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Synthesis of coumarin–nucleoside conjugates via Huisgen 1,3-dipolar cycloaddition

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Abstract—An efficient synthesis of fluorescent coumarin–nucleoside conjugates via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition is described. Starting from azidonucleosides and coumarin derivatives, products are obtained in good yields. The fluorescent properties of the newly prepared coumarin–nucleoside conjugates are determined.

1. Introduction

Covalent linking of two molecular entities for preparing new bioconjugates with desirable properties is a great challenge for chemists. Bioconjugates, biomolecules bearing unnatural organic structures, have found during the past two decades an increasing number of applications in molecular and cell biology.[1] Conjugated groups provide biomolecules with novel properties, such as fluorescence emission, catalytic activity, altered hydrophobicity or bioaffinity, resistance towards biodegradation or the ability to carry metal ions.

One of the most powerful linking reactions for developing an expanding set of new structures is Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition,[2–9] the formation of 1,4-disubstituted 1,2,3-triazoles from azides and terminal alkynes. This reaction is unique due to its complete specificity, biocompatibility of the reactants and high degree of dependability. Cu(I) catalysed or the so-called Huisgen–Sharpless 1,3-dipolar cycloaddition is premiere example of a click reaction[10–13] employed in a wide range of applications, including modification of cell surfaces,[14] specific labelling of virus particles,[15] proteins,[16] oligonucleotides[17] and the synthesis of new glycoproteins,[8] neoglycoconjugates,[18] dendrimers[6] or fluorescent labels.[19,20]

A very promising area for the preparation of new bioconjugates is the synthesis of azidonucleosides. The first azidonucleoside (5′-azido-5′-deoxyuridine) was prepared by Horwitz et al.[21] by azidation reaction of 5′-tosylnucleoside and lithium azide. In general, azidoanalogs have been used mostly as intermediates in the preparation of aminonucleosides. But finding that 3′-azido-3′-deoxythymidine (AZT), as an inhibitor of HIV reverse transcriptase,[22] is an efficient therapeutic agent has triggered explosive developments in the synthetic chemistry of azidonucleosides. Many azidonucleosides exhibit cytotoxic and antiviral properties[23] and are convenient photoaffinity probes.[24]

Coumarin derivatives are widely used as fluorescent probes, labels and pigments,[25–28] laser dyes[29–34] and signalling units in sensors.[35,36] They are also attractive molecules due to their extended spectral range, high emission quantum yields, photostability and good solubility in safe solvents.[37]

Here, we report on the efficient synthesis of fluorescent triazole linked coumarin–nucleoside conjugates via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition. The spectral characteristics of new conjugates and the corresponding coumarin derivatives will be compared.

2. Results and discussion

Huisgen–Sharpless 1,3-dipolar cycloaddition to form 1,4-disubstituted triazole bridges is a very popular and unique reaction for the preparation of bioconjugates. The stereospecific reaction gives very high yields and generates inoffensive byproducts only. The triazole bridge serves as a rigid linking unit that places the carbon atom, attached to the 4-position of 1,2,3-triazole ring, at a distance of 5.0 Å

Keywords: Huisgen 1,3-dipolar cycloaddition; Bioconjugate; Nucleoside; Coumarin; Fluorescent probe.
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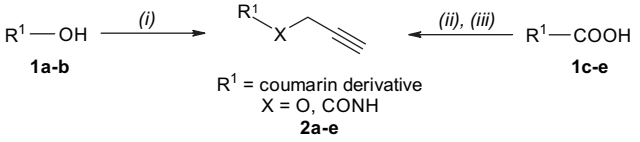
from N1. It cannot be cleaved hydrolytically or otherwise and is almost impossible to oxidise or reduce.

We prepared novel coumarin–nucleoside conjugates by Huisgen–Sharpless 1,3-dipolar cycloaddition. Our key substrates for this reaction were coumarin derivatives with terminal alkyne function and azidonucleosides. Most of the coumarin derivatives are commercially available[25] and have very good fluorescent properties. Among them 7-hydroxycoumarin derivatives **1a–b** are the most often used due their fluorescent quantum yields. Coumarin-4-acetic acids **1c–e** were synthesised in our laboratory in the scope of new coumarins studies. Further functionalization of basic coumarin skeleton of **1a–e** was necessary, and the coumarin derivatives with terminal alkynes **2a–e** (Scheme 1) were prepared. The synthesis of prop-2-yn-1-yloxy derivatives **2a–b** was achieved via an established method.[38] Reaction of 7-hydroxycoumarins **1a–b** with propargylbromide gives products **2a–b** in excellent yields. The synthesis of *N*-(prop-2-yn-1-yl)acetamide derivatives **2c–e** was achieved via a method common to the peptide synthesis.[39–41] The carboxylic acid was activated by 1-hydroxybenzotriazole (HOBt) in the presence of dicyclohexylcarbodiimide (DCC) as a coupling agent. Further reaction of the reactive intermediates with propargylamine led to acetamides **2c–e**. Although, the conversion of substrates **1c–e** was almost quantitative in all the cases (Table 1), the lengthy separation of products from contaminating dicyclohexylurea (DCU) lowered the yields. As simple filtration of DCU was not sufficient, the isolated yields of the corresponding products were between 62 and 78%.



Scheme 1. Preparation of coumarin derivatives with terminal alkyne functionality. Reaction conditions: (i) 1.0 molar equiv K_2CO_3, 1.0 molar equiv propargylbromide, abs acetone; (ii) 1.0 molar equiv HOBt, 2.0 molar equiv DCC, abs dioxane; (iii) 1.0 molar equiv propargylamine.

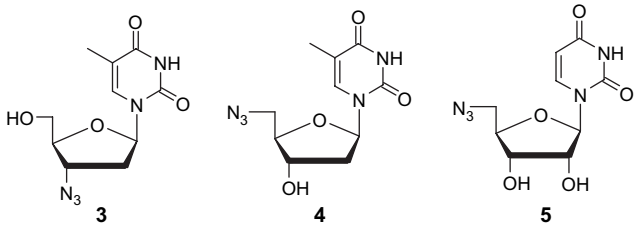
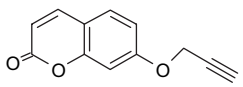
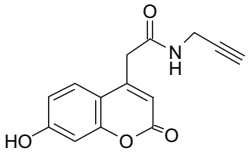
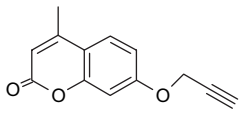
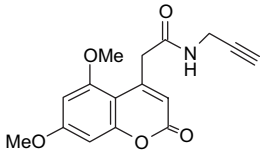
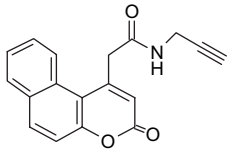


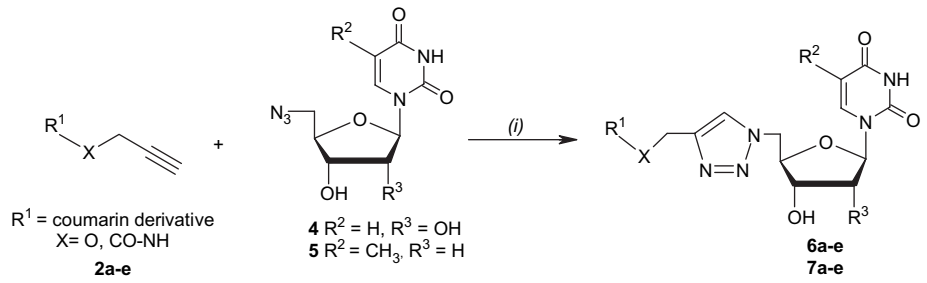
Figure 1. Azidonucleosides for coumarin–nucleoside conjugates preparation.

Azidonucleosides are our key substrates for the synthesis of new coumarin–nucleoside conjugates via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition. They are available by several methods;[23] however, azidation reactions are usually efficient and afford products in good yields. We prepared azidonucleoside **3** (Fig. 1) via Mitsunobu type reaction,[42] along with azidonucleosides **4** and **5** (Fig. 1) from 5′-tosylated intermediates.[43]

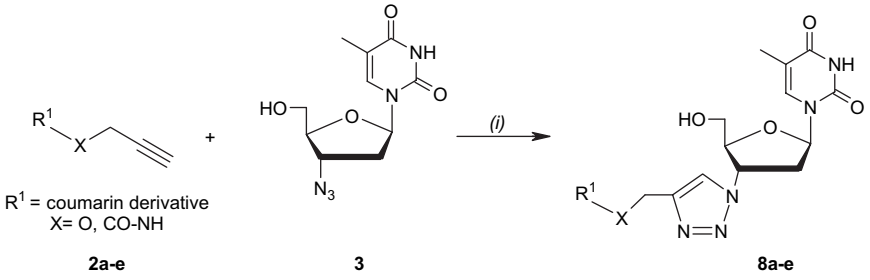
We chose Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition as a simple and efficient method for the synthesis of our tailored bioconjugates possessing the desired properties. Starting from azidonucleosides **3–5** and coumarin derivatives **2a–e**, with interesting fluorescent properties, we obtained the conjugates in good yields. The reaction is regioselective only in the presence of Cu(I) salts as a catalyst, to give the desired 1,4-disubstituted triazole bridge. In the literature Cu(I) catalysed Huisgen cycloaddition was studied using various (1–30%, in most cases 5%) concentrations of $CuSO_4$ in the presence of sodium ascorbate.[5–9,20,44–46] Using 0.05 molar equiv of catalyst in our preliminary experiments, we observed incomplete reaction even after 72 h. Our analogous experiments with different Cu(I) sources—CuI in the presence of DIPEA,[3] did not improve the conversion, but reactions were not optimised. The best results we obtained using 0.15 molar equiv of $CuSO_4 \cdot 5H_2O$ in aqueous *tert*-BuOH (Schemes 2 and 3). The reaction was complete after 6–7 h in the case of substrates **2a–b**. We used 0.15 molar equiv of catalyst also for substrates **2c–e**, but the

Table 1. Isolated yields of coumarin derivatives **2a–e** with terminal alkyne functionality

	Functionalized coumarin derivative	Yield (%)		Functionalized coumarin derivative	Yield (%)
2a		95	**2c**		62
2b		93	**2d**		69
			2e		78



Scheme 2. Preparation of 5′-triazole bridged nucleoside conjugates via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition. Reaction conditions: (i) 0.15 molar equiv $CuSO_4 \cdot 5H_2O$, 0.30 molar equiv sodium ascorbate, *tert*-BuOH/H_2O=1/1 (v/v).



Scheme 3. Preparation of 3′-triazole bridged nucleoside conjugates via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition. Reaction conditions: (i) 0.15 molar equiv $CuSO_4 \cdot 5H_2O$, 0.30 molar equiv sodium ascorbate, *tert*-BuOH/H_2O=1/1 (v/v).

reactions were slower (12–16 h) in comparison with **2a–b**. Higher concentrations of catalyst (0.30 molar equiv) accelerated the reaction, but the work-up of reaction mixture was more complicated. The conversion of all the reactions was almost quantitative and isolated yields of the products are summarised in the Table 2. As detected by TLC and confirmed by ^{1}H NMR, minor byproducts 7-hydroxycoumarin **1a** and 7-hydroxy-4-methylcoumarin **1b** were formed along with the desired products **6a–b**, **7a–b** and **8a–b**. We suppose that under the influence of Cu(I) polarisation of the C–O bond between the coumarin and propargyl group causes the fragmentation of **2a–b** to **1a–b**. Our isolated yields were in the range 81–89%. Derivatives **6c–e**, **7c–e** and **8c–e** were isolated in 69–87% yields, due to less straightforward separation of the products from the reaction mixture. Emulsions were created during the ethyl acetate washings, with polar products in both phases. Initially products were purified most effectively by chromatography on silica. Later, we realised that simple filtration and subsequent chromatography of crude reaction mixture was the most convenient procedure.

Table 2. Isolated yields and characteristics of prepared conjugates **6a–e** to **8a–e**

Compd[a]	Yield (%)	Mp (°C)	λ_{abs} (nm)	ε ($cm^{-1}\,M^{-1}$)	λ_{ems} (nm)	FI (A.U.)
1a	—	—	325	14,509	392	748
6a	83	137–142	320	9552	388	183
7a	85	249–253	319	10,761	381	178
8a	89	188–192	320	14,076	385	143
1b	—	—	322	15,552	387	1530
6b	81	226–230	319	3725	381	379
7b	86	267–272	321	10,398	387	451
8b	88	154–157	319	12,903	381	389
1c	—	—	326	12,487	392	1955
6c[b]	69	231–235	326	4274	395	1930
7c	75	260–263	326	6923	396	2394
8c	79	187–191	326	7196	397	2214
1d	—	—	323	3032	418	2260
6d	78	189[c]	323	2028	427	1471
7d[b]	81	193–197	323	9260	428	2453
8d	82	200[c]	322	7590	429	2524
1e	—	—	318/349	7444	417	719/930
6e	83	247–251	319/350	7764	417	869/1080
7e	87	178–179	319/350	5315	419	822/952
8e	74	183–185	319/350	6108	419	785/881

[a] $c=10^{-4}$ M in methanol.
[b] $c=0.5\times10^{-4}$ M in methanol.
[c] Compound decomposed.

The structure of isolated products **6a–e**, **7a–e** and **8a–e** (Fig. 2), determined by ^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{13}C–^{1}H, HSQC and ^{13}C–^{1}H HMBC measurements, confirmed only the expected regioisomer. Only one characteristic signal for the triazole hydrogen was observed. The spectral

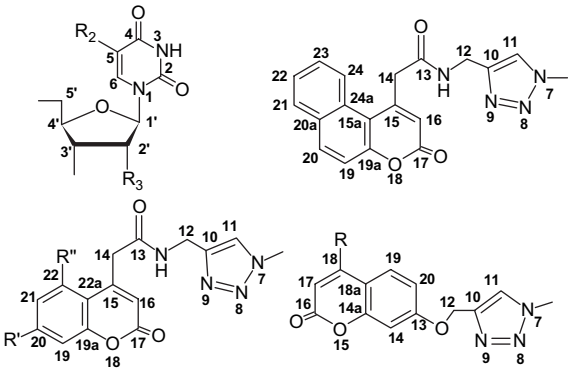


Figure 2. Designation of atoms for interpretation of NMR data.

characteristics of the isolated products are summarised in Table 2. We found that all newly prepared conjugates display only one peak in the fluorescence spectrum in methanol. The process of conjugation did not cause a shift in the absorption and fluorescence maxima of our compounds in comparison with maxima of **1a**–**e**. The fluorescence intensity of conjugates depends on the position of coumarin modification. We observed only slight changes in fluorescence intensity in the series of coumarin-4-acetic acid derivatives (**6c**–**e**, **7c**–**e** and **8c**–**e**). In contrast, the coumarin C7-hydroxy group modification (**6a**–**b**, **7a**–**b** and **8a**–**b**) caused decrease in intensity in comparison with the intensity of the corresponding unmodified coumarins **1a**–**b**.

3. Conclusion

New coumarin–nucleoside conjugates were prepared via Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition. This smooth and convenient reaction combines the fluorescent coumarin and biospecific nucleoside to the new molecule with promising fluorescent properties. Products were obtained in good yields and their spectral characteristics were determined. Work is in progress to extend this flexible approach for the preparation of different types of bioconjugates, including oligonucleotides, and substrates for enzyme assays.

4. Experimental

4.1. General methods

Solvents were distilled and dried via established methods.[47] Melting points were measured on a Kofer hot stage and are uncorrected. NMR spectra were recorded in $CDCl_3$ and DMSO with Varian VX UNITY spectrometer (300 MHz/75 MHz for $^1H/^{13}C$). Chemical shifts are referenced to Me_4Si (^1H) or the residual solvent signal (^{13}C). All measurements were carried out at room temperature. The ^1H and ^{13}C assignments were based on ^1H–^1H COSY, ^{13}C–^1H HSQC and ^{13}C–^1H HMBC experiments. Infrared spectra were obtained on Perkin–Elmer Spectrum GX FT-IR spectrometer with ATR sampling accessory. Absorption spectra were recorded using UV–Vis spectrophotometer Agilent 8453, cuvette length 1 cm. Fluorescence spectra were recorded using Hitachi F-2000. TLC was performed on precoated plates of silica gel 60 F_{254} (Merck) using chloroform/methanol (9/1) as eluent. The crude products were purified using column chromatography on silica gel using chloroform/methanol (9/1) as eluent. 3′-Azido-3′-deoxythymidine[42] **3**, 5′-azido-5′-deoxyuridine[43] **4** and 5′-azido-5′-deoxythymidine[43] **5** were prepared as described in the literature. CAUTION: the handling of low-molecular weight azides is dangerous, due to their potential explosive character. Neat azidonucleosides must not be heated and all the reactions should be carried out on a small scale. 7-Hydroxy-2*H*-chromen-2-one (7-hydroxycoumarin) and 7-hydroxy-4-methyl-2*H*-chromen-2-one (7-hydroxy-4-methylcoumarin) were obtained from Aldrich and 2-(2-oxo-2*H*-chromen-4-yl)-acetic acids were prepared as described in the literature.[48] Propargylamine and propargylbromide (80% solution in toluene) were obtained from Across Organics. Stock solution of sodium ascorbate (100 mg/mL) was prepared from 1.00 g (5.68 mmol) of ascorbic acid (Across Organics) to which 11.25 mL of distilled water and 0.48 g (5.68 mmol) of sodium bicarbonate were added.

4.2. General procedure A

To a solution of coumarins **1a**,**b** in dry acetone, anhydrous potassium carbonate (1.0 molar equiv) and propargylbromide (1.0 molar equiv) were added. The resultant mixture was stirred at 50 °C for 18 h, then the mixture was cooled and the solvent was removed under reduced pressure. The residue was treated with 15 mL of water and extracted with ethyl acetate. The combined organic phases were washed with water, dried over anhydrous sodium sulfate and evaporated in vacuum. The crude product was purified by crystallisation from ethyl acetate/hexane mixture.

4.2.1. 7-(Prop-2-yn-1-yloxy)-2*H*-chromen-2-one (2a). Light yellow solid product, 586 mg (2.93 mmol, 95%), mp=118–120 °C (lit.[49] 119 °C). ^1H NMR (DMSO): 8.01 (1H, d, J_{3-4}=9.4 Hz, H-4), 7.66 (1H, d, J_{5-6}=8.6 Hz, H-5), 7.06 (1H, d, J_{6-8}=2.5 Hz, H-8), 7.00 (1H, dd, J_{5-6}=8.6 Hz, J_{6-8}=2.5 Hz, H-6), 6.33 (1H, d, J_{3-4}=9.4 Hz, H-3), 4.94 (2H, d, J_{9-11}=2.3 Hz, H-9), 3.67 (1H, t, J_{9-11}=2.3 Hz, H-11); ^{13}C NMR (DMSO): 160.19 (2), 160.18 (7), 155.13 (8a), 144.24 (4), 129.53 (5), 112.98 (3), 112.86 (4a), 112.83 (6), 101.78 (8), 78.94 (10), 78.52 (11), 56.11 (9).

4.2.2. 4-Methyl-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one (2b). Light yellow solid product, 565 mg (2.64 mmol, 93%), mp=130–134 °C (lit.[49] 134 °C). ^1H NMR ($CDCl_3$): 7.51 (1H, dd, J_{4-5}=7.5 Hz, H-4), 6.93 (1H, d, J_{5-6}=2.6 Hz, H-6), 6.91 (1H, dd, J_{4-5}=7.5 Hz, J_{5-6}=2.6 Hz, H-5), 6.15 (1H, d, $J_{3\text{-Me}}$=1.2 Hz, H-3), 4.75 (2H, d, J_{9-11}=2.3 Hz, H-9), 2.56 (1H, t, J_{9-11}=2.5 Hz, H-11), 2.39 (3H, d, $J_{3\text{-Me}}$=1.1 Hz, CH_3-4); ^{13}C NMR ($CDCl_3$): 161.34 (2), 160.36 (7), 155.08 (4), 152.40 (8a), 125.62 (5), 114.29 (4a), 112.75 (6), 112.47 (3), 102.17 (8), 76.50 (11), 56.17 (9), 18.70 (CH_3-4).

4.3. General procedure B

To a solution of 2-(2-oxo-2*H*-chromen-4-yl)acetic acids **1c**–**e** and 1-hydroxybenzotriazole (HOBt, 1.0 molar equiv) in dry dioxane, 1,3-dicyclohexylcarbodiimide (DCC, 2.0 molar equiv) in dry dioxane was added. The resultant mixture was stirred at room temperature for 4 h. Then propargylamine (1.0 molar equiv) was added and the mixture was stirred at room temperature for 5 h. The DCU byproduct was filtered off, the solvent was removed under reduced pressure and the crude product was purified by column chromatography.

4.3.1. 2-(7-Hydroxy-2-oxo-2*H*-chromen-4-yl)-*N*-(prop-2-yn-1-yl)acetamide (2c). White solid product, 362 mg (1.04 mmol, 62%), mp=249–253 °C. $C_{14}H_{11}NO_4$ (257.24), calculated: 65.37% C, 4.31% H, 5.44% N, 24.88% O; found: 65.22% C, 4.42% H, 5.53% N. ^1H NMR (DMSO): 8.67 (1H, t, J_{NH-11}=6.6 Hz, HN–CO), 7.57 (1H, t, J_{5-6}=8.8 Hz, H-5), 6.79 (1H, dd, J_{5-6}=8.8 Hz, J_{6-8}=2.2 Hz, H-6), 6.72 (1H, t, J_{6-8}=2.5 Hz, H-8), 6.17 (1H, s, H-3), 3.87 (1H, dd, $J_{11\text{-NH}}$=5.8 Hz, J_{11-13}=2.5 Hz, H-11), 3.66 (2H, s, H-9), 2.47 (1H, t, J_{11-13}=2.5 Hz, H-13); ^{13}C NMR (DMSO): 167.50 (10), 161.26 (2), 160.19 (7), 154.99 (4), 150.87 (8a), 126.66 (5),

112.92 (6), 111.70 (3), 111.35 (4a), 102.29 (8), 80.78 (12), 73.24 (13), 40.34 (9), 28.19 (11); IR (neat, cm^{-1}): 1694, 1622, 1609, 1565, 1326, 1143, 999, 740.

4.3.2. 2-(5,7-Dimethoxy-2-oxo-2*H*-chromen-4-yl)-*N*-(prop-2-yn-1-yl)acetamide (2d). Light yellow solid product, 237 mg (0.79 mmol, 69%), mp=108–111 °C. $C_{16}H_{15}NO_5$ (301.29), calculated: 63.78% C, 5.02% H, 4.65% N, 26.55% O; found: 63.54% C, 4.93% H, 4.58% N. ^{1}H NMR (DMSO): 8.31 (1H, t, $J_{NH\text{-}11}$=5.8 Hz, HN–CO), 6.60 (1H, d, $J_{6–8}$=2.2 Hz, H-6), 6.45 (1H, d, $J_{6–8}$=2.2 Hz, H-8), 6.09 (1H, s, H-3), 3.87 (1H, dd, $J_{11\text{-}NH}$=5.8 Hz, $J_{11–13}$=2.5 Hz, H-11), 3.71 (2H, s, H-9), 3.11 (1H, t, $J_{11–13}$=2.5 Hz, H-13); ^{13}C NMR (DMSO): 168.48 (10), 162.71 (7), 159.79 (2), 158.32 (5), 156.32 (4), 150.74 (8a), 113.36 (3), 103.71 (4a), 95.41 (8), 93.62 (6), 81.32 (12), 72.80 (13), 56.12 (CH_3O-5), 55.92 (CH_3O-7), 42.68 (9), 27.87 (11); IR (neat, cm^{-1}): 1731, 1626, 1611, 1310, 1259, 1081, 1016, 795.

4.3.3. 2-(3-Oxo-3*H*-benzo[*f*]chromen-1-yl)-*N*-(prop-2-yn-1-yl)acetamide (2e). White solid product, 443 mg (1.52 mmol, 78%), mp=185–189 °C. $C_{18}H_{13}NO_3$ (291.3), calculated: 74.22% C, 4.50% H, 4.81% N, 16.48% O; found: 74.38% C, 4.34% H, 4.53% N. ^{1}H NMR (DMSO): 8.73 (1H, t, $J_{NH\text{-}13}$=5.2 Hz, HN–CO), 8.38 (1H, d, $J_{7–8}$=7.9 Hz, H-7), 8.20 (1H, d, $J_{9–10}$=9.3 Hz, H-9), 8.07 (1H, dd, $J_{6–7}$=7.4 Hz, $J_{7–8}$=1.7 Hz, H-7), 7.66 (1H, dd, $J_{5–6}$=7.1 Hz, $J_{6–7}$=1.9 Hz, H-6), 7.61 (1H, d, $J_{5–6}$=7.1 Hz, H-5), 7.59 (1H, d, $J_{9–10}$=8.8 Hz, H-10), 6.59 (1H, s, H-3), 4.21 (2H, s, H-11), 3.87 (1H, dd, $J_{13\text{-}NH}$=5.5 Hz, $J_{13–15}$=2.3 Hz, H-13), 3.12 (1H, t, $J_{13–15}$=2.5 Hz, H-15); ^{13}C NMR (DMSO): 167.92 (12), 159.22 (2), 154.22 (4), 151.35 (10a), 133.90 (9), 130.88 (5a), 129.60 (8), 129.08 (8a), 128.04 (6), 125.49 (7), 124.61 (5), 118.05 (10), 117.51 (3), 113.80 (4a), 80.79 (15), 73.13 (14), 43.42 (11), 28.12 (13); IR (neat, cm^{-1}): 1703, 1625, 1573, 1311, 1260, 1087, 1018, 798.

4.4. General procedure C

To a solution of compounds **2a–e** in *tert*-BuOH/H_2O 1/1 (v/v), $CuSO_4 \cdot 5H_2O$ (0.15 molar equiv) and sodium ascorbate (0.30 molar equiv) were added. The mixture was stirred at room temperature for 15 min. Then nucleoside (**3**, **4** or **5**, 1.0 molar equiv) was added and the resulting reaction mixture was stirred at room temperature until the starting material was consumed as judged by TLC. Then the reaction mixture was washed with ethyl acetate, the combined organic phases were washed with water, dried over anhydrous sodium sulfate and evaporated in vacuum. The crude product was purified by column chromatography and crystallised from ethyl acetate/hexane mixture.

4.4.1. 5′-{4-[(2-Oxo-2*H*-chromen-7-yloxy)methyl]-1*H*-1,2,3-triazol-1-yl}uridine (6a). White solid product, 144 mg (0.31 mmol, 83%), mp=137–142 °C. $C_{21}H_{19}N_5O_8$ (469.1), calculated: 53.73% C, 4.08% H, 14.92% N, 27.27% O; found: 53.38% C, 3.95% H, 14.74% N. ^{1}H NMR (DMSO): 11.37 (1H, s, H-3), 8.26 (1H, s, H-11), 7.99 (1H, d, $J_{17–18}$=9.7 Hz, H-18), 7.64 (1H, d, $J_{19–20}$=8.6 Hz, H-19), 7.53 (1H, d, $J_{5–6}$=8.1 Hz, H-6), 7.17 (1H, d, $J_{14–20}$=2.5 Hz, H-14), 7.02 (1H, dd, $J_{19–20}$=8.6 Hz, $J_{14–20}$=2.5 Hz, H-20), 6.30 (1H, d, $J_{17–18}$=9.5 Hz, H-17), 5.75 (1H, d, $J_{1′–2′}$=5.5 Hz, H-1′), 5.63 (1H, d, $J_{5–6}$=8.1 Hz, H-5), 5.53 (1H, d, $J_{2′\text{-}OH}$=5.5 Hz, OH-2′), 5.41 (1H, d, $J_{3′\text{-}OH}$=5.0 Hz, OH-3′), 5.26 (2H, s, H-12), 4.79–4.64 (2H, m, H-5′), 4.16 (1H, m, H-4′), 4.10 (1H, m, H-2′), 3.99 (1H, m, H-3′); ^{13}C NMR (DMSO): 163.0 (4), 161.2 (16), 160.3 (13), 156.3 (14a), 150.6 (2), 144.3 (18), 141.9 (10), 141.1 (6), 129.5 (19), 125.7 (11), 112.9 (20), 112.6 (18a), 102.2 (14), 101.6 (5), 88.8 (1′), 81.7 (4′), 72.1 (2′), 70.6 (3′), 61.6 (12), 51.3 (5′); IR (neat, cm^{-1}): 1689, 1612, 1260, 1079, 1019, 795.

4.4.2. 5′-{4-[(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)methyl]-1*H*-1,2,3-triazol-1-yl}uridine (6b). White solid product, 160 mg (0.33 mmol, 81%), mp=226–230 °C. $C_{22}H_{21}N_5O_8$ (483.1), calculated: 54.66% C, 4.38% H, 14.49% N, 26.48% O; found: 54.45% C, 4.63% H, 14.67% N. ^{1}H NMR (DMSO): 8.26 (1H, s, H-11), 7.69 (1H, d, $J_{19–20}$=8.8 Hz, H-19), 7.53 (1H, d, $J_{5–6}$=8.0 Hz, H-6), 7.15 (1H, d, $J_{14–20}$=2.5 Hz, H-14), 7.04 (1H, dd, $J_{14–20}$=2.5 Hz, $J_{19–20}$=8.8 Hz, H-20), 6.23 (1H, d, $J_{17\text{-}Me}$=1.4 Hz, H-17), 5.75 (1H, d, $J_{1′–2′}$=5.2 Hz, H-1′), 5.63 (1H, d, $J_{5–6}$=8.0 Hz, H-5), 5.54 (1H, d, $J_{2′\text{-}OH}$=5.5 Hz, OH-2′), 5.42 (1H, d, $J_{3′\text{-}OH}$=5.5 Hz, OH-3′), 5.26 (2H, s, H-12), 4.80–4.65 (2H, m, H-5′), 4.17 (1H, m, H-4′), 4.10 (1H, m, H-2′), 4.00 (1H, m, H-3′), 2.40 (3H, s, CH_3-18); ^{13}C NMR (DMSO): 162.98 (4), 161.03 (16), 160.14 (13), 154.66 (18), 153.43 (14a), 150.63 (2), 142.01 (10), 141.09 (6), 126.51 (19), 125.70 (11), 113.37 (19a), 112.58 (17), 111.31 (20), 102.10 (14), 101.56 (5), 88.78 (1′), 81.71 (4′), 72.06 (2′), 70.56 (3′), 61.56 (12), 51.32 (5′); IR (neat, cm^{-1}): 1730, 1652, 1621, 1555, 1430, 1287, 1138, 1056, 835, 753.

4.4.3. 5′-{4-[2-(7-Hydroxy-2-oxo-2*H*-chromen-4-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}uridine (6c). Light yellow product, 120 mg (0.23 mmol, 69%), mp=231–235 °C. $C_{23}H_{22}N_6O_9$ (526.1), calculated: 52.47% C, 4.21% H, 15.96% N, 27.35% O; found: 52.19% C, 4.52% H, 16.21% N. ^{1}H NMR (DMSO): 11.38 (1H, s, H-3), 10.55 (1H, s, HO-21), 8.72 (1H, t, $J_{NH\text{-}12}$=5.5 Hz, HN–C=O), 7.91 (1H, s, H-11), 7.57 (1H, d, $J_{21–22}$=8.8 Hz, H-22), 7.52 (1H, d, $J_{5–6}$=8.2 Hz, H-6), 6.77 (1H, dd, $J_{21–22}$=8.8 Hz, $J_{19–21}$=2.2 Hz, H-21), 6.71 (1H, d, $J_{19–21}$=2.2 Hz, H-19), 6.17 (1H, s, H-16), 5.74 (1H, d, $J_{1′–2′}$=5.5 Hz, H-1′), 5.65 (1H, d, $J_{5–6}$=8.0 Hz, H-5), 5.53 (1H, d, $J_{2′\text{-}OH}$=5.5 Hz, OH-2′), 5.40 (1H, d, $J_{3′\text{-}OH}$=5.5 Hz, OH-3′), 4.73–4.58 (2H, m, H-5′), 4.32 (2H, d, $J_{12\text{-}NH}$=5.5 Hz, H-12), 4.12 (1H, m, H-4′), 4.07 (1H, m, H-2′), 3.96 (1H, m, H-3′), 3.67 (2H, s, H-14); ^{13}C NMR (DMSO): 168.30 (13), 163.66 (4), 161.82 (17), 160.89 (20), 155.66 (15), 151.73 (19a), 151.30 (2), 145.06 (10), 141.72 (6), 127.41 (22), 113.54 (19), 112.44 (16), 112.15 (22a), 102.94 (19), 102.78 (5), 89.41 (1′), 82.40 (4′), 72.73 (2′), 71.20 (3′), 51.84 (5′), 39.00 (14), 35.05 (12); IR (neat, cm^{-1}): 1707, 1673, 1605, 1389, 1262, 1096, 1079, 1053, 857, 818, 740.

4.4.4. 5′-{4-[2-(5,7-Dimethoxy-2-oxo-2*H*-chromen-4-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}uridine (6d). Light yellow product, 76 mg (0.13 mmol, 78%), mp=189 °C–decomposed. $C_{25}H_{26}N_6O_{10}$ (570.2), calculated: 52.63% C, 4.59% H, 14.73% N, 28.04% O; found: 52.37% C, 4.74% H, 14.39% N. ^{1}H NMR (DMSO): 11.40 (1H, s, H-3), 8.40 (1H, t, $J_{12\text{-}NH}$=5.4 Hz, HN–C=O), 7.88 (1H, s,

H-11), 7.56 (1H, d, J_{5-6}=8.2 Hz, H-6), 6.58 (1H, d, J_{19-21}= 2.3 Hz, H-21), 6.39 (1H, d, J_{19-21}=2.3 Hz, H-19), 6.07 (1H, s, H-16), 5.74 (1H, d, $J_{1'-2'}$=5.4 Hz, H-1′), 5.65 (1H, d, J_{5-6}=8.1 Hz, H-5), 5.55 (1H, d, $J_{2'\text{-OH}}$=5.6 Hz, HO-2′), 5.42 (1H, d, $J_{3'\text{-OH}}$=5.3 Hz, HO-3′), 4.74–4.57 (2H, m, H-5′), 4.30 (2H, d, $J_{12\text{-NH}}$=5.4 Hz, H-12), 4.13 (1H, m, H-4′), 4.07 (1H, m, H-2′), 3.96 (1H, m, H-3′), 3.84 (3H, s, CH_3O-22), 3.71 (2H, s, H-14), 3.59 (3H, s, CH_3O-20); ^{13}C NMR (DMSO): 168.71 (13), 163.06 (4), 162.72 (17), 159.87 (20), 158.37 (22), 156.34 (15), 151.04 (19a), 150.69 (2), 144.85 (10), 141.18 (6), 123.80 (11), 113.36 (16), 103.80 (22a), 102.15 (5), 95.33 (19), 93.62 (21), 88.83 (1′), 81.84 (4′), 72.14 (3′), 70.58 (2’), 55.96 (CH_3O-22), 55.82 (CH_3O-20), 51.27 (5′), 42.82 (14), 34.15 (12); IR (neat, cm^{-1}): 1707, 1673, 1605, 1389, 1262, 1096, 1079, 1053, 857, 818, 740.

4.4.5. 5′-{4-[2-(3-Oxo-3*H*-benzo[*f*]chromen-1-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}uridine (6e). Yellow solid product, 130 mg (0.23 mmol, 83%), mp=249–253 °C. $C_{27}H_{24}N_6O_8$ (560.5), calculated: 57.86% C, 4.32% H, 14.99% N, 22.84% O; found: 57.59% C, 4.12% H, 14.57% N. ^{1}H NMR (DMSO): 11.38 (1H, s, H-3), 8.80 (1H, t, $J_{12\text{-NH}}$=5.5 Hz, HN–C=O), 8.35 (1H, d, J_{21-22}= 8.8 Hz, H-21), 8.20 (1H, d, J_{19-20}=9.1 Hz, H-20), 8.05 (1H, d, J_{23-24}=8.0 Hz, H-24), 7.74 (1H, s, H-11), 7.59 (1H, dd, H-23), 7.57 (1H, d, J_{19-20}=9.1 Hz, H-19), 7.53 (1H, dd, H-22), 7.52 (1H, d, J_{5-6}=8.0 Hz, H-6), 6.59 (1H, s, H-16), 5.74 (1H, d, $J_{1'-2'}$=5.2 Hz, H-1′), 5.64 (1H, d, J_{5-6}=8.0 Hz, H-5), 5.53 (1H, d, $J_{2'\text{-OH}}$=5.5 Hz, OH-2′), 5.41 (1H, d, $J_{3'\text{-OH}}$=5.5 Hz, OH-3′), 4.70–4.55 (2H, m, H-5′), 4.32 (2H, d, $J_{12\text{-NH}}$=5.2 Hz, H-12), 4.22 (1H, s, H-14), 4.12 (m, 1H, H-4′), 4.07 (1H, m, H-2′), 3.97 (1H, m, H-3′); ^{13}C NMR (DMSO): 168.11 (13), 163.07 (4), 159.34 (17), 154.27 (15), 151.56 (2), 150.68 (19a), 144.55 (10), 141.16 (6), 133.92 (20), 130.89 (20a), 129.61 (24a), 129.13 (24), 127.94 (22), 125.53 (23), 124.72 (21), 123.52 (11), 118.26 (16), 117.58 (15a), 113.92 (19), 102.18 (5), 88.67 (1′), 81.75 (4′), 72.15 (2′), 70.57 (3′), 51.27 (5′), 43.62 (14), 34.37 (12); IR (neat, cm^{-1}): 1698, 1674, 1623, 1542, 1457, 1271, 1221, 1112, 1017, 836, 772, 751.

4.4.6. 5′-{4-[(2-Oxo-2*H*-chromen-7-yloxy)methyl]-1*H*-1,2,3-triazol-1-yl}thymidine (7a). Light yellow solid product, 146 mg (0.31 mmol, 85%), mp=247–251 °C. $C_{22}H_{21}N_5O_7$ (467.1), calculated: 56.53% C, 4.53% H, 14.98% N, 23.96% O; found: 56.28% C, 4.42% H, 15.05% N. ^{1}H NMR (DMSO): 8.26 (1H, s, H-11), 8.00 (1H, d, J_{17-18}=9.6 Hz, H-18), 7.64 (1H, d, J_{19-20}=8.8 Hz, H-19), 7.36 (1H, d, $J_{6\text{-Me}}$=1.1 Hz, H-6), 7.16 (1H, d, J_{14-20}= 2.5 Hz, H-14), 7.01 (1H, dd, J_{19-20}=8.8 Hz, J_{14-20}= 2.2 Hz, H-20), 6.30 (1H, d, J_{17-18}=9.3 Hz, H-17), 6.17 (1H, t, $J_{1'-2'}$=6.8 Hz, H-1′), 5.52 (1H, d, $J_{3'\text{-OH}}$=4.4 Hz, HO-3′), 5.26 (2H, s, H-12), 4.78–4.61 (2H, m, H-5′), 4.29 (1H, m, H-3′), 4.09 (1H, m, H-4′), 2.23–2.06 (2H, m, H-2′), 1.79 (3H, d, $J_{6\text{-Me}}$=0.8 Hz, CH_3-5); ^{13}C NMR (DMSO): 164.32 (4), 161.78 (16), 160.92 (13), 155.97 (14a), 151.06 (2), 144.96 (18), 142.67 (10), 136.73 (6), 130.18 (19), 126.28 (11), 113.57 (20), 113.26 (18a), 111.72 (17), 110.56 (5), 102.23 (14), 84.73 (1′), 84.62 (3′), 71.45 (4′), 62.27 (12), 51.97 (5′), 38.54 (2′), 12.75 (CH_3-5); IR (neat, cm^{-1}): 1719, 1656, 1613, 1478, 1263, 1199, 1079, 1019, 859, 802, 651.

4.4.7. 5′-{4-[(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)methyl]-1*H*-1,2,3-triazol-1-yl}thymidine (7b). Light yellow solid product, 153 mg (0.32 mmol, 86%), mp=267–272 °C. $C_{23}H_{23}N_5O_7$ (481.5), calculated: 57.38% C, 4.82% H, 14.55% N, 23.26% O; found: 57.21% C, 4.93% H, 14.74% N. ^{1}H NMR (DMSO): 8.26 (1H, s, H-11), 7.68 (1H, d, J_{19-20}=8.6 Hz, H-19), 7.35 (1H, d, $J_{6\text{-Me}}$=1.1 Hz, H-6), 7.15 (1H, d, J_{14-20}=2.5 Hz, H-14), 7.03 (1H, dd, J_{19-20}=8.8 Hz, J_{14-20}=2.3 Hz, H-20), 6.22 (1H, d, $J_{17\text{-Me}}$= 1.1 Hz, H-17), 6.16 (1H, t, $J_{1'-2'}$=6.6 Hz, H-1′), 5.52 (1H, d, $J_{3'\text{-OH}}$=4.1 Hz, HO-3′), 5.26 (2H, s, H-12), 4.78–4.61 (2H, m, H-5′), 4.29 (1H, m, H-3′), 4.09 (1H, m, H-4′), 2.40 (3H, d, $J_{17\text{-Me}}$=1.1 Hz, CH_3-18), 2.39–2.13 (2H, m, H-2′), 1.79 (3H, d, $J_{6\text{-Me}}$=0.8 Hz, CH_3-5); ^{13}C NMR (DMSO): 163.47 (4), 160.83 (16), 159.94 (13), 154.47 (18), 153.23 (14a), 150.21 (2), 141.86 (10), 135.86 (6), 126.32 (19), 125.42 (11), 113.19 (18a), 112.43 (17), 111.13 (20), 109.70 (5), 101.42 (14), 83.88 C (1′), 83.77 (3′), 70.61 (4′), 61.41 (12), 51.12 (5′), 37.70 (2′), 17.97 (CH_3-18), 11.90 (CH_3-5); IR (neat, cm^{-1}): 1720, 1656, 1616, 1478, 1270, 1199, 1079, 1019, 840, 792.

4.4.8. 5′-{4-[2-(7-Hydroxy-2-oxo-2*H*-chromen-4-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}thymidine (7c). Light yellow solid product, 98 mg (0.19 mmol, 75%), mp=260–263 °C. $C_{24}H_{24}N_6O_8$ (524.2), calculated: 54.96% C, 4.61% H, 16.02% N, 24.40% O; found: 54.83% C, 4.74% H, 15.92% N. ^{1}H NMR (DMSO): 11.39 (1H, s, H-3), 10.64 (1H, s, HO-20), 8.79 (1H, t, $J_{12\text{-NH}}$=5.8 Hz, HN–C=O), 7.99 (1H, s, H-11), 7.63 (1H, d, J_{21-22}= 8.9 Hz, H-22), 7.44 (1H, d, $J_{6\text{-Me}}$=1.0 Hz, H-6), 6.82 (1H, dd, J_{21-22}=8.8 Hz, J_{19-21}=2.3 Hz, H-21), 6.77 (1H, d, J_{19-21}=2.3 Hz, H-19), 6.23 (1H, t, $J_{1'-2'}$=7.0 Hz, H-1′), 6.22 (1H, s, H-16), 5.57 (1H, s, HO-3′), 4.78–4.61 (2H, m, H-5′), 4.37 (2H, d, $J_{12\text{-NH}}$=5.6 Hz, H-12), 4.32 (1H, m, H-3′), 4.11 (1H, m, H-4′), 3.72 (2H, s, H-14), 2.26–2.17 (2H, m, H-2′), 1.85 (3H, d, $J_{6\text{-Me}}$=0.9 Hz, CH_3-5); ^{13}C NMR (DMSO): 168.05 (13), 164.1 (4), 161.60 (17), 160.66 (20), 155.40 (15), 151.50 (19a), 150.84 (2), 144.80 (10), 136.52 (6), 127.16 (22), 113.28 (19), 112.19 (16), 111.87 (22a), 110.31 (5), 102.69 (19), 84.45 (1′), 71.16 (3′), 51.61 (5′), 39.00 (14), 38.27 (2′), 34.81 (12), 12.52 (CH_3-5); IR (neat, cm^{-1}): 1703, 1683, 1611, 1397, 1260, 1079, 1056, 1020, 794, 668.

4.4.9. 5′-{4-[2-(5,7-Dimethoxy-2-oxo-2*H*-chromen-4-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}thymidine (7d). Light yellow solid product, 78 mg (0.14 mmol, 81%), mp=193–197 °C. $C_{26}H_{28}N_6O_9$ (568.2), calculated: 54.93% C, 4.96% H, 14.78% N, 25.33% O; found: 55.21% C, 4.87% H, 14.92% N. ^{1}H NMR (DMSO): 11.34 (1H, s, H-3), 8.39 (1H, t, $J_{12\text{-NH}}$=5.5 Hz, HN–C=O), 7.90 (1H, s, H-11), 7.40 (1H, d, $J_{6\text{-Me}}$=1.1 Hz, H-6), 6.58 (1H, d, J_{19-21}=2.5 Hz, H-21), 6.38 (1H, d, J_{19-21}=2.5 Hz, H-19), 6.16 (1H, t, $J_{1'-2'}$=7.1 Hz, H-1′), 6.07 (1H, s, H-16), 5.52 (1H, d, $J_{3'\text{-OH}}$=3.9 Hz, HO-3′), 4.73–4.54 (2H, m, H-5′), 4.30 (2H, $J_{12\text{-NH}}$=6.1 Hz, H-14), 4.26 (1H, m, H-3′), 4.06 (1H, m, H-4′), 3.83 (3H, s, CH_3O-22), 3.70 (2H, s, H-14), 3.58 (3H, s, CH_3O-20), 2.3–2.05 (2H, m, H-2′), 1.79 (3H, s, CH_3-5); ^{13}C NMR (DMSO): 168.57 (13), 163.64 (4), 162.64 (17), 159.72 (20), 158.72 (22), 156.29 (15), 150.94 (19a), 150.39 (2), 144.77 (10), 136.06 (6), 123.68 (11), 113.29 (16), 109.83 (5), 103.74 (22a), 95.31 (19), 93.54

(21), 84.09 (1′), 84.07 (4′), 70.78 (3′), 55.89 (CH_3O-22), 55.71 (CH_3O-20), 51.2 (5′), 42.77 (14), 37.89 (2′), 34.11 (12), 12.04 (CH_3-5); IR (neat, cm^{-1}): 1723, 1656, 1599, 1274, 1163, 1079, 1038, 794, 668.

4.4.10. 5′-{4-[2-(3-Oxo-3*H*-benzo[*f*]chromen-1-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}thymidine (7e). Light yellow solid product, 189 mg (0.34 mmol, 87%), mp=178–179 °C. $C_{28}H_{26}N_6O_7$ (558.2), calculated: 60.21% C, 4.69% H, 15.05% N, 20.05% O; found: 60.34% C, 4.81% H, 14.88% N. ^{1}H NMR (DMSO): 11.33 (1H, s, H-3), 8.82 (1H, t, $J_{12\text{-NH}}$=5.4 Hz, HN–C=O), 8.36 (1H, d, $J_{21–22}$=8.7 Hz, H-21), 8.19 (1H, d, $J_{19–20}$=8.9 Hz, H-20), 8.06 (1H, dd, $J_{23–24}$=7.9 Hz, $J_{22–24}$=1.5 Hz, H-24), 7.77 (1H, s, H-11), 7.58 (d, 1H, $J_{19–20}$=8.9 Hz, H-19), 7.56 (1H, dd, $J_{22–23}$=7.3 Hz, H-23), 7.50 (1H, dd, $J_{22–23}$=7.1 Hz, $J_{22–24}$=1.5 Hz, H-22), 7.39 (1H, d, $J_{6\text{-Me}}$=1.0 Hz, H-6), 6.58 (1H, s, H-16), 6.16 (1H, t, $J_{1′–2′}$=6.8 Hz, H-1′), 5.53 (1H, s, HO-3′), 4.71–4.50 (2H, m, H-5′), 4.32 (2H, d, $J_{12\text{-NH}}$=5.4 Hz, H-12), 4.26 (1H, m, H-3′), 4.22 (2H, s, H-14), 4.04 (1H, m, H-4′), 2.3–2.1 (2H, m, H-2′), 1.79 (3H, d, $J_{6\text{-Me}}$=0.9 Hz, CH_3-5); ^{13}C NMR (DMSO): 168.44 (13), 164.09 (4), 159.69 (17), 155.75 (15), 154.65 (2), 151.96 (19a), 144.89 (10), 136.58 (6), 134.28 (20), 131.28 (20a), 129.97 (21), 129.52 (24a), 128.30 (23), 125.87 (22), 125.13 (24), 123.88 (11), 118.60 (19), 117.95 (15a), 114.32 (16), 110.29 (5), 84.46 (1′), 71.18 (3′), 51.63 (5′), 43.98 (14), 38.33 (2′), 34.77 (12), 12.62 (CH_3-5); IR (neat, cm^{-1}): 1717, 1698, 1654, 1542, 1508, 1272, 1207, 1097, 1018, 1043, 812, 753.

4.4.11. 3′-{4-[(2-Oxo-2*H*-chromen-7-yloxy)methyl]-1*H*-1,2,3-triazol-1-yl}thymidine (8a). White solid product, 154 mg (0.33 mmol, 89%), mp=188–192 °C. $C_{22}H_{21}N_5O_7$ (467.1), calculated: 56.53% C, 4.53% H, 14.98% N, 23.96% O; found: 56.42% C, 4.29% H, 15.21% N. ^{1}H NMR (DMSO): 11.36 (1H, s, H-3), 8.48 (1H, s, H-11), 8.01 (1H, d, $J_{17–18}$=9.3 Hz, H-18), 7.82 (1H, d, $J_{6\text{-Me}}$=1.1 Hz, H-6), 7.66 (1H, d, $J_{19–20}$=8.5 Hz, H-19), 7.18 (1H, d, $J_{14–20}$=2.5 Hz, H-14), 7.04 (1H, dd, $J_{14–20}$=2.41 Hz, $J_{19–20}$=8.5 Hz, H-20), 6.43 (1H, t, $J_{1′–2′}$=6.6 Hz, H-1′), 6.31 (1H, d, $J_{17–18}$=9.6 Hz, H-17), 5.41 (1H, m, H-3′), 5.29 (2H, s, H-12), 5.29 (1H, m, HO-5′), 4.24 (1H, m, H-4′), 3.76–3.57 (2H, m, H-5′), 2.80–2.60 (2H, m, H-2′), 2.08 (3H, d, $J_{6\text{-Me}}$=1.1 Hz, CH_3-5); ^{13}C NMR (DMSO): 164.15 (4), 161.56 (16), 160.70 (13), 155.76 (14a), 150.88 (2), 144.74 (18), 142.32 (10), 136.68 (6), 129.99 (19), 125.05 (11), 113.34 (18a), 113.17 (17), 113.07 (20), 110.08 (5), 102.00 (14), 84.86 (1′), 84.32 (4′), 62.10 (12), 61.20 (3′), 59.81 (5′), 37.62 (2′), 12.71 (CH_3-5); IR (neat, cm^{-1}): 1716, 1670, 1616, 1630, 1276, 1093, 1050, 1008, 836, 771, 618.

4.4.12. 3′-{4-[(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)methyl]-1*H*-1,2,3-triazol-1-yl}thymidine (8b). White solid product, 157 mg (0.33 mmol, 88%), mp=154–157 °C. $C_{23}H_{23}N_5O_7$ (481.5), calculated: 57.38% C, 4.82% H, 14.55% N, 23.26% O; found: 57.62% C, 4.78% H, 14.84% N. ^{1}H NMR (DMSO): 11.37 (1H, s, H-3), 8.48 (1H, s, H-11), 7.83 (1H, d, $J_{6\text{-Me}}$=1.3 Hz, H-6), 7.71 (1H, d, $J_{19–20}$=9.1 Hz, H-19), 7.17 (1H, d, $J_{14–20}$=2.5 Hz, H-14), 7.06 (1H, d, $J_{14–20}$=2.4 Hz, $J_{19–20}$=8.8 Hz, H-20), 6.43 (1H, t, $J_{1′–2′}$=6.6 Hz, H-1′), 6.24 (1H, d, $J_{17\text{-Me}}$=1.1 Hz, H-17), 5.40 (1H, m, H-3′), 5.29 (2H, s, H-12), 5.29 (1H, m, HO-5′), 5.24 (1H, m, H-4′), 3.75–3.59 (2H, m, H-5′), 2.8–2.6 (2H, m, H-2′), 2.41 (3H, d, $J_{17\text{-Me}}$=1.1 Hz, CH_3-18), 1.81 (3H, d, $J_{6\text{-Me}}$=0.8 Hz, CH_3-5); ^{13}C NMR (DMSO): 163.71 (4), 161.01 (16), 160.10 (13), 154.66 (14a), 153.40 (18), 150.42 (2), 142.22 (10), 136.22 (6), 126.53 (19), 124.57 (11), 113.40 (18a), 112.56 (17), 111.32 (20), 109.62 (5), 101.56 (14), 84.41 (1′), 83.89 (4′), 61.62 (12), 60.75 (3′), 59.35 (5′), 37.16 (2′), 18.13 (CH_3-18), 12.71 (CH_3-5); IR (neat, cm^{-1}): 1695, 1622, 1293, 1271, 1146, 1100, 1072, 839, 771, 618.

4.4.13. 3′-{4-[2-(7-Hydroxy-2-oxo-2*H*-chromen-4-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}thymidine (8c). Light yellow solid product, 240 mg (0.44 mmol, 79%), mp=187–191 °C. $C_{24}H_{24}N_6O_8$ (524.2), calculated: 54.96% C, 4.61% H, 16.02% N, 24.40% O; found: 54.78% C, 4.76% H, 16.33% N. ^{1}H NMR (DMSO): 11.43 (1H, s, H-3), 8.84 (1H, t, $J_{12\text{-NH}}$=5.4 Hz, HN–C=O), 8.16 (1H, s, H-11), 7.88 (1H, d, $J_{6\text{-Me}}$=0.9 Hz, H-6), 7.64 (1H, d, $J_{21–22}$=8.6 Hz, H-22), 6.83 (1H, dd, $J_{19–21}$=2.2 Hz, $J_{21–22}$=8.6 Hz, H-21), 6.78 (1H, d, $J_{19–21}$=2.2 Hz, H-19), 6.47 (1H, t, $J_{1′–2′}$=6.6 Hz, H-1′), 6.23 (1H, s, H-16), 5.42 (1H, m, H-3′), 5.40 (1H, m, HO-5′), 4.40 (2H, d, $J_{12\text{-NH}}$=5.4 Hz, H-12), 4.25 (1H, m, H-4′), 3.78 (1H, m, H-5′), 3.75 (1H, m, H-5′), 3.75 (2H, s, H-14), 2.82–2.64 (2H, m, H-2′), 1.87 (3H, s, CH_3-5); ^{13}C NMR (DMSO): 168.10 (13), 164.17 (4), 161.60 (17), 160.66 (20), 155.44 (19a), 151.47 (22a), 150.88 (15), 145.10 (10), 136.67 (6), 127.16 (22), 123.10 (11), 113.28 (21), 112.25 (16), 111.90 (22a), 110.08 (5), 102.71 (19), 84.88 (1′), 84.29 (4′), 61.13 (5′), 59.57 (3′), 39.00 (14), 37.57 (2′), 34.83 (12), 12.71 (CH_3-5); IR (neat, cm^{-1}): 1684, 1638, 1620, 1567, 1267, 1141, 1100, 1046, 847, 776, 681, 633.

4.4.14. 3′-{4-[2-(5,7-Dimethoxy-2-oxo-2*H*-chromen-4-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}thymidine (8d). White solid product, 154 mg (0.28 mmol, 82%), mp=200 °C–decomposed. $C_{26}H_{28}N_6O_9$ (568.2), calculated: 54.93% C, 4.96% H, 14.78% N, 25.33% O; found: 55.19% C, 5.16% H, 14.92% N. ^{1}H NMR (DMSO): 11.42 (1H, s, H-3), 8.48 (1H, t, $J_{12\text{-NH}}$=5.6 Hz, HN–C=O), 8.17 (1H, s, H-11), 7.87 (1H, d, $J_{6\text{-Me}}$=1.1 Hz, H-6), 6.64 (1H, d, $J_{19–21}$=2.3 Hz, H-19), 6.47 (1H, d, $J_{19–21}$=2.0 Hz, H-21), 6.47 (1H, t, $J_{1′–2′}$=6.7 Hz, H-1′), 6.13 (1H, s, H-16), 5.46 (1H, m, H-3′), 5.32 (m, HO-5′), 4.37 (2H, d, $J_{12\text{-NH}}$=5.5 Hz, H-12), 4.28–4.22 (1H, m, H-4′), 3.89 (3H, s, CH_3O-20), 3.78 (2H, s, H-14), 3.73 (1H, m, H-5′), 3.68 (1H, m, H-5′), 3.66 (3H, s, CH_3O-22), 2.75–2.66 (2H, m, H-2′), 1.87 (3H, d, $J_{6\text{-Me}}$=0.9 Hz, H-5); ^{13}C NMR (DMSO): 168.46 (13), 163.55 (4), 162.48 (17), 159.62 (20), 158.10 (22), 156.12 (15), 150.76 (19a), 150.26 (2), 144.81 (10), 136.04 (6), 122.70 (11), 113.14 (16), 109.46 (5), 103.56 (22a), 95.16 (21), 93.39 (19), 84.23 (1′), 83.66 (4′), 60.54 (5′), 58.93 (3′), 55.72 (CH_3O-20), 55.57 (CH_3O-22), 42.61 (14), 39.99 (2′), 33.95 (12), 12.08 (CH_3-5); IR (neat, cm^{-1}): 1707, 1655, 1630, 1261, 1098, 1061, 1015, 849, 801, 625.

4.4.15. 3′-{4-[2-(3-Oxo-3*H*-benzo[*f*]chromen-1-yl)acetamidomethyl]-1*H*-1,2,3-triazol-1-yl}thymidine (8e). White solid product, 140 mg (0.25 mmol, 74%), mp=183–185 °C. $C_{28}H_{26}N_6O_7$ (558.2), calculated: 60.21% C, 4.69% H, 15.05% N, 20.05% O; found: 60.43% C, 4.82% H,

15.35% N. ^{1}H NMR (DMSO): 11.44 (1H, s, H-3), 8.92 (1H, t, $J_{12\text{-NH}}$=5.8 Hz, HN–C═O), 8.40 (1H, d, $J_{21–22}$=8.2 Hz, H-21), 8.25 (1H, d, $J_{19–20}$=9.1 Hz, H-20), 8.11 (1H, d, $J_{23–24}$=8.0 Hz, H-24), 8.00 (1H, s, H-11), 7.88 (1H, s, H-6), 7.66 (1H, dd, H-23), 7.63 (1H, d, $J_{19–20}$=9.1 Hz, H-19), 7.59 (1H, dd, H-22), 6.64 (1H, s, H-16), 6.47 (1H, t, $J_{1'–2'}$=6.6 Hz, H-1′), 5.42 (1H, m, H-3′), 5.34 (1H, m, HO-5′), 4.40 (2H, d, $J_{12\text{-NH}}$=5.5 Hz, H-12), 4.29 (2H, s, H-14), 4.21 (1H, m, H-4′), 3.76 (1H, m, H-5′), 3.73 (1H, m, H-5′), 2.68 (2H, t, $J_{1'–2'}$=6.6 Hz, H-2′), 1.88 (3H, s, H-5); ^{13}C NMR (DMSO): 168.03 (13), 163.72 (4), 159.23 (17), 154.22 (19a), 151.48 (15), 150.44 (2), 144.65 (10), 136.22 (6), 133.85 (20), 130.85 (20a), 129.56 (24), 129.07 (24a), 127.84 (22), 125.43 (19), 124.64 (23), 122.63 (15a), 118.22 (16), 117.53 (22), 113.86 (5), 109.62 (6), 84.42 (1′), 83.89 (4′), 60.70 (5′), 59.10 (3′), 43.57 (14), 37.14 (4′), 34.32 (2′), 33.35 (12), 12.27 (CH_3-5); IR (neat, cm^{-1}): 1700, 1678, 1644, 1554, 1278, 1092, 1072, 1017, 805, 737, 664, 620.

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