br s, 1.2H), 1.72 (br s, 1.8H), 1.73 (br s, 1.8H), 1.75 (br s, 1.2H), 3.53–3.59 (m, 4H), 4.42–4.48 (m, 2H), 4.57 (s, 0.8H), 4.76 (s, 1.2H), 4.90 (s, 1.2H), 4.92 (s, 1.2H), 4.98 (s, 0.8H), 5.09 (s, 0.8H), 5.77 (s, 1.2H), 5.86 (s, 0.8H), 7.25–7.42 (m, 5H), 7.41 (br d, $^4J_{HH}$ 1.0, 0.4H), 7.46 (br d, $^4J_{HH}$ 1.0, 0.6H), 7.53 (br d, $^4J_{HH}$ 1.0, 0.4H), 7.55 (br d, $^4J_{HH}$ 1.0, 0.6H), 11.27 (br s, 1.2H, NH), 11.31 (br s, 0.8H, NH). HRMS *m*/*z* calcd for $C_{27}H_{30}N_{10}O_6Na$ $(M+Na)^+$ 613.2247, found 613.2235.

4.6.1.2. From runs (iii) and (iv), Scheme 2a. The runs (iii) and (iv) were performed from 200 mg (0.92 mmol) of azide **14**. A mixture of azide **14** and 2-(benzyloxy)ethanol (**15a**) was prepared in accordance with a **14**/**15a**/1,4-dioxane ratios given in Scheme 2a and stirred at 55 °C overnight. The reaction mixture was cooled to 20 °C. Column chromatography of the mixture ($CHCl_3$/MeOH, from 99/1 to 95/5, v/v) gave **16a** (157 mg, 46% from run (iii); or 218, mg 64% from run (iv)) and **17** (71 mg, 25% from run (iii); or 20 mg, 7% from run (iv)). The spectroscopic data of **16a** and **17** were in accordance with those reported in Section 4.6.1.1.

*4.6.2. 1-((5-((2-Hydroxyethoxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**9a**).* A mixture of **16a** (211 mg, 0.57 mmol), methanol (8 mL), cyclohexene (8 mL), and palladium (10% on charcoal, 20 mg) was stirred at 50 °C for 2 days under an argon atmosphere. The reaction mixture was cooled to 20 °C and filtered through a Celite pad. Volatiles were distilled off from the filtrate. Column chromatography of the residue ($CHCl_3$/MeOH, 7/3, v/v) gave **9a** (152 mg, 95%) as a white solid (mp 144–146 °C). δ_H (200 MHz, DMSO-d_6) 1.74 (d, $^4J_{HH}$ 1.0, 3H), 3.43–3.45 (AA′BB′-t, 2H), 3.50–3.52 (AA′BB′-t, 2H), 4.59 (s, 2H), 4.95 (s, 2H), 7.53 (br s, 1H), 11.34 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6/TFA) 12.15, 41.29, 60.36, 62.46, 72.04, 109.14, 140.18, 140.43, 141.42, 151.10, 164.55. HRMS *m*/*z* calcd for $C_{11}H_{15}N_5O_4Na$ $(M+Na)^+$ 304.1022, found 304.1029.

4.7. 1-((5-((2,3-Dihydroxypropoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (9b)

*4.7.1. 1-((5-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**16b**).* According to the procedure described in Section 4.6.1.2, compound **16b** was obtained from azide **14** (100 mg, 0.46 mmol) and 2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane (**15b**, 845 mg, 6.4 mmol). Column chromatography ($CHCl_3$/MeOH, from 99/1 to 95/5, v/v) gave **16b** (86 mg, 54%) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 1.32 (s, 3H), 1.38 (br s, 3H), 1.84 (s, 3H), 3.56 (d, $^3J_{HH}$ 5.0, 2H), 3.67 (δ_A) and 4.02 (δ_B) (AB part of ABX system, $^2J_{AB}$ 7.0, $^3J_{Ax}$ 7.5, $^3J_{Bx}$ 7.5, 2H), 4.23–4.31 (X part of ABX system, 1H), 4.76 (s, 2H), 5.02 (AB quartet, $^2J_{AB}$ 17.0, 2H), 7.38 (s, 1H), 10.19 (br s, 1H, NH), 13.79 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6) 12.00, 25.35, 26.67, 40.98, 62.57, 66.02, 70.98, 74.16, 108.56, 108.92, 139.92, 140.37, 141.10, 150.86,

164.33. HRMS *m*/*z* calcd for $C_{15}H_{22}N_5O_5$ $(M+H)^+$ 352.1616, found 352.1615.

*4.7.2. 1-((5-((2,3-Dihydroxypropoxy)methyl)-NH-1,2,3-triazol-4-yl) methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**9b**).* A mixture of **16b** (78 mg, 0.22 mmol), methanol (1 mL), water (0.5 mL), and TFA (0.1 mL) was kept at 20 °C for 2 days. Volatiles were distilled off to give **9b** (62 mg, 82%) as a white solid (mp 133–135 °C). δ_H (200 MHz, DMSO-d_6) 1.74 (br s, 3H), 3.27–3.47 (m, 4H), 3.53–3.61 (m, 1H), 4.58 (s, 2H), 4.94 (s, 2H), 7.55 (br s, 1H), 11.30 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6) 12.00, 41.04, 62.55, 63.03, 70.46, 72.10, 108.83, 139.91, 140.20, 141.25, 150.84, 164.32. HRMS *m*/*z* calcd for $C_{12}H_{17}N_5O_5Na$ $(M+Na)^+$ 334.1127, found 334.1138.

4.8. 1-((5-((Ethoxyhydroxyphosphorylmethoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (9c)

*4.8.1. 1-((5-((Diethoxyphosphorylmethoxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**16c**).* According to the procedure described in Section 4.6.1.2, compound **16c** was obtained from azide **14** (100 mg, 0.46 mmol) and diethyl (hydroxymethyl)phosphonate (**15c**, 1.2 g, 6.4 mmol). Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) gave **16c** (84 mg, 47%) as a colorless oil. δ_H (500 MHz, $CDCl_3$) 1.19–1.22 (t-like m, 6H), 1.74 (d, $^4J_{HH}$ 1.0, 3H), 3.82 (d, $^3J_{HP}$ 8.5, 2H), 4.00–4.05 (quintet-like m, 4H), 4.70 (s, 2H), 4.95 (s, 2H), 7.54 (br d, $^4J_{HH}$ 1.0, 1H). δ_C (125 MHz, $CDCl_3$) 12.00, 16.32 (d, $^4J_{CP}$ 5.9), 40.91, 61.89 (d, $^3J_{CP}$ 6.8), 63.26 (d, $^2J_{CP}$ 162.4), 64.11 (d, $^3J_{CP}$ 13.6), 108.96, 139.46, 140.35, 141.15, 150.88, 164.34. HRMS *m*/*z* calcd for $C_{14}H_{22}N_5O_6PNa$ $(M+Na)^+$ 410.1205, found 410.1191.

*4.8.2. 1-((5-((Ethoxyhydroxyphosphorylmethoxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**9c**).* A mixture of **16c** (96 mg, 0.25 mmol), ammonium hydroxide (4 mL), and methanol (1 mL) was kept at 70 °C for 4 days (sealed tube). Volatiles were distilled off to give **9c** (70 mg, 81%) as a slightly yellow oil. δ_H (200 MHz, DMSO-d_6) 1.05–1.12 (t-like m, 3H), 1.74 (br s, 3H), 3.43 (d, $^3J_{HP}$ 8.2, 2H), 3.68–3.82 (quintet-like m, 2H), 4.65 (s, 2H), 4.92 (s, 2H), 7.65 (br s, 1H), 9.63 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 11.89, 16.90 (d, $^4J_{CP}$ 5.7), 33.94, 59.18 (d, $^3J_{CP}$ 5.7), 63.49 (d, $^3J_{CP}$ 10.3), 66.80 (d, $^2J_{CP}$ 154.0), 108.71, 138.87, 139.39, 141.40, 150.82, 164.31. HRMS *m*/*z* calcd for $C_{12}H_{19}N_5O_6P$ $(M+H)^+$ 360.1068, found 360.1085.

4.9. 1-((5-((1,3-Dihydroxypropan-2-oxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (9d)

*4.9.1. 1-((5-((1,3-Bis(benzyloxy)propan-2-oxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**16d**).* According to the procedure described in Section 4.6.1.2, compound **16d** was obtained from azide **14** (100 mg, 0.46 mmol) and 1,3-bis(benzyloxy)propan-2-ol (**15d**, 1.7 g, 6.4 mmol). Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) gave **16d** (89 mg, 39%) as a colorless oil. δ_H (200 MHz, $CDCl_3$) 1.80 (br s, 3H), 3.52–3.71 (m, 4H), 3.80–3.91 (m, 1H), 4.54 (br s, 4H), 4.89 (s, 2H), 4.92 (s, 2H), 7.28–7.34 (m, 11H), 9.18 (br s, 1H, NH). δ_C (50 MHz, $CDCl_3$) 12.34, 41.45, 62.99, 70.11, 73.71, 78.37, 111.07, 127.98, 128.07, 128.61, 137.63, 140.72, 151.27, 164.42. The ^{13}C resonances for the triazole carbon atoms of the compound were not determined. HRMS *m*/*z* calcd for $C_{26}H_{29}N_5O_5Na$ $(M+Na)^+$ 514.2067, found 514.2067.

*4.9.2. 1-((5-((1,3-Dihydroxypropan-2-oxy)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**9d**).* According to the procedure described in Section 4.6.2, compounds **9d** was obtained from 80 mg of **16d**. Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) gave **9d** (32 mg, 65%) as a white solid (mp 151–153 °C). δ_H (200 MHz, DMSO-d_6) 1.74 (br s, 3H), 3.38–3.52 (m, 7H), 4.72 (s, 2H), 4.95 (s, 2H), 7.57 (br s, 1H), 11.27 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6/TFA) 12.08, 41.18, 60.96, 61.59, 81.44, 109.14, 140.21, 140.49, 141.42, 151.16, 164.57. HRMS *m*/*z* calcd for $C_{12}H_{17}N_5O_5Na$ $(M+Na)^+$ 334.1127, found 334.1127.

4.10. 5-Methyl-1-((5-((((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4′,5′-*d*]pyran-5-yl)methoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione (10a)

According to the procedure described in Section 4.6.1.2, compound **10a** was obtained from azide **14** (50 mg, 0.23 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[18a] (**18a**, 830 mg, 3.2 mmol). Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) gave **10a** (64 mg, 58%) as a colorless syrup. δ_H (500 MHz, $CDCl_3$) 1.26 (s, 3H), 1.27 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.82 (br s, 3H), 3.58–3.74 (m, 2H), 3.96–4.06 (m, 1H), 4.20 (δ_A) and 4.57 (δ_B) (AB part of ABX system, $^2J_{AB}$ 8.0, $^3J_{Ax}$ 0.0, $^3J_{Bx}$ 2.0, 2H), 4.28–4.29 (m, 1H), 4.72 and 4.76 (AB system, $^2J_{AB}$ 12.0, 2H), 4.97 and 5.07 (AB system, $^2J_{AB}$ 14.5, 2H), 5.51 (d, $^3J_{HH}$ 5.0, 1H), 7.45 (br s, 1H), 10.18 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6) 11.93, 24.18, 24.78, 25.81, 25.87, 41.18, 62.93, 66.35, 68.96, 69.73, 70.51, 70.51, 95.66, 107.75, 108.32, 108.78, 141.10, 141.51, 141.73, 150.76, 164.23. $[\alpha]_D^{27}$ −36.7 (*c* 2.30, MeOH). HRMS *m*/*z* calcd for $C_{21}H_{30}N_5O_8$ $(M+H)^+$ 480.2089, found 480.2092.

4.11. 1-((5-((((3a*R*,4*R*,6*R*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (10b)

According to the procedure described in Section 4.6.1.2, compound **10b** was obtained from azide **14** (100 mg, 0.46 mmol) and 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose[18b] (**18b**, 1.3 g, 6.4 mmol). Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) gave **10b** (84 mg, 43%) as a colorless syrup. δ_H (500 MHz, $CDCl_3$) 1.28 (s, 3H), 1.45 (s, 3H), 1.85 (br s, 3H), 3.03 (s, 3H), 3.55 (δ_A) and 3.61 (δ_B) (AB part of ABX system, $^2J_{AB}$ 10.0, $^3J_{Ax}$ 6.5, $^3J_{Bx}$ 6.5, 2H), 4.32–4.35 (X part of ABX system, 1H), 4.57 (d, $^3J_{HH}$ 6.5, 1H), 4.65 (d, $^3J_{HH}$ 6.5, 1H), 4.73 and 4.79 (AB system, $^2J_{AB}$ 12.5, 2H), 4.97 (s, 1H), 5.01 (s, 2H), 7.37 (br s, 1H), 9.93 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6) 11.94, 24.63, 26.23, 41.05, 54.10, 62.79, 70.81, 81.55, 84.20, 84.43, 108.46, 108.86, 111.48, 141.04, 141.60, 141.67, 150.83, 164.26. $[\alpha]_D^{26}$ −31.6 (*c* 1.36, MeOH). HRMS *m*/*z* calcd for $C_{18}H_{26}N_5O_7$ $(M+H)^+$ 424.1827, found 424.1829.

4.12. 1-((5-((((3a′*R*,4′*R*,6′*R*,6a′*R*)-4′-Hydroxytetrahydrospiro[cyclohexane-1,2′-furo[3,4-*d*][1,3]dioxol]-6′-yl)methoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (10c)

According to the procedure described in Section 4.6.1.2, compound **10c** was obtained from azide **14** (50 mg, 0.23 mmol) and 2,3-*O*-cyclohexylidene-β-D-ribofuranose[18c] (**18c**, 740 mg, 3.2 mmol). Column chromatography ($CHCl_3$/MeOH, 95/5, v/v) gave **10c** (69 mg, 67%) as a white foam. δ_H (200 MHz, DMSO-d_6) 1.30–1.54 (m, 10H, H-2′b), 1.74 (br s, 3H, H-5″a), 3.45–3.75 (m, 2H, H-5′), 3.98–4.19 (t-like m, 1H, H-4′), 4.43–4.52 (m, 2H, H-2′, H-3′), 4.62 (s, 2H, H-5a), 4.95 (s, 2H, H-4a), 5.20 (s, 1H, H-1′), 7.52 (br s, 1H, H-6″a), 11.30 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 12.00 (C-5″a), 23.44 (C-2′b), 23.69 (C-2′b), 24.65 (C-2′b), 33.94 (C-2′b), 35.89 (C-2′b), 40.98 (C-4a), 62.52 (C-5a), 71.57 (C-5′), 81.77 (C-3′), 84.00 (C-4′), 85.29 (C-2′), 102.10 (C-1′), 108.89 (C-5″), 111.94 (C-2′a), 139.98 (C-4 or C-5), 140.24 (C-5 or C-4), 141.11 (C-6″), 150.87 (C-2″), 164.29 (C-4″).

$[\alpha]_D^{23}$ −10.9 (*c* 1.24, MeOH). HRMS *m*/*z* calcd for $C_{20}H_{28}N_5O_7$ $(M+H)^+$ 450.1983, found 450.1990.

4.13. 1-((5-((((3a*R*,5*R*,6*S*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methoxy)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (10d)

According to the procedure described in Section 4.6.1.2, compound **10d** was obtained from azide **14** (50 mg, 0.23 mmol) and 1,2-*O*-isopropylidene-α-D-xylofuranose[18d] (**18d**, 610 mg, 3.2 mmol). Column chromatography ($CHCl_3$/MeOH, 99/1, v/v) gave **10d** (63 mg, 67%) as a colorless syrup. δ_H (500 MHz, DMSO-d_6) 1.23 (s, H-1′b, 3H), 1.37 (s, H-1′b, 3H), 1.76 (d, $^4J_{HH}$ 1.0, 3H, H-5″a), 3.54 (δ_A) and 3.68 (δ_B) (AB part of ABX system, $^2J_{AB}$ 10.5, $^3J_{Ax}$ 7.0, $^3J_{Bx}$ 4.5, 2H, H-5′), 3.99 (br s, 1H, H-3′), 4.10–4.13 (X part of ABX system, 1H, H-4′), 4.39 (d, $^3J_{HH}$ 3.5, 1H, H-2′), 4.62 (s, 2H, H-5a), 4.96 (s, 2H, H-4a), 5.82 (d, $^3J_{HH}$ 4.0, 1H, H-1′), 7.48 (br d, $^4J_{HH}$ 1.0, 1H, H-6″a), 11.14 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 12.02 (C-5″a), 26.11 (C-1′b), 26.64 (C-1′b), 41.69 (C-4a), 63.27 (C-5a), 68.41 (C-5′), 73.85 (C-3′), 79.36 (C-4′), 84.95 (C-2′), 104.46 (C-1′), 108.88 (C-5″), 110.48 (C-1′a), 140.28 (C-4 or C-5), 141.12 (C-6″), 142.18 (C-5 or C-4), 150.86 (C-2″), 164.29 (C-4″). $[\alpha]_D^{23}$ −13.8 (*c* 1.38, MeOH) HRMS *m*/*z* calcd for $C_{17}H_{24}N_5O_7$ $(M+H)^+$ 410.1670, found 410.1677.

4.14. 1-((5-(((((3a*R*,5*R*,6*S*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl)amino)methyl)-*NH*-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (10e)

*4.14.1. 1-((5-((Benzyl(((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl)amino)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**19**).* According to the procedure described in Section 4.6.1.2, compound **19** was obtained from azide **14** (132 mg, 0.6 mmol) and 5-(benzylamino)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[18e] (**18e**, 2.33 g, 8.3 mmol). Column chromatography ($CHCl_3$/MeOH, from 99/1 to 95/5, v/v) gave **19** (255 mg, 85%) as a pale yellow oil. δ_H (500 MHz, DMSO-d_6) 1.21 (s, 3H, H-1′b), 1.34 (s, 3H, H-1′b), 1.73 (d, $^4J_{HH}$ 1.0, 3H, H-5″a), 2.63 (δ_A) and 2.75 (δ_A) (AB part of ABX system, $^2J_{AB}$ 14.0, $^3J_{Ax}$ 7.0, $^3J_{Bx}$ 4.0, 2H, H-5′), 3.62 and 3.64 (AB system, $^2J_{AB}$ 14.5, 2H, CH_2-Ph), 3.79 (s, 2H, H-5a), 3.88 (d, $^3J_{HH}$ 2.5, 1H, H-3′), 4.16–4.18 (m, 1H, H-4′), 4.34 (d, $^3J_{HH}$ 4.0, 1H, H-2′), 4.89 and 4.94 (AB system, $^2J_{AB}$ 15.5, 2H, H-4a), 5.79 (d, $^3J_{HH}$ 4.0, 1H, H-1′), 7.18–7.21 (m, 2H, Ph), 7.29–7.31 (m, 3H, Ph), 7.48 (d, $^4J_{HH}$ 1.0, 1H, H-6″), 11.23 (br s, 1H, NH). δ_C (125 MHz, DMSO-d_6) 12.06 (C-5″a), 26.21 (C-1′b), 26.71 (C-1′b), 41.20 (C-4a), 47.97 (C-5a), 52.05 (C-5′), 58.23 (CH_2-Ph), 74.62 (C-3′), 78.57 (C-4′), 84.95 (C-2′), 104.39 (C-1′), 108.91 (C-5″), 110.47 (C-1′a), 127.01 (Ph), 128.25 (Ph), 128.88 (Ph), 137.80 (C-4 or C-5), 138.79 (Ph), 140.38 (C-5 or C-4), 141.41 (C-6″), 150.92 (C-2″), 164.43 (C-4″). $[\alpha]_D^{26}$ −25.5 (*c* 1.96, MeOH). HRMS *m*/*z* calcd for $C_{24}H_{31}N_6O_6$ $(M+H)^+$ 499.2300, found 499.2298.

*4.14.2. 1-((5-(((((3aR,5R,6S,6aR)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl)amino)methyl)-NH-1,2,3-triazol-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**10e**).* A mixture of **19** (150 mg, 0.3 mmol), palladium (10% on charcoal, 30 mg), and ethanol (5 mL) was hydrogenated (21 atm) at 25 °C for 6 days. The volatiles were distilled off from the reaction mixture. Column chromatography of the residue ($CHCl_3$/MeOH, from 9/1 to 8/2, v/v) gave **10e** (97 mg, 79%) as a colorless syrup. δ_H (500 MHz, DMSO-d_6) 1.20 (s, 3H), 1.34 (s, 3H), 1.74 (br s, 3H), 2.70 (δ_A) and 2.77 (δ_B) (AB part of ABX system, $^2J_{AB}$ 12.0, $^3J_{Ax}$ 6.3, $^3J_{Bx}$ 5.3, 2H), 3.84 (s, 2H), 3.95 (d, $^3J_{HH}$ 2.5, 1H), 4.02–4.05 (m, 1H), 4.37 (d, $^3J_{HH}$ 3.5, 1H), 4.93 (s, 2H), 5.79 (d, $^3J_{HH}$ 4.0, 1H), 7.58 (d, $^4J_{HH}$ 1.0, 1H). δ_C (125 MHz, DMSO-d_6) 12.01, 26.16, 26.69, 41.04, 42.44, 46.93, 74.16, 79.45, 85.20, 104.28, 108.88, 110.42, 139.28, 140.53, 141.32, 150.94, 164.37. HRMS *m*/*z* calcd for $C_{17}H_{25}N_6O_6$ $(M+H)^+$ 409.1836, found 409.1830. An optical rotation of the compound was not determined due to its low solubility in water or common organic solvents.

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15. This variant is recommended for low-molecular weight propargyl azides owing to their susceptibility to explosion (see, Ref. 13).
16. TLC analysis of the crude reaction mixtures showed additional, highly-polar by-products. However, the by-products were not isolated from the column chromatography. Mass balance from the chromatography, calculated relative to azide **14**, might indicate on an oligomeric/polymeric structure of the by-products. The mass balance deficiency of **15a** recovered from runs (iii) and (iv), calculated relative to products **16a** and **17**, was less than 10%.

17. The reaction between an initially formed triazole and a triazafulvene intermediate formed from a propargyl azide was suggested in Ref. 14. However to the best of our knowledge, products resulting from the reaction were for the first time identified in our study.
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