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A convenient method for constructing novel tetrahydropyrido[4′,3′:4,5]-thieno[2,3-*d*]-pyrimidinones-carbohydrate and amino acid conjugates via copper(I)-catalyzed alkyne-azide 'Click Chemistry'

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ABSTRACT

Novel conjugates of tetrahydropyridothienopyrimidones and carbohydrates or amino acids linked by 1,2,3-triazoles were synthesized. After establishing the tetrahydropyridothienopyrimidones ring system by ring closure, propargyl groups were introduced by N-alkylation. Cu-catalyzed cycloaddition of the propargyl products with azido group containing hexoses or amino acids gives the corresponding 1,2,3-triazoles in high yields. This methodology also allowed attaching two carbohydrate molecules to the tetrahydropyridothienopyrimidone core. Interesting dependence of the regioselectivity of the N-propargylation of the pyrimidone ring on the exocyclic substituent found adjacent to the pyrimidine-*N*-atom was observed. A remarkable case of a non-catalyzed intramolecular [3+2]-cycloaddition of an alkyne with an azide to a 1,2,3-triazole was observed, which occurred in the solid state at rt or below.

1. Introduction

Derivatives of fused pyrimidones have been in the focus of interest over many years. This is probably due to the fact that many compounds containing fused pyrimidones, such as guanosine, flavine, ureic acid, and folate play an important role in the biochemistry of living cells. Recent development of physiologically highly potent purine analogues with interesting antiviral, anti-allergic and specially anticancer activities has promoted a great current interest in facile and general routes to these molecules in synthetically useful yields.[1] The thienopyrimidone skeleton does not occur in nature but nevertheless attracts interest because of remarkable biological properties of its derivatives. For example, some 2-alkoxy- or 2-alkyl-substituted thienopyrimidones showed significant antifungal and antibacterial activities,[2a–d] whereas others exhibited good anticonvulsant and angiotensin II or H_1 receptor antagonistic activities.[2e–h] Among promising targeting therapies for cancer treatment, substituted thienopyrimidones have continued to retain attention of both academic institutions and pharmaceutical companies in the last few years.[3–5]

The Cu-catalyzed [3+2]-cycloaddition of azides and alkynes (Meldal–Sharpless 'click'-reaction) to 1,2,3-triazoles have been used extensively to tether a variety of functions to biomolecules.[6–9] There were cases reported where the incorporation of a 1,2,3-triazole into pharmacophors increased the pharmacological activity.[10] Furthermore, the introduction of carbohydrates and amino acids into pharmacophors can lead to new functionalities, e.g., biological targeting abilities, and thus has been used in the development of therapeutics.[11,12]

Herein we report on the application of the Cu-catalyzed cycloaddition of alkynes and azides to tetrahydropyridothienopyrimidone systems in order to tether carbohydrates or amino acids to this pharmacophor via 1,2,3-triazole linkers. In addition, novel fused heterocyclic ring systems will be disclosed.

2. Results and discussion

The readily available ethyl 2-amino-3-(aminocarbonyl)-4,7-dihydrothieno[2,3-*c*]-pyridine-6(5*H*)-carboxylate (**1**)[13] was chosen as starting material, which served as precursor for pyridothienopyrimidones before. In order to apply the [3+2]-cycloaddition either the alkyne or the azide moiety or both need to be attached to the heterocyclic skeleton. The hitherto unknown chloromethyl derivative **3** seemed to be a suitable starting material to introduce either of these functions. It was obtained in a straightforward way by *N*-acetylating

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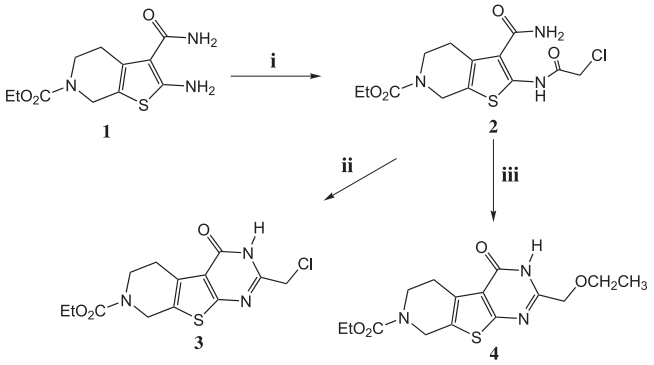
of the aminothiophene carboxamide **1** with chloroacetyl chloride and dehydration of the resulting chloroacetamide **2** under acid conditions. In order to block the exocyclic methylene group of the pyridothienopyrimidone system, the chloroacetamide **2** was cyclized in the presence of 2 equiv sodium ethoxide giving rise to the ethoxymethyl derivative **4**. (Scheme 1).



Scheme 1. Reagents and conditions: (i) $ClCH_2COCl$, CH_2Cl_2, rt, 2 h; (ii) TsOH, toluene, reflux, 24 h; (iii) Na, ethanol, reflux, 2 h.

N-Alkylation of compound **4** with propargyl bromide yielded the 3-propargylated product **5**. Although pyrimidine-4(3*H*)-ones are known to undergo alkylation predominantly at N3,[14] a few instances of N1 and O-alkylation have been reported.[15] Therefore, to confirm without doubt the position of propargyl group in compound **5**, an X-ray crystallographic study was carried out (Fig. 1). It indicated clearly that alkylation had proceeded at N3. Its NMR-data turned out useful for the assignment of other propargylation products (v.i.)

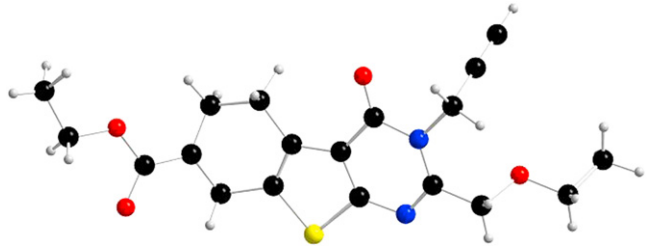
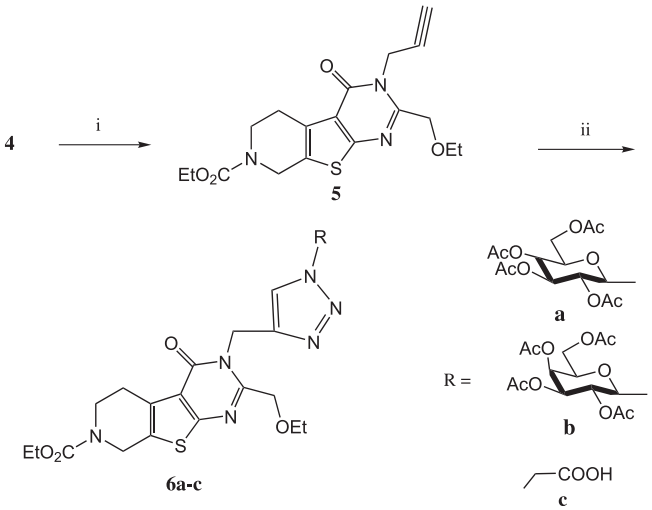


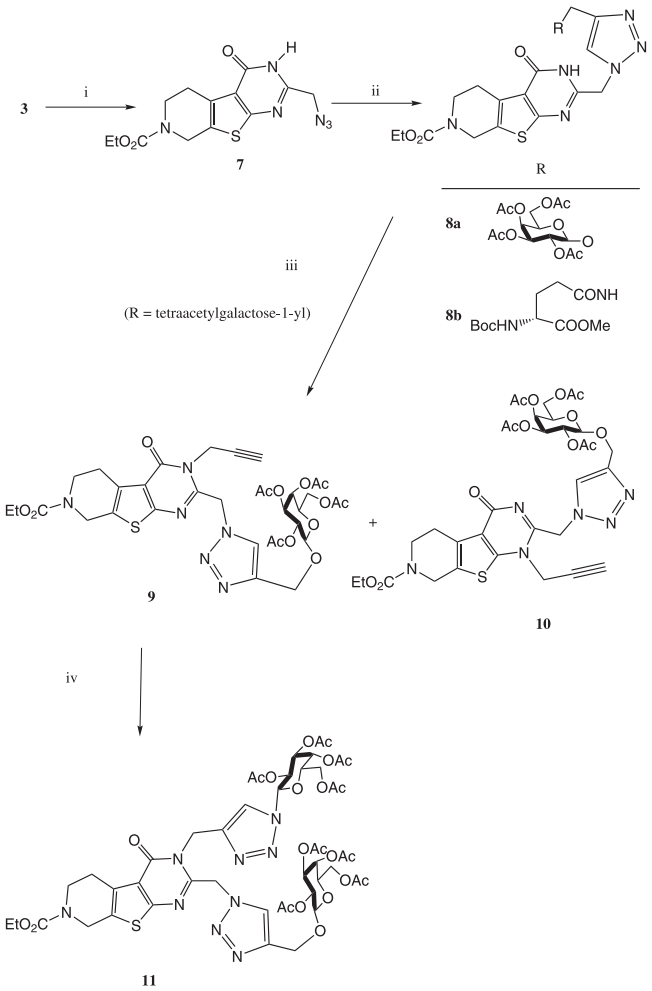
Figure 1. X-ray crystal analysis of the ethyl 2-(ethoxymethyl)-4-oxo-3-(2-propynyl)-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(4*H*)-carboxylate (**5**).

Under the broadly known reaction conditions ($CuSO_4$/sodium ascorbate, THF/H_2O (1:1)) for Cu-catalyzed alkyne/azide click (CuAAC) the cycloaddition of ethyl 2-(ethoxymethyl)-4-oxo-3-(2-propynyl)-3,5,6,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7(4*H*)-carboxylate (**5**) with 1-azido-1-deoxy-2,3,4,6-tetraacetyl-β-D-hexoses (glucose and galactose) and glycine-azide[16] provided excellent yields of the 1,2,3-triazolylmethyl products **6a–c** (Scheme 2).

Making use of the 2-chloromethyl-pyridothienopyrimidone **3** we sought to introduce azide as well as propargyl to enable tethering two different biomolecules to the pyridothienopyrimidone core by 1,2,3-triazoles. Thus, in the first step azide was introduced by nucleophilic displacement of chloride (Scheme 3). The resulting azidomethyl product **7** was submitted to Cu-catalyzed cycloaddition with peracetylated 1-propargylgalactose or *N*-Boc-protected methyl *N*′-propargyl glutamate[17] to introduce the first biomolecule. High yields of the corresponding 2-triazolylmethyl products **8a** and **8b** were obtained. It is worth mentioning that product **8b** represents an *N*-protected amino acid where the two functional groups (amino and carboxyl) are situated a rather long distance apart.



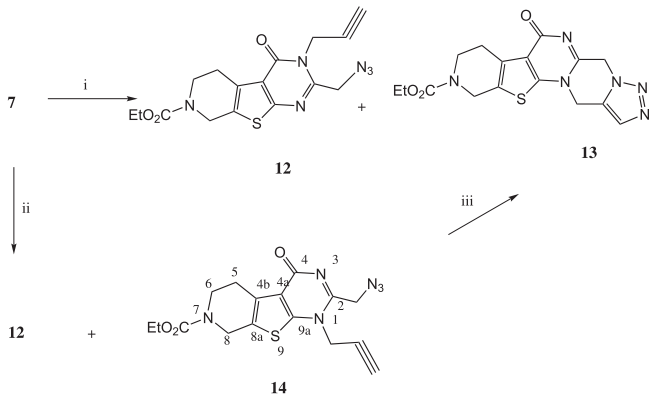
Scheme 2. Reagents and conditions: (i) propargyl bromide, DIPEA, DMF, 16 h, 60–70 °C; (ii) (a) 1-azido-1-deoxy-2,3,4,6-tetraacetyl-β-D-glucose; (b) 1-azido-1-deoxy-2,3,4,6-tetraacetyl-β-D-galactose or (c) glycine-azide, $CuSO_4$, Na-ascorbate, THF/H_2O (1:1), 1–2 days, rt.



Scheme 3. Reagents and conditions: (i) NaN_3, CH_3CN, 6 h, reflux; (ii) (a) propargyl tetra-*O*-acetyl-D-galactopyranoside or (b) *N*-Boc-protected methyl *N*′-propargyl glutamate, $CuSO_4$, Na-ascorbate, THF/H2O (1:1), 1–3 days, rt; (iii) propargyl bromide, DIPEA, DMF, 20 h, rt; (iv) 1-azido-1-deoxy-2,3,4,6-tetraacetyl-β-D-galactose, $CuSO_4$, Na-ascorbate, THF/H_2O (1:1), 24 h, rt.

When **8a** was further on propargylated under similar conditions as in the transformation of **4** into **5**, the propargyl group entered into position 3 as well as in position 1 to form regioisomeric products **9** and **10** in (2:1) ratio. The position of the propargyl group at the heterocyclic core was elucidated by ^{13}C NMR spectroscopy (δ=31 ppm and 54 ppm for HCC–*C*H$_2$ in **9** and **10**, respectively, as compared with δ=31 ppm for **5**) and also HMBC-investigations. In order to link galactose as second biomolecule to the pyridothienopyrimidone skeleton of the galactose derivative **9** a subsequent [3+2]-cycloaddition reaction with 1-azido-1-deoxy-2,3,4,6-tetraacetyl-β-D-galactose was performed providing the expected product **11** in high yield. This result demonstrates that the pyridothienopyrimidine core can serve as scaffold for two biomolecules.

Based on these results we turned our attention to apply a similar methodology to produce di-1,2,3-triazolylpyridothienopyrimidones in a one-step procedure by double [3+2]-cycloaddition. Thus the azido compound **7** was first propargylated applying the same conditions (heating in DMF/DIPEA 60–70 °C) as before in the synthesis of **5**, **9** and **10**. A mixture of products was obtained (Scheme 4). One compound was an expected propargylation product **12**. The other one turned out as already cyclized 1,2,3-triazole (formation of **13**, vide infra) where the azido function had reacted intramolecularily with the introduced propargyl moiety of the expected propargyl derivative of **7** by an uncatalyzed [3+2]-cycloaddition. Thus milder conditions (rt, 2 days) were applied in the propargylation of **7**. Indeed, no cyclization product was found under these conditions. However, a mixture of products was formed again which turned out to be regioisomeric N-propargylation products **12** and **14** in a ratio of 1:3. The structure assignment was possible by ^{13}C NMR spectroscopy. The 1-propargyl product **12** exhibited a propargyl signal at 31.6 ppm similar to the unambiguous structure **5** (see X-ray analysis) while in the isomer **14** this signal was found at 54 ppm. The latter structure was also confirmed by HMBC-investigations (coupling of propargyl-*C*H$_2$ with C-9a). At this point it can be stated that the regioselectivity of propargylation of pyridothienopyrimidones depends very much at the substitutent at the exocyclic methylene group in position 2. The ethoxy group governs the incoming propargyl group into position 3 (formation of **5**). Mixtures of regioisomers are formed when 1,2,3-triazole or azide is found at the exocyclic methylene group wherein the 3-propargylation or 1-propargylation product predominates, respectively (Fig. 2).



Scheme 4. Reagents and conditions: (i) propargyl bromide, DIPEA, DMF, 32 h, 60–70 °C; (ii) propargyl bromide, DIPEA, DMF, 2 days, rt; (iii) $CuSO_4$, Na-ascorbate, THF/H_2O (1:1), 24 h, rt.

The 1-propargyl, isomer **14** turned out to be strikingly prone to intramolecular [3+2]-cycloaddition giving the same cyclization product as obtained before when **7** was heated with propargyl bromide and DIPEA in DMF. Thus this pentacyclic product can be

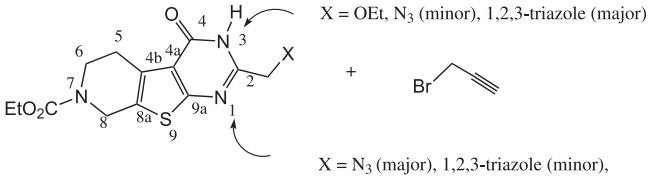


Figure 2. Regioselectivity of the propargylation at N1 and N3 of the pyrimidone moiety depending on the substituent X at the 2-methyl group.

assigned as the isomer **13** representing a novel type of condensed heterocycles. Unexpectedly, **14** did not only cyclize to **13** under heating in DMF but also during attempts to recrystallize it with methanol, and even after longer standing at rt in DMF or as a solid. Such a rt solid state [3+2]-cycloaddition seems to be a very rare case. Attempts to use the 1-propargyl-2-azidomethylpyridothienopyrimidone **14** in Cu-catalyzed [3+2]-cycloadditions with other azides or alkynes in an intermolecular way failed because the intramolecular reaction to **13** won in each case. Thus we tried to perform intermolecular Cu-catalyzed [3+2]-cycloadditions with the 3-propargyl isomer **12** and azides and alkynes. However, we could not obtain [3+2] cycloadducts but complex mixtures of products and starting materials. Remarkably, an intramolecular [3+2]-cycloaddition of the isomer **12** similar to the transformation of **14** into **13** did not occur even after prolonged heating in DMF. So far we do not have an explanation for the reluctance of the isomer **12** in [3+2]-cycloadditions. There is no doubt that both functional groups for [3+2]-cycloaddition, i.e., the alkyne as well as the azido function are present in **13** as could be proved by IR-spectroscopy (see Experimental section).

In conclusion, a straightforward way to tether carbohydrates or amino acids to tetrahydropyridothienopyrimidones via 1,2,3-triazole units was elaborated based on Cu-catalyzed [3+2]-cycloaddition of *N*-propargyl units or azidomethyl group with correspondingly functionalized partners. In the course of the introduction of the propargyl group an interesting dependence of the regioselectivity on the substituent found at the 2-methyl group of the pyrimidone ring was observed. By sequential [3+2]-cycloadditions it was possible to link two galactose moieties to the pyridothienopyrimidone skeleton. If a propargyl group was introduced into the 2-azidomethyl-substituted pyrimidone ring, two isomers were formed, one of them being extremely prone to intramolecular [3+2]-cycloaddition to a novel heterocyclic ring system consisting of five condensed heterocyclic rings. Remarkably this cycloaddition occurs also at rt in the solid state. All products obtained were hitherto unknown. A number of them are presently under pharmacological screening.

2.1. X-ray crystal analysis of compound 5[18]

Empirical formula: $C_{18}H_{21}N_3O_4S$, formula weight: 375.44 g/mol, temperature: 100(2) K, wavelength: 0.71073 Å, crystal system: monoclinic, space group: *P*21, unit cell dimensions: a=4.1780(2) Å, α=90°, b=27.8410(10) Å, β=97.528(3)°, c=7.6422(3) Å, V=90°, volume, 881.28(6) Å^3, Z=2, density (calculated): 1.407 Mg/m^3, absorption coefficient: 0.212 mm^{-1}, F(000): 394, crystal size: 0.50×0.40×0.35 mm, theta range for data collection: 2.69–29.14°, limiting indices: $-5\le h\le 5$, $-38\le k\le 38$, $-10\le l\le 10$; reflections collected/unique: 15,721/4760 [R(int.)=0.0382], completeness to θ=29.14 is 99.7%, absorption correction: none, max./min. transmission: 0.9296/0.9015, refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 4760/1/238, goodness-of-fit on F^2: 1.103, final R indices [$I>2\sigma(I)$]: $R1$=0.0356, $wR2$=0.0996, R indices (all data): $R1$=0.0361, $wR2$=0.1000, absolute structure

parameter: 0.03(6), extinction coefficient: 0.014(3), largest diff. peak and hole: 0.590 and −0.320 e/Å^3.

3. Experimental section[18]

3.1. General remarks

All reactions were carried out with oven-dried glassware. Solvents were dried and deoxygenated by standard procedure. Starting materials were purchased from Aldrich and Merck. Compounds **1**, alkynes and azides of biomolecules were synthesized, respectively, according to literature procedure.[13,16,17] TLC analysis was performed on Merck silica gel 60 F_{254} plates and visualized by UV illumination and by charring with phosphomolybdic acid, potassium permanganate or ninhydrin. Silica gel 60 (0.035–0.070 mm, Acros) was used for preparative column chromatography. Melting points were determined on a Boetius hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC-300 with TMS as internal standard. Elemental analyses were ascertained with a Euro EA analyser. High resolution mass spectra (ESI) were measured with a Thermo Finnigan LTQ-FT-ICR-MS with MeOH as solvent. Optical rotations were determined with a Perkin Elmer-241 polarimeter. IR-spectra were recorded on a Perkin Elmer FTIR spectrometer 1760 by ATR-technique on diamond.

3.2. Ethyl 3-(aminocarbonyl)-2-[(2-chloroacetyl)amino]-4,7-dihydrothieno[2,3-*c*]pyridine-6(5*H*)-carboxylate (2)

To a suspension of *o*-amino amide **1** (2.7 g, 10 mmol) in CH_2Cl_2 (30 mL) in ice bath, chloroacetyl chloride (3.4 g, 30 mmol) was added dropwise. The mixture was vigorously stirred at rt for 1–2 h, after which time TLC indicated complete transformation of the amine. The white precipitate was formed, filtered off, washed with ethanol, dried well and recrystallized from THF to afford pure acetylated product **2** (2.6 g, 7.6 mmol, 76%) as colourless crystals, mp 222–223 °C. ^{1}H NMR (DMSO-d_6): δ=1.23 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 2.83 (t, 2H, J=5.1 Hz, H-4), 3.62 (t, 2H, J=5.5 Hz, H-5), 4.11 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.52 (s, 4H, H-7, CH_2Cl), 6.90 (br s, 2H, NH_2), 12.18 (s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ=15.1 (CH_3), 25.5 (C-4), 41.1 (C-5), 42.9 (CH_2Cl), 42.9 (C-7), 61.5 (CH_2, carbamate), 117.4 (C-7a), 123.8 (C-3a), 128.7 (C-3), 142.5 (C-2), 155.1 (C=O, carbamate), 164.2 ($COCH_2Cl$), 167.2 (C=O, amide). Elemental analysis calcd for $C_{13}H_{16}ClN_3O_4S$ (345.80): C, 45.15; H, 4.66; Cl, 10.25; N, 12.15; S, 9.27. Found: C, 45.14; H, 4.69; Cl, 10.86; N, 12.02; S, 9.21. HRMS (ESI): m/z calcd. $C_{13}H_{17}ClN_3O_4S$ $[M+H]^+$: 346.0550, found: 346.0583.

3.3. Ethyl 2-(chloromethyl)-4-oxo-3,5,6,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7(4*H*)-carboxylate (3)

The amide **2** (3.45 g, 10 mmol) was suspended in toluene (100 mL) with 500 mg (30 mol %) of toluenesulfonic acid monohydrate and heated under reflux with a condenser equipped with a Dean and Stark trap for 20 h. The mixture was allowed to cool to ambient temperature then diluted with ethyl acetate (100 mL), washed with saturated aqueous sodium hydrogen carbonate (3×100 mL), brine (100 mL), dried ($MgSO_4$) then evaporated to dryness. Column chromatography purification gave the title compound **3**. Yield 2.8 g (8.7 mmol, 87%) as colourless crystals, mp 197 °C (decomp.), R_f=0.45 (EtOAc/cyclohexane, 7:3). ^{1}H NMR ($CDCl_3$): δ=1.34 (t, 3H, J=7.2 Hz, $COOCH_2CH_3$), 3.14 (t, 2H, J=5.6 Hz, H-5), 3.82 (t, 2H, J=5.4 Hz, H-6), 4.26 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.57 (s, 2H, CH_2Cl), 4.72 (s, 2H, H-8), 12.49 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 25.7 (C-5), 41.1 (C-6), 42.5 (C-8), 43.2 (CH_2-Cl), 61.9 (CH_2, carbamate), 111.0 (C-4a), 121.4 (C-8a), 130.7 (C-4b), 151.0 (C-9a), 155.6 (C=O, carbamate), 160.1 (C-2), 164.2 (C=O). Elemental analysis calcd for $C_{13}H_{14}ClN_3O_3S$ (327.79): C, 47.63; H, 4.30; Cl, 10.82; N, 12.82; S, 9.78. Found: C, 47.91; H, 4.27; Cl, 10.92; N, 12.61; S, 9.70. HRMS (ESI): m/z calcd $C_{13}H_{15}ClN_3O_3S$ $[M+H]^+$: 328.0444, found: 328.0462.

3.4. Ethyl 2-(ethoxymethyl)-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7(4*H*)-carboxylate (4)

N-Acetylated compound **2** (3.45 g, 10 mmol) was dissolved in 2 equiv sodium ethoxide solution (0.46 g Na, 20 mmol in 30 mL ethanol). The reaction mixture was refluxed for 2 h. The solvent was evaporated, water was added, and pH was adjusted to 1–2 by using 2 N HCl. The precipitate that formed was collected and recrystallized from methanol to give pale yellow crystals in (2.3 g, 7 mmol) 69% yield, mp 161–162 °C. ^{1}H NMR (DMSO-d_6): δ=1.17 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.23 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 2.96 (t, 2H, J=5.6 Hz, H-5), 3.57 (q, 2H, J=7.0 Hz, OCH_2CH_3), 3.68 (t, 2H, J=5.7 Hz, H-6), 4.12 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.34 (s, 2H, CH_2–O), 4.62 (s, 2H, H-8), 12.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ=15.0 (CH_3), 15.4 (CH_3), 25.8 (C-5), 41.2 (C-6), 43.3 (C-8), 61.6 (CH_2, carbamate), 66.5 (CH_2, ether), 69.8 (CH_2–O), 111.0 (C-4a), 121.3 (C-8a), 129.8 (C-4b), 139.7 (C-9a), 154.9 (C=O, carbamate), 158.6 (C-2), 163.6 (C=O). Elemental analysis calcd for $C_{15}H_{19}N_3O_4S$ (337.39): C, 53.40; H, 5.68; N, 12.45; S, 9.50. Found: C, 53.30; H, 5.62; N, 12.41; S, 9.18.

3.5. Ethyl 2-(azidomethyl)-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7(4*H*)-carboxylate (7)

A mixture of compound **3** (0.99 g, 3 mmol) and sodium azide (0.3 g, 4.5 mmol) was heated at reflux in acetonitrile (15 mL) for 6 h, during which time the mixture became a red homogeneous solution. After this time, the solvent was removed in vacuo. The mixture was re-dissolved in dichloromethane (30 mL), washed with water (2×20 mL), dried ($MgSO_4$), and evaporated to dryness to give the desired compound **7**, which was subjected to column chromatography yielding white solid product. Yield 0.94 g (2.8 mmol, 94%), mp 168 °C (decomp.), R_f=0.48 (EtOAc/cyclohexane, 8:2). ^{1}H NMR ($CDCl_3$): δ=1.34 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 3.12 (t, 2H, J=5.6 Hz, H-5), 3.81 (t, 2H, J=5.4 Hz, H-6), 4.26 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.50 (s, 2H, CH_2–N), 4.71 (s, 2H, H-8), 12.43 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 25.7 (C-5), 41.1 (C-6), 43.2 (C-8), 52.2 (CH_2–N), 61.9 (CH_2, carbamate), 112.8 (C-4a), 121.2 (C-8a), 130.1 (C-4b), 150.8 (C-9a), 155.5 (C=O, carbamate), 160.1 (C=O), 164.5 (C-2). HRMS (ESI): m/z calcd $C_{13}H_{15}N_6O_3S$ $[M+H]^+$: 335.0848, found: 335.0884.

3.6. Synthesis of 5, 9, 10, 12, 13 and 14 (general procedure)

Propargyl bromide (9 mmol) was added to a suspension of compound **4**, **7** or **8a** (3 mmol) and *i*-Pr_2NEt (9 mmol) in DMF (15 mL) and resulting mixture was stirred at 60–70 °C for 16–32 h. The solvent was evaporated to dryness in vacuo. The residue was diluted with water and then extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The obtained oily product was purified by column chromatography to yield the corresponding product.

3.7. Ethyl 2-(ethoxymethyl)-4-oxo-3-(2-propynyl)-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno-[2,3-*d*]pyrimidine-7(4*H*)-carboxylate (5)

The product was obtained, following the general procedure under heating for 16 h, as colourless crystals in (1.0 g, 2.7 mmol) 89% yield, mp 103–104 °C, R_f=0.53 (CH_3OH/CH_2Cl_2, 5:95). ^{1}H NMR ($CDCl_3$): δ=1.28 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.32 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 2.30 (t, 1H, J=2.5 Hz, C–CH), 3.16 (t, 2H, J=5.6 Hz, H-5), 3.64 (q, 2H, J=7.0 Hz, OCH_2CH_3), 3.78 (t, 2H, J=5.7 Hz, H-6), 4.23 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.68 (s, 2H, CH_2–O), 4.69 (s, 2H, H-8), 5.09 (d, 2H, J=2.5 Hz, CH_2–C). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 15.0 (CH_3), 25.5 (C-5), 31.6 (CH_2–C), 41.1 (C-6), 43.2 (C-8), 61.8 (CH_2, carbamate), 66.6 (CH_2, ether), 71.5 (CH_2–O), 72.3 (C–CH), 77.8 (C–CH), 111.0 (C-4a), 121.2 (C-8a), 130.3 (C-4b), 152.2 (C-9a), 155.5 (C=O, carbamate), 157.7 (C=O), 161.7 (C-2). Elemental analysis calcd for $C_{18}H_{21}N_3O_4S$ (375.44): C, 57.58; H, 5.64; N, 11.19; S, 8.54. Found: C, 57.62; H, 5.67; N, 11.09; S, 8.31. HRMS (ESI): m/z calcd $C_{18}H_{22}N_3O_4S$ $[M+H]^+$: 376.1252, found: 376.1285.

3.8. Ethyl 4-oxo-3-(2-propynyl)-2-((4-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)oxy-methyl]-1*H*-1,2,3-triazol-1-yl)methyl)-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno-[2,3-*d*]-pyrimidine-7(4*H*)-carboxylate (9)

The product **9** was obtained as a mixture with **10** (**9**/**10**=2:1), following the general procedure under stirring at r t for 2 days, as colourless oil in (1.5 g, 1.9 mmol) 64% yield, R_f=0.48 (EtOAc/cyclohexane, 8:2). ^{1}H NMR ($CDCl_3$): δ=1.28 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 1.97 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_3$), 2.42 (t, 1H, J=2.4 Hz, C–CH), 3.10 (t, 2H, J=5.5 Hz, H-5), 3.74 (t, 2H, J=5.7 Hz, H-6), 3.94 (dd, 1H, J_1=6.4 Hz, J_2=13.1 Hz, C_5H–CH_2–OCO), 4.17 (m, 4H, $COOCH_2CH_3$, C_5H–CH_2–OCO), 4.64 (d, 1H, J=8.0 Hz, CH_2–$N_{triazole}$), 4.68 (s, 2H, H-8), 4.84 (d, 1H, J=12.5 Hz, CH_2–$N_{triazole}$), 5,01 (m, 4H, C_2H, C_4H), 5,10 (d, 2H, J=1.9 Hz, $N_{pyrim.}$–CH_2–C), 5.22 (dd, 1H, J_1=2.5 Hz, J_2=10.4 Hz, C_3H), 5.39 (d, 1H, J=3.2 Hz, C_1H–O), 5.83 (s, 2H, CH_2–O), 7.77 (s, 1H, $CH_{ar\text{-}triazole}$). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 20.6, 20.7, 20.7, 20.8 ($4COCH_3$), 25.5 (C-5), 31.8 ($N_{pyrim.}$–CH_2–C), 41.0 (C-6), 43.2 (C-8), 52.3 (CH_2–O), 61.2 (CH_2–N), 61.8 (CH_2, carbamate), 62.8 (C_5H–CH_2–OCO), 67.0 (C_4H), 68.7 (C_2H), 70.8 (C_5H), 70.9 (C_3H), 76.9 (CH-C), 77.3 (CH–C), 100.4 (C_1H), 115.4 (C-4a), 121.2 (C-8a), 124.0 ($CH_{ar\text{-}triazole}$), 131.8 (C-4b), 149.0 ($CH_{q\text{-}triazole}$), 152.9 (C-9a), 156.9 (C=O, carbamate), 157.4 (C=O), 161.2 (C-2), 169.5, 170.1, 170.2, 170.4 ($4COCH_3$). HRMS (ESI): m/z calcd $C_{33}H_{39}N_6O_{13}S$ $[M+H]^+$: 759.2217, found: 759.2290.

3.9. Ethyl 4-oxo-1-(2-propynyl)-2-((4-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)oxy-methyl]-1*H*-1,2,3-triazol-1-yl)methyl)-1,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7(4*H*)-carboxylate (10)

The product was obtained in mixture with **9**, following the general procedure under stirring at rt for 2 days, as colourless oil in (0.7 g, 0.9 mmol, 31%) yield, R_f=0.63 (EtOAc/cyclohexane, 8:2). ^{1}H NMR ($CDCl_3$): δ=1.30 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 1.96 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.57 (t, 1H, J=2.4 Hz, C–CH), 3.10 (t, 2H, J=5.5 Hz, H-5), 3.82 (t, 2H, J=5.7 Hz, H-6), 3.97 (dd, 1H, J_1=6.4 Hz, J_2=13.1 Hz, C_5H–CH_2–OCO), 4.24 (m, 4H, $COOCH_2CH_3$, C_5H–CH–OCO), 4.68 (d, 1H, J=8.0 Hz, CH_2–$N_{triazole}$), 4.74 (s, 2H, H-8), 4.87 (d, 1H, J=12.5 Hz, CH_2–$N_{triazole}$), 5.05 (m, 4H, C_2H, C_4H, $N_{pyrim.}$–CH_2–C), 5.25 (dd, 1H, J_1=2.5 Hz, J_2=10.4 Hz, C_3H), 5.41 (d, 1H, J=3.2 Hz, C_1H–O), 5.75 (s, 2H, CH_2–O), 7.85 (s, 1H, $CH_{ar\text{-}triazole}$). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 20.6, 20.7, 20.7, 20.8 ($4COCH_3$), 25.9 (C-5), 41.0 (C-6), 43.4 (C-8), 54.3 ($N_{pyrim.}$–CH_2–C), 55.4 (CH–O), 61.3 (CH_2–N), 61.9 (CH_2, carbamate), 62.9 (C_5H–CH_2–OCO), 67.1 (C_4H), 68.7 (C_2H), 70.8 (C_5H), 70.9 (C_3H), 75.6 (CH–C), 83.6 (CH-C), 100.1 (C_1H), 117.2 (C-4a), 120.0 (C-8a), 124.1 ($CH_{ar\text{-}triazole}$), 136.2 (C-4b), 144.2 ($CH_{q\text{-}triazole}$), 147.9 (C-9a), 157.2 (C=O, carbamate), 162.7 (C-2), 168.2 (C=O), 169.5, 170.1, 170.3, 170.4 ($4COCH_3$). HRMS (ESI): m/z calcd $C_{33}H_{39}N_6O_{13}S$ $[M+H]^+$: 759.2217, found: 759.2290.

3.10. Ethyl 2-(azidomethyl)-4-oxo-3-(2-propynyl)-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(4*H*)-carboxylate (12)

The product was obtained, in a mixture with compound **14** (**14**/**12**=3:1) following the general procedure under stirring at rt for 3 days, as colourless oil in 20% yield, R_f=0.61 (EtOAc/cyclohexane, 4:6). ^{1}H NMR ($CDCl_3$): δ=1.32 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 2.36 (t, 1H, J=2.5 Hz, C–CH), 3.14 (t, 2H, J=5.7 Hz, H-5), 3.78 (t, 2H, J=5.7 Hz, H-6), 4.20 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.58 (s, 2H, CH_2–N_3), 4.69 (s, 2H, H-8), 4.96 (d, 2H, J=2.5 Hz, CH_2–C). ^{13}C NMR ($CDCl_3$): δ=14.5 (CH_3), 26.7 (C-5), 31.5 (CH_2–C), 40.5 (C-6), 43.1 (C-8), 52.8 (CH_2–N_3), 61.7 (CH_2, carbamate), 73.1 (C–CH), 77.3 (C–CH), 116.4 (C-4a), 120.9 (C-8a), 130.4 (C-4b), 150.2 (C-9a), 155.4 (C=O, carbamate), 157.1 (C=O), 161.3 (C-2). IR (ATR on diamond): 2107 cm^{-1} (C≡C), 2164 (N_3). HRMS (ESI): m/z calcd $C_{16}H_{17}N_6O_3S$ $[M+H]^+$: 373.1005, found: 373.1033.

3.11. Ethyl 7-oxo-5,7,8,11-tetrahydro-14*H*-pyrido[4′,3′:4,5]thieno[3,2-*e*][1,2,3]triazolo[1′,5′:4,5]pyrazino[1,2-*a*]pyrimidine-10(9*H*)-carboxylate (13)

The product **13** was obtained, in a mixture with compound **12** (**13**/**12**=3:1) following the general procedure, under heating at 60–70 °C for 32 h, as yellow crystals in 47% yield, mp 215–216 °C, R_f=0.27 (EtOAc/cyclohexane, 8:2). ^{1}H NMR (DMSO-d_6): δ=1.23 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 2.96 (br s, 2H, H-5), 3.69 (br s, 2H, H-6), 4.13 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.64 (s, 2H, H-8), 5.28 (s, 2H, N–CH_2), 5.74 (s, 2H, CH_2-N), 7.87 (s, 1H, $CH_{ar\text{-}triazole}$). ^{13}C NMR (DMSO-d_6): δ=15.0 (CH_3), 25.8 (C-5), 38.5 (N–CH_2–C), 41.1 (C-6), 43.4 (C-8), 49.1 (CH_2-N), 61.7 (CH_2, carbamate), 110.0 (C-4a), 119.9 ($C_{q\text{-}triazole}$), 129.4 (C-8a), 129.8 (C-4b), 130.3 ($CH_{ar\text{-}triazole}$), 149.0 (C-9a), 155.2 (C=O, carbamate), 157.1 (C=O), 162.1 (C-2). Elemental analysis calcd for $C_{16}H_{16}N_6O_3S$ (372.40): C, 51.60; H, 4.33; N, 22.57; S, 8.61. Found: C, 51.49; H, 4.39; N, 21.99; S, 8.06. HRMS (ESI): m/z calcd $C_{16}H_{17}N_6O_3S$ $[M+H]^+$: 373.1005, found: 373.1044.

3.12. Ethyl 2-(azidomethyl)-4-oxo-1-(2-propynyl)-1,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno-[2,3-*d*]pyrimidine-7(4*H*)-carboxylate (14)

The product was obtained, following the general procedure under stirring at rt for 3 days, as colourless crystals in (0.68 g, 1.8 mmol) 61% yield, mp 211–212 °C. R_f=0.23 (EtOAc/cyclohexane, 4:6). ^{1}H NMR ($CDCl_3$): δ=1.34 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 2.55 (t, 1H, J=2.4 Hz, C–CH), 3.13 (t, 2H, J=5.6 Hz, H-5), 3.84 (t, 2H, J=5.7 Hz, H-6), 4.25 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 4.47 (s, 2H, CH_2–N_3), 4.76 (s, 2H, H-8), 5.18 (d, 2H, J=2.4 Hz, CH_2–C). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 25.8 (C-5), 40.7 (C-6), 43.5 (C-8), 54.4 (CH_2–C), 55.2 (CH_2-N_3), 61.8 (CH_2, carbamate), 75.4 (CH–C), 77.8 (CH–C), 116.9 (C-4a), 123.0 (C-8a), 127.2 (C-4b), 155.5 (C-9a), 159.6 (C=O, carbamate), 162.7 (C-2), 168.5 (C=O). Elemental analysis calcd for $C_{16}H_{16}N_6O_3S$ (372.40): C, 51.60; H, 4.33; N, 22.57; S, 8.61. Found: C, 51.89; H, 4.34; N, 22.07; S, 8.38. HRMS (ESI): m/z calcd $C_{16}H_{17}N_6O_3S$ $[M+H]^+$: 373.1005, found: 373.1033.

3.13. Synthesis of 6a–c, 8a,b and 11 (general procedure)

Azido compound (1.0 mmol) was added to the alkyne substrate (1.0 mmol), in THF/H_2O (1:1) (25 mL), then sodium ascorbate (0.4 mmol) and $CuSO_4 \cdot 5H_2O$ (0.2 mmol) were added. After

sonication, the mixture was stirred at rt for the specified time. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Column chromatography purification gave the clicked product.

*3.13.1. Ethyl 2-(ethoxymethyl)-3-[(1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methyl]-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (**6a**).* The product was obtained, following the general procedure under stirring at rt for 3 days as colourless crystals in (0.68 g, 0.91 mmol) 91% yield, mp 98–99 °C, $[\alpha]_D^{22}$ −35.6 (*c* 1, $CHCl_3$), R_f=0.42 (CH_2Cl_2/CH_3OH, 96:4). ^{1}H NMR ($CDCl_3$): δ=1.27 (t, 3H, *J*=7.1 Hz, OCH_2CH), 1.30 (t, 3H, *J*=7.1 Hz, $COOCH_2CH_3$), 1.83 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 3.16 (t, 2H, *J*=5.2 Hz, H-5), 3.71 (q, 2H, *J*=7.0 Hz, OCH_2CH_3), 3.79 (t, 2H, *J*=5.5 Hz, H-6), 4.00 (ddd, 1H, J_1=2.1 Hz, J_2=4.8 Hz, J_3=10.1 Hz, C_5H–CH_2–OCO), 4.14 (dd, 1H, J_1=2.1 Hz, J_2=12.6 Hz, C_5H–CH_2–OCO), 4.23 (q, 2H, *J*=7.1 Hz, $COOCH_2CH_3$), 4.31 (dd, 1H, J_1=4.8 Hz, J_2=12.7 Hz, C_5H–CH_2–OCO), 4.69 (s, 2H, H-8), 4.78 (d, 1H, *J*=12.0 Hz, CH_2–$C_{triazole}$), 4.94 (d, 1H, *J*=12.0 Hz, CH_2–$C_{triazole}$), 5.26 (m, 1H, C_3H), 5.41 (m, 2H, C_2H, C_4H), 5.55 (s, 2H, $CH_{2\text{-ether}}$), 5.83 (dd, 1H, J_1=2.7 Hz, J_2=6.6 Hz, C_1H–$N_{triazole}$), 7.94 (s, 1H, $CH_{ar\text{-}triazole}$). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 15.1 (CH_3), 20.1, 20.5, 20.7, 20.8 ($4COCH_3$), 25.5 (C-5), 37.6 (CH_2–C), 40.9 (C-6), 43.2 (C-8), 61.5 (C_5H–CH_2–OCO), 61.8 (CH_2, carbamate), 66.9 (OCH_2CH_3), 67.6 (C_3H), 70.4 (C_4H), 71.6 (CH_2–O), 72.6 (C_2H), 75.2 (C_5H), 85.8 (C_1H–$N_{triazole}$), 120.0 (C-4a), 121.1 (C-8a), 122.7 ($CH_{ar\text{-}triazole}$), 129.0 (C-4b), 145.7 ($C_{q\text{-}triazole}$), 153.2 (C-9a), 155.5 (C=O, carbamate), 158.3 (C=O), 161.9 (C-2), 168.7, 169.3, 169.9, 170.5 ($4COCH_3$). Elemental analysis calcd for $C_{32}H_{40}N_6O_{13}S$ (748.76): C, 51.33; H, 5.38; N, 11.22; S, 4.28. Found: C, 51.15; H, 5.43; N, 10.89; S, 4.17.

*3.13.2. Ethyl 2-(ethoxymethyl)-3-[(1-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl)methyl]-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (**6b**).* The product was obtained, following the general procedure under stirring at rt for 2 days, as colourless crystals in (0.7 g, 0.94 mmol, 94%) yield, mp 95–96 °C, $[\alpha]_D^{22}$ −10.1 (*c* 1, $CHCl_3$), R_f=0.41 (CH_2Cl_2/CH_3OH, 96:4). ^{1}H NMR ($CDCl_3$): δ=1.27 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 1.30 (t, 3H, *J*=7.1 Hz, $COOCH_2CH_3$), 1.84 (s, 3H, $COCH_3$), 2.00 (s, 3H, COCH), 2.04 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$), 3.15 (t, 2H, *J*=5.2 Hz, H-5), 3.73 (q, 2H, *J*=7.0 Hz, OCH_2CH_3), 3.77 (t, 2H, *J*=5.5 Hz, H-6), 4.23 (m, 5H, $COOCH_2CH_3$, C_5H–CH_2–OCO, C_5H–CH_2–OCO), 4.68 (s, 2H, H-8), 4.77 (d, 1H, *J*=11.9 Hz, CH_2–$C_{triazole}$), 5.03 (d, 1H, *J*=12.1 Hz, CH_2–$C_{triazole}$), 5.25 (dd, 1H, J_1=3.4 Hz, J_2=10.3 Hz, C_3H), 5.53 (m, 2H, C_2H, C_4H), 5.57 (s, 2H, $CH_{2\text{-ether}}$), 5.80 (d, 1H, *J*=9.2 Hz, C_1H–$N_{triazole}$), 8.01 (s, 1H, $CH_{ar\text{-}triazole}$). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 15.1 (CH_3), 20.2, 20.5, 20.6, 20.8 ($4COCH_3$), 25.6 (C-5), 37.6 (CH_2-C), 40.6 (C-6), 43.2 (C-8), 61.2 (C_5H–CH_2–OCO), 61.8 (CH_2, carbamate), 66.7 (C_4H), 67.9 (C_2H), 68.0 (OCH_2CH_3), 70.7 (C_3H), 71.6 (CH_2–O), 74.1 (C_5H), 86.4 (C_1H–$N_{triazole}$), 120.1 (C-4a), 121.1 (C-8a), 122.7 ($CH_{ar\text{-}triazole}$), 131.1 (C-4b), 144.8 ($C_{q\text{-}triazole}$), 152.9 (C-9a), 158.4(C=O, carbamate), 160.5 (C=O), 161.9 (C-2), 168.9, 169.8, 170.1, 170.3 ($4COCH_3$). Elemental analysis calcd for $C_{32}H_{40}N_6O_{13}S$ (748.76): C, 51.33; H, 5.38; N, 11.22; S, 4.28. Found: C, 51.18; H, 5.36; N, 10.90; S, 4.18.

*3.13.3. 2-(4-([7-(Ethoxycarbonyl)-2-(ethoxymethyl)-4-oxo-5,6,7,8-tetrahydropyrido[4′,3′:4,5]-thieno[2,3-d]pyrimidin-3(4H)-yl]methyl)-1H-1,2,3-triazol-1-yl)acetic acid (**6c**).* The product was obtained, following the general procedure under stirring at rt for 2 days, as colourless crystals in (0.41 g, 0.86 mmol) 86% yield, mp 218–219 °C, R_f=0.18 (CH_2Cl_2/CH_3OH, 92:8). ^{1}H NMR (DMSO-d_6): δ=1.16 (t, 3H, *J*=7.0 Hz, OCH_2CH_3), 1.22 (t, 3H, *J*=7.1 Hz, $COOCH_2CH_3$), 2.94 (t, 2H, *J*=5.6 Hz, H-5), 3.59 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 3.65 (t, 2H, *J*=5.5 Hz, H-6), 4.20 (q, 2H, *J*=7.1 Hz, $COOCH_2CH_3$), 4.68 (s, 2H, CH_2O), 4.74 (s, 2H, H-8), 4.79 (s, 2H, $N_{\text{-triazole}}$–CH_2), 5.39 (s, 2H, $N_{\text{-pyrim.}}$–CH_2), 7.93 (s, 1H, $CH_{ar.}$). ^{13}C NMR (DMSO-d_6): δ=15.0 (CH_3), 15.3 (CH_3), 25.8 (C-5), 38.0 (CH_2–$C_{triazole}$), 40.6 (C-6), 43.4 (C-8), 53.7 ($N_{\text{-triazole}}$–CH_2), 61.6 (CH_2, carbamate), 66.4 (OCH_2), 71.1 (CH_2–O), 103.4 (C-4a), 120.7 (C-8a), 125.3 ($CH_{ar.}$), 130.0 (C-4b), 133.1 ($C_{q\text{-triazole}}$), 142.0 (C-9a), 154.0 (C=O, carbamate), 155.2 (C=O), 157.8 (C-2), 161.6 (COOH). HRMS (ESI): *m*/*z* calcd $C_{20}H_{24}N_6O_6S$ $[M-H]^-$: 475.1428, found: 475.1405.

*3.13.4. Ethyl 4-oxo-2-((4-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxymethyl]-1H-1,2,3-triazol-1-yl)methyl)-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (**8a**).* The product was obtained, following the general procedure under stirring at rt for 24 h, as white needles in (0.63 g, 0.87 mmol, 87%) yield, mp 122–123 °C, $[\alpha]_D^{22}$ −18.2 (*c* 1, $CHCl_3$), R_f=0.23 (CH_2Cl_2/CH_3OH, 97:3). ^{1}H NMR ($CDCl_3$): δ=1.31 (t, 3H, *J*=7.1 Hz, $COOCH_2CH_3$), 1.98 (s, 6H, $2COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 3.12 (t, 2H, *J*=5.2 Hz, H-5), 3.79 (t, 2H, *J*=5.6 Hz, H-6), 3.99 (ddd, 1H, J_1=5.8 Hz, J_2=6.7 Hz, J_3=13.0 Hz, C_5H–CH_2–OCO), 4.23 (m, 4H, $COOCH_2CH_3$, C_5H–CH_2–OCO), 4.67 (d, 1H, *J*=8.0 Hz, CH_2–$N_{triazole}$), 4.69 (s, 2H, H-8), 4.87 (d, 1H, *J*=12.5 Hz, CH_2–$N_{triazole}$), 5.05 (m, 2H, C_2H, C_4H), 5.25 (dd, 1H, J_1=2.5 Hz, J_2=9.4 Hz, C_3H), 5.39 (d, 1H, *J*=2.7 Hz, C_1H–O), 5.63 (s, 2H, CH_2–O), 7.86 (s, 1H, $CH_{ar\text{-}triazole}$), 12.47 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 20.6, 20.7, 20.7, 20.8 ($4COCH_3$), 25.6 (C-5), 41.0 (C-6), 43.2 (C-8), 51.9 (CH_2–N), 61.3 (CH_2–O), 61.9 (CH_2, carbamate), 62.9 (C_5H–CH_2–OCO), 67.1 (C_4H), 68.8 (C_2H), 70.8 (C_5H), 70.9 (C_3H), 77.3 (C_1H), 100.5 ($CH_{ar\text{-}triazole}$), 115.1 (C-4a), 121.6 (C-8a), 136.2 (C-4b), 148.8 ($C_{q\text{-}triazole}$), 155.6 (C-9a), 158.0 (C=O, carbamate), 159.6 (C=O), 163.9 (C-2), 169.6, 170.1, 170.2, 170.5 ($4COCH_3$). Elemental analysis calcd for $C_{30}H_{36}N_6O_{13}S$ (720.7): C, 50.00; H, 5.03; N, 11.66; S, 4.45. Found: C, 49.46; H, 5.05; N, 11.08; S, 4.38. HRMS (ESI): *m*/*z* calcd $C_{30}H_{37}N_6O_{13}S$ $[M+H]^+$: 721.2061, found: 721.2134.

*3.13.5. (2S)-2-[(tert-Butoxycarbonyl)amino]-5-([(1-([7-(ethoxycarbonyl)-4-oxo-3,4,5,6,7,8-hexa-hydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-2-yl]methyl)-1H-1,2,3-triazol-4-yl)methyl]-amino)-5-oxopentanoic acid (**8b**).* The product was obtained, following the general procedure under stirring at rt for 24 h, as colourless crystals in (0.45 g, 0.71 mmol, 71%) yield, mp 207–208 °C, $[\alpha]_D^{22}$ −1.7 (*c* 1, CH_3OH), R_f=0.28 (EtOAc/cyclohexane, 8:2). ^{1}H NMR (DMSO-d_6): δ=1.22 (t, 3H, *J*=7.1 Hz, $COOCH_2CH_3$), 1.36 (s, 9H, $C(CH_3)_3$), 1.77 (m, 1H, CH–CH_2–$CH_{2\text{-glu.}}$), 1.97 (m, 1H, CH–CH_2–$CH_{2\text{-glu.}}$), 2.20 (dd, 2H, J_1=6.1 Hz, J_2=13.6 Hz, CH–CH_2–$CH_{2\text{-glu}}$), 2.93 (t, 2H, *J*=5.6 Hz, H-5), 3.61 (s, 3H, $COOCH_3$), 3.65 (t, 2H, *J*=5.9 Hz, H-6), 3.99 (m, 1H, $CH_{\text{-glu}}$), 4.11 (q, 2H, *J*=7.0 Hz, $COOCH_2CH_3$), 4.32 (dd, 2H, J_1=7.0 Hz, J_2=11.9 Hz, NH–CH_2), 4.61 (s, 2H, H-8), 5.56 (s, 2H, CH_2–N), 7.24 (d, 1H, *J*=7.6 Hz, *NH*-Boc), 8.00 (s, 1H, $CH_{\text{-ar-triazole}}$), 8.37 (s, 1H, *NH*–CH_2), 12.36 (s, 1H, $NH_{pyrim.}$). ^{13}C NMR (DMSO-d_6): δ=15.0 (CH_3), 25.6 (C-5), 27.0 (CH–CH_2–$CH_{2\text{-glu.}}$), 28.6 ($C(CH_3)_3$), 31.9 (CH–CH_2–$CH_{2\text{-glu.}}$), 34.6 (NH–CH_2), 40.1 (C-6), 43.3 (C-8), 51.1 (CH_2–N), 52.2 ($COOCH_3$), 53.5 (CH–CH_2–$CH_{2\text{-glu.}}$), 61.6 (CH_2, carbamate), 78.7 ($C(CH_3)_3$), 110.0 (C-4a), 121.3 (C-8a), 124.7 ($CH_{\text{-ar.}}$), 129.8 (C-4b), 133.7 ($C_{q\text{-triazole}}$), 136.7 (C-9a), 151.1 (C=O, Boc), 156.0 (C=O), 158.6 (C=O, carbamate), 163.9 (C-2), 171.7 (NHCO), 173.4 ($COOCH_3$). Elemental analysis calcd for $C_{27}H_{36}N_8O_8S$ (632.69): C, 51.26; H, 5.74; N, 17.71; S, 5.07. Found: C, 50.23; H, 5.76; N, 16.82; S, 5.62. HRMS (ESI): *m*/*z* calcd $C_{27}H_{37}N_8O_8S$ $[M+H]^+$: 633.2450, found: 633.2444.

*3.13.6. Ethyl 4-oxo-2-((4-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxymethyl]-1H-1,2,3-triazol-1-yl)methyl)-3-[(1-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl)methyl]-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (**11**).* The product was obtained, following the general procedure under stirring at rt for 2 days, as colourless oil in (0.92 g,

0.81 mmol) 81% yield, $[\alpha]_D^{22}$ −19.0 (*c* 1, $CHCl_3$), R_f=0.37 (EtOAc/cyclohexane, 8:2). ^1H NMR ($CDCl_3$): δ=1.26 (t, 3H, *J*=7.1 Hz, $COOCH_2CH_3$), 1.84 (s, 3H, $COCH_3$), 1.93 (s, 3H, $COCH_3$), 1.94 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.20 (s, 3H, $COCH_3$), 3.07 (t, 2H, *J*=5.5 Hz, H-5), 3.71 (t, 2H, *J*=5.7 Hz, H-6), 3.92 (dd, 1H, J_1=6.45 Hz, J_2=13.7 Hz, C_5H–CH_2–OCO), 4.19 (m, 7H, C_5H–CH_2–OCO, $COOCH_2CH_3$, $2C_5H$–CH_2–OCO), 4.67 (m, 3H, H-8, C_1H–O), 4.80–5.01 (m, 3H, $C_{\text{-triazole}}$–CH_2–O, C_3H), 5.23 (m, 2H, C_2H, C_4H), 5.58 (m, 5H, CH_2–C_{triazole}, C_2H, C_4H, C_3H), 5.79 (dd, 1H, *J*=9.3 Hz, C_1H–N), 5.98 (d, 1H, *J*=15.8 Hz, CH_2–N_{triazole}), 6.19 (d, 1H, *J*=15.8 Hz, CH_2–N_{triazole}), 7.75 (s, 1H, $CH_{\text{ar-triazole}}$), 8.01 (s, 1H, $CH_{\text{ar-triazole}}$). ^{13}C NMR ($CDCl_3$): δ=14.7 (CH_3), 20.3, 20.5, 20.6, 20.7, 20.7, 20.7, 20.8, 20.8 (8×$COCH_3$), 25.5 (C-5), 37.7 (CH_2–C_{triazole}), 41.0 (C-6), 43.2 (C-8), 52.7 (CH_2–N_{triazole}), 61.2, 61.3 ($2C_5H$–CH_2–OCO), 61.8 (CH_2, carbamate), 62.7 ($C_{\text{-triazole}}$–CH_2–O), 66.1 (C_4H), 66.7 (C_3H), 68.1 (C_2H), 68.7 (C_4H), 70.6 (C_2H), 70.9 (C_5H), 74.2 (C_5H), 86.4 (C_1H), 100.3 (C_1H), 121.1 (C-4a), 122.9 ($CH_{\text{ar-triazole}}$), 124.1 ($CH_{\text{ar-triazole}}$), 130.2 (C-8a), 132.4 (C-4b), 142.7, 144.7 (2×$C_{\text{q-triazoles}}$), 149.7 (C-9a), 156.7 (C═O, carbamate), 157.7 (C═O), 161.6 (C-2), 169.1, 169.5, 169.8, 170.0, 170.1, 170.2, 170.3, 170.4 (8×$COCH_3$). HRMS (ESI): *m*/*z* calcd $C_{47}H_{58}N_9O_{22}S$ $[M+H]^+$: 1132.3339, found: 1132.3412.

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References and notes

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