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Synthesis of new triazole linked carbohybrids with ROS-mediated toxicity in breast cancer†

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Carbohybrids are an important class of molecules which exhibit diverse biological activities and are present as structural motifs in many natural products. Two series of new triazole linked *N*-glycosides of coumarins and quinolones (*n* = 27) were efficiently synthesized starting from 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-glucose and 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-galactose reacting with various 4-*O*-propargyl coumarins and 4-*O*-propargyl quinolones in shorter reaction time (30 min) under microwave assisted conditions. Anticancer activity of these newly synthesized triazole linked *N*-glycosides of coumarins and quinolones was determined in detail through cellular assays against MCF-7 (breast cancer cell line), HepG2 (liver cancer cell line), HCT-116 (colon cancer cell line) and Huh-7.5 cell lines. The selected library member displayed low micromolar (IC_{50} 10.97 μM) and selective toxicity against the breast cancer cell line (MCF-7). Mechanistic studies showed that the anticancer activity of the active compound was because of the generation of reactive oxygen species (ROS).

1. Introduction

Molecular hybridization, which involves linking or merging two biologically privileged molecules to form potentially active molecules, evolved with considerable research interest among medicinal chemists and chemical biologists.[1] Hybrid molecules have better pharmacokinetic and pharmacodynamic properties.[2] Different hybrid structural motifs have already been prepared with enhanced activity suggesting their importance in current drug discovery processes.[3] The carbohydrates are stereochemically diverse molecules and known for their involvement in molecular recognition and various intracellular functions.[4] In recent years, the Warburg effect, which is defined as the presence of a high rate of aerobic glycolysis and marked carbohydrate avidity in cancerous cells, especially glucose, proved to be an efficient strategy in anticancer therapy.[5] Linking or merging carbohydrates with bioactive molecules provides a viable source for chemical libraries in drug discovery and development.[6] Masking the free polar hydroxyl group with a hydrophobic acyl group to enhance bioavailability and to enable a therapeutic concentration of the drug to reach the blood stream is an approach to overcome the poor bioavailability of carbohydrate derived drugs.[7] The acyl group gets cleaved in the blood through enzymatic hydrolysis,[8] thus providing an important pro-drug moiety to the pharmaceutical industry.[9] The glycosylation of bioactive molecules of both synthetic and natural origin most often improves the pharmacological properties and ADMET parameters of the drug.[10] In view of these points, glyco-conjugation has emerged as one of the most effective approaches for targeting cancerous cells by linking or merging the pharmacophoric moiety to the glycosyl/carbohydrate unit.[11] In connection with this glycosylated paclitaxel[12] and 4′-demethylepipodophyllotoxin[13] have been prepared to increase their water solubility as well as reduce toxicity. It has been reported that glycosylated diphyllin is a more potent topoisomerase II inhibitor than parent diphyllin.[14] It has also been reported that acyl protected sugar units in etopophos,[15] *i.e.* tafluposide, enhanced the biological activity compared to etopophos itself.

The natural and synthetic coumarin derivatives attract great attention among medicinal chemists due to their wide range of biological activities, including anticancer,[16] anti-inflammatory[17] and antibacterial,[18] *etc.* Recently their cancer chemo preventive properties have been highlighted in the literature.[19,20] The apoptosis and differentiation induced anticancer activities of coumarin derivatives extend to several different cell line models *in vitro*, and very promising results have been obtained.[21] There are various mechanisms that have been postulated in the literature for their anticancer activity including telomerase inhibitors, protein kinase inhibitors, down regulating oncogene expression or by inducing the caspase-9 mediated apoptosis, arresting the cell cycle

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in G0/G1[22] G2/M phases[23] *etc.* Similarly, natural and synthetic quinolone molecules are considered as privileged heterocyclic structural motifs present in numerous therapeutically relevant drug molecules. Quinolones and their derivatives exhibit diverse biological activity such as anticancer, HIV protease inhibitor,[24] antimalarial[25] and broad-spectrum antibacterial[26] *etc.*

Considering the Warburg effect and auspicious activity of coumarin and quinolone derivatives, we planned to link coumarin and quinolone structural motifs with acylated glucose and galactose through a triazole ring to prepare triazole linked *N*-glycosides as carbohybrids and evaluate them for their potential anticancer activity in detail. The copper(I)-catalyzed 1,2,3-triazole formation from azides and terminal acetylenes is a powerful tool for linking two privileged medicinal scaffolds, due to its high degree of dependability, complete specificity, and the biocompatibility of the reactants.[27,28] The 1,2,3-triazole moiety is considered as a bioisosteric replacement[29–31] for the amide because it resembles an amide moiety in size, dipolar character, and H-bond acceptor properties. The high chemical stability of the 1,2,3-triazole ring under various chemical conditions[32] is an additional supportive factor to use this moiety as a linking tool. In this context, we exploited D-glucose and D-galactose derived azido glycosides as the stereo diversity surrogates to couple with the diverse substituted alkyne-modified 4-hydroxy-coumarins and 4-hydroxy-quinolones to get triazole linked *N*-glycosides as carbohybrids. These molecules have the advantages of structural diversity, improved solubility and most importantly selective anticancer activity (MCF-7). The details of synthesis along with their detailed anticancer activity are disclosed in this paper.

2. Results and discussion

2.1. Chemistry

For the efficient synthesis of 1,2,3-triazole linked *N*-glycosides of coumarins and quinolone hybrids, we selected diverse 4-hydroxycoumarin and 4-hydroxyquinolone substrates which can get transformed into 4-*O*-propargyl coumarins **11–16** and 4-*O*-propargyl quinolones **17–20** having suitably functionalized terminal alkyne groups.[33] When the diverse 4-hydroxycoumarins were treated with propargyl bromide in DMF using K_2CO_3 as the base at elevated temperature it furnishes 4-*O*-propargyl coumarins **11–16** in very good yields (ESI,† Table S1, entries 1–6). Similarly, when 4-hydroxyquinolones were treated with propargyl bromide in DMF using K_2CO_3 as the base at elevated temperature it furnishes 4-*O*-propargyl quinolones **17–20** in acceptable yields (ESI,† Table S1, entries 7–10). It is worth mentioning here that propargylation on 4-hydroxyquinolones shows the formation of multiple products. These were di- and tri-propargyl products (confirmed by NMR and mass spectra).[34] After having prepared 4-*O*-propargyl coumarins **11–16** and 4-*O*-propargyl quinolones **17–20**, 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-glucose **23** and 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-galactose **24** were prepared in excellent yields (ESI,† Scheme S1).[35]

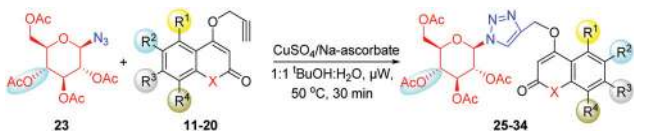
The first 'click chemistry' reaction of 4-*O*-propargyl coumarin **11** with 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-glucose **23** was performed under thermal conditions (50 °C) in ^{t}BuOH : H_2O (1 : 1) for 6 h using $CuSO_4{\cdot}5H_2O$ and sodium ascorbate, and it furnished the desired 1,2,3-triazole linked *N*-glycosides of coumarin **25** in 76% isolated yields with some recovered starting material.[36] At this juncture we planned to use microwave assisted click-chemistry in order to accelerate the reaction for completion and get desired products in shorter reaction time and better yields. Thus, when a similar reaction was undertaken under microwave heating conditions at 50 °C in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in ^{t}BuOH : H_2O (1 : 1), 1,2,3-triazole linked *N*-glycoside **25** was obtained in very good isolated yield (90%) in a highly regioselective manner within 30 min (Table 1, entry 1). However, in the absence of sodium ascorbate, the above reaction does not go to completion even after 30 min. This indicates that both sodium ascorbate and Cu(I) are required for this transformation, not only to accelerate the reaction but also to induce the regioselectivity on these substrates. The structure of new 1,2,3-triazole linked *N*-glycoside **25** was unambiguously established by 1D and 2D NMR (HSQC, COSY and NOE) experiments. The regiochemistry of the newly synthesized compound **25** was confirmed as 1,4-substituted coumarin by NMR spectra where triazole protons appear as a singlet at δ 7.97 (s, 1H). Adopting a similar reaction protocol carbohybrids **26–34** were prepared in very good yields (Table 1).

We were also interested to see the activity profile of 1,2,3-triazole linked *N*-glycosides derived from D-galactose. Therefore by adopting an optimized reaction protocol, 1,2,3-triazole linked *N*-glycosides of D-galactose were prepared under microwave conditions in very good yields as shown in Table 2. Thus, diversely substituted coumarins and quinolones **11–20** were linked *via* triazole with per-*O*-acetylated galactose **24** and 1,2,3-triazole linked *N*-glycosides of D-galactose **35–44** were prepared in good yields (Table 2).

In order to see the effect of acyl groups on the biological activity, some of the *N*-glycoside derivatives **27–28**, **33**, and **35–39**, with acyl groups, were deacylated using sodium methoxide in methanol to get polyhydroxylated *N*-glycosides **45–51** in excellent yields as shown in Table 3.

The anticancer activity of all the prepared compounds was investigated using the cell viability assay method involving MCF-7 (human breast cancer cell line), HepG2 (human hepato

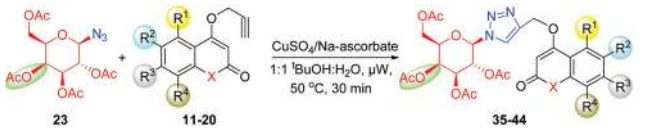
Table 1 Synthesis of triazole linked *N*-glucopyranosides **25–34**



23 11-20 25-34

Entry	R^1	R^2	R^3	R^4	X	Product	Yield (%)
1	H	H	H	H	O	**25**	90
2	H	OCH_3	H	H	O	**26**	75
3	H	Cl	H	H	O	**27**	80
4	H	CH_3	H	H	O	**28**	91
5	H	Br	H	H	O	**29**	86
6	H	H	F	H	O	**30**	75
7	H	H	H	H	NH	**31**	69
8	H	H	H	F	NH	**32**	67
9	H	H	H	NO_2	NH	**33**	71
10	H	H	H	OCF_3	NH	**34**	85

Table 2 Synthesis of triazole linked *N*-galactopyranosides **35–44**



Entry	R^1	R^2	R^3	R^4	X	Product	Yield (%)
1	H	H	H	H	O	**35**	90
2	H	OCH_3	H	H	O	**36**	78
3	H	Cl	H	H	O	**37**	80
4	H	CH_3	H	H	O	**38**	94
5	H	Br	H	H	O	**39**	77
6	H	H	F	H	O	**40**	81
7	H	H	H	H	NH	**41**	70
8	H	H	H	F	NH	**42**	69
9	H	H	H	NO_2	NH	**43**	70
10	H	H	H	OCF_3	NH	**44**	87

Table 3 Preparation of deacetylated triazole linked *N*-glycopyranosides **45–51**

Entry	R′	R″	R^1	R^2	R^3	R^4	X	Product	Yield (%)
1	OH	H	H	Cl	H	H	O	**45**	80
2	OH	H	H	CH_3	H	H	O	**46**	89
3	H	OH	H	H	H	H	O	**47**	91
4	H	OH	H	OCH_3	H	H	O	**48**	90
5	H	OH	H	CH_3	H	H	O	**49**	88
6	H	OH	H	Br	H	H	O	**50**	81
7	OH	H	H	H	H	NO_2	NH	**51**	79

carcinoma cell lines), HCT-116 (colon cancer cell line) and Huh-7.5 cell lines and detailed anticancer activity is discussed below.

2.2. Anticancer activity

2.2.1. Cell line specific anticancer activity. To identify the anticancer property of compounds from a library of twenty-seven compounds, we initially performed cell viability assays in two different tissue specific cell lines. HepG2 (human hepato carcinoma cell lines) and MCF-7 (human breast cancer cell lines) were used in this study where HepG2 did not show any remarkable cell death in the presence of these compounds (**25–51**), tested at 20 μM concentration (Table 4).[37] However, in the case of MCF-7 cell lines, we observed significant cell death in the presence of compound **28**, under similar conditions (Table 4). Thus, compound **28** possesses cell line specific anticancer activity. Cell death was noticed followed by morphological changes in MCF-7 cells after 48 h of compound treatment. The half maximal inhibitory concentration (IC_{50}) for compound **28** (Fig. 1b) was found to be 10.97 μM. **Doxorubicin** was used as a positive control in the assay.

The selected compounds **26, 28, 40** and **44** were further screened against HCT-116 (colon cancer cell lines) and Huh-7.5 cell lines in order to understand the anticancer activity profile of these compounds. As the results shown in Fig. S2 (ESI†) these compounds do not possess potential anticancer activity against HCT-116 (colon cancer cell lines) and Huh-7.5 cell lines as it was observed with the HepG2 cell line (Fig. S1, ESI† and Table 4). Thus compound **28** is very specific to the human breast cancer cell line (MCF-7).

2.2.2. Compound 28 is involved in ROS generation in MCF-7 cells. We were further interested to know the mechanism of cell death induced by compound **28** in MCF-7 cells, and whether compound **28** is capable of causing DNA damage in MCF-7 cell lines. To study this, we performed the comet assay and found very low effect of compound **28** on DNA damage (Fig. 2).[38] Anticancer compounds can target different pathways for generating their anticancer effects. Therefore, to understand further we were interested to study Reactive Oxygen Species (ROS) generation in selected compound **26**, **28**, **40** and **44** treated cancer cells (HepG2, MCF-7, HCT-116 and Huh-7.5). Here with MCF-7 cells, in contrast to the control (DMSO), ROS generation was observed in compound **28** treated cells (concentration 10 μM, 48 h) (Fig. 3). This depicts that the ROS are responsible for decreased cell viability in the effect of anticancer compound **28** against MCF-7 cells. Meanwhile, the same set of compounds **26, 28, 40** and **44** did not show any sign

Table 4 Anticancer screening results

	Cell viability (%) ± SD			Cell viability (%) ± SD	
Compounds[a]	HepG2	MCF-7	Compounds[a]	HepG2	MCF-7
25	87.55 ± 2.05	81.9 ± 3.39	**39**	95.55 ± 2.61	89.45 ± 1.90
26	93.45 ± 1.62	96.7 ± 1.2	**40**	89.6 ± 1.69	90.0 ± 1.13
27	90.6 ± 1.13	91.55 ± 1.48	**41**	88.05 ± 5.30	92.1 ± 2.12
28	87.95 ± 5.58	**34.85 ± 4.73**	**42**	97.2 ± 6.78	97.6 ± 4.80
29	95.2 ± 5.37	86.85 ± 0.49	**43**	77.3 ± 3.11	92.45 ± 4.03
30	87.15 ± 4.87	90.5 ± 2.40	**44**	86.5 ± 3.25	90.2 ± 2.40
31	96.25 ± 4.03	84.4 ± 4.52	**45**	91.25 ± 2.47	87.55 ± 4.31
32	97.00 ± 9.89	98.5 ± 4.94	**46**	93.35 ± 3.04	95.65 ± 0.91
33	85.6 ± 4.94	83.7 ± 1.13	**47**	93.1 ± 3.53	89.25 ± 1.06
34	91.9 ± 1.41	86.85 ± 3.32	**48**	90.6 ± 4.94	98.25 ± 6.71
35	70.05 ± 6.43	88.9 ± 7.63	**49**	92.6 ± 0.56	95.15 ± 3.32
36	88.8 ± 0.28	85.8 ± 3.25	**50**	86.15 ± 4.03	91.55 ± 4.31
37	80.9 ± 2.26	85.5 ± 1.41	**51**	84.8 ± 3.11	93.3 ± 4.66
38	86.1 ± 3.53	88.8 ± 3.25	**Doxorubicin**	15.3 ± 0.77	15.2 ± 0.84

[a] A concentration of 20 μM for each compound was used for MCF-7 and HepG2 cells.

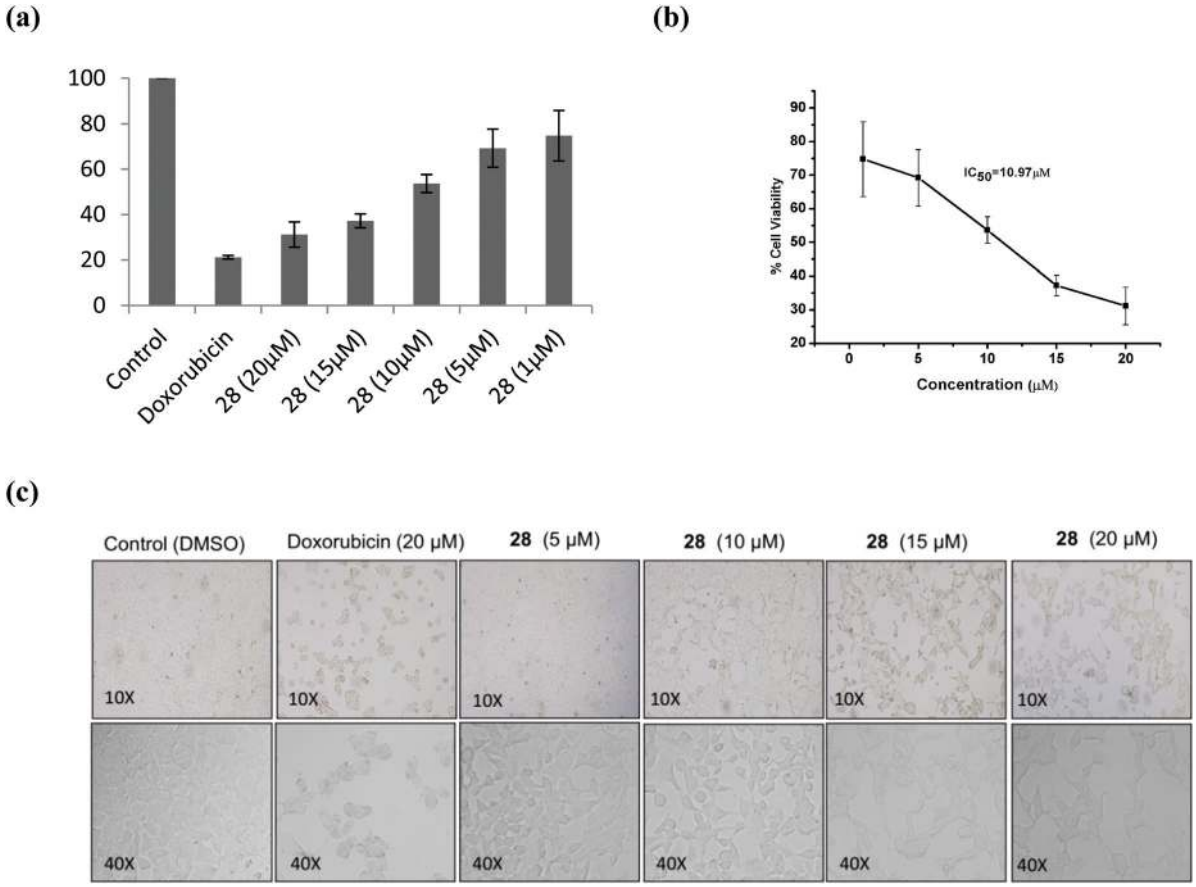


Fig. 1 Cytotoxicity of triazole linked *N*-glycoside of the coumarin compound **28**. (a) To calculate the half-maximal inhibitory concentration (IC_{50}) values of compound **28,** MCF-7 cells were treated with different concentrations (1, 5, 10, 15 and 20 μM) for 48 h. The percent cell viability was determined by counting number of viable cells after treatment. (b) IC_{50} values were determined by plotting the values of percent cell viability against the concentration of compound **28**. The IC_{50} values for compound **28** against MCF-7 cells are 10.97 μM; the experiments were performed in triplicate, n = 3, and the ±SD value was calculated for each data point. (c) Morphological analysis of MCF-7 cells was performed after treating cells with DMSO (control), **doxorubicin** (20 μM) and different concentrations (1, 5, 10, 15 and 20 μM) of compound **28** for 48 h. Cells were viewed under Nikon-Ti Microscope with a 10× (magnification – 100×) and 40× (magnification – 400×) objective lens.

of ROS generation in HepG2, HCT-116 and Huh-7.5 cancer cells (Fig. S3–S5, ESI†); these results were also in agreement with their observed anticancer activity profile.

3. Conclusions

In summary, we have designed and synthesized a library of 1,2,3-triazole linked *N*-glycosides of coumarins and quinolones as carbohybrids. The method involves microwave assisted facile synthesis utilizing 'click-chemistry' starting from freshly prepared diverse 4-*O*-propargylated coumarins, quinolones and 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-glycopyranosides derived from D-glucose and D-galactose. The method is endowed with several unique merits including simple reaction conditions, shorter reaction time, broad substrate scope and good to very good yields.

The method has been successfully applied to diverse substituted 4-*O*-propargylated coumarins and quinolones bearing electron donating and withdrawing groups and a library of twenty-seven 1,2,3-triazole-linked *N*-glycosides as carbohybrids were prepared. Subsequently, we have demonstrated that a selected library member displayed micromolar (IC_{50} 10.97 μM) but selective anticancer activity (MCF-7). Further study revealed that the anticancer activity of the active compound was due to the formation of reactive oxygen species (ROS) however without significant nuclear DNA damage. Apart from causing DNA lesions, ROS production in the cell can also cause oxidative modifications of proteins leading to their altered functions in the cell or leads to lipid peroxidation which can generate toxic products in the cell. Since in our study the active compound showed breast cancer cell line (MCF-7) specific cell death without significant nuclear DNA damage, it might be possible that other cellular macromolecules like proteins or lipids essential for the survival of targeted cell lines could be the target of this ROS generation.

4. Experimental section

4.1. General experimental methods

All experiments were performed in oven-dried apparatus and in anhydrous solvents in a CEM microwave synthesiser.

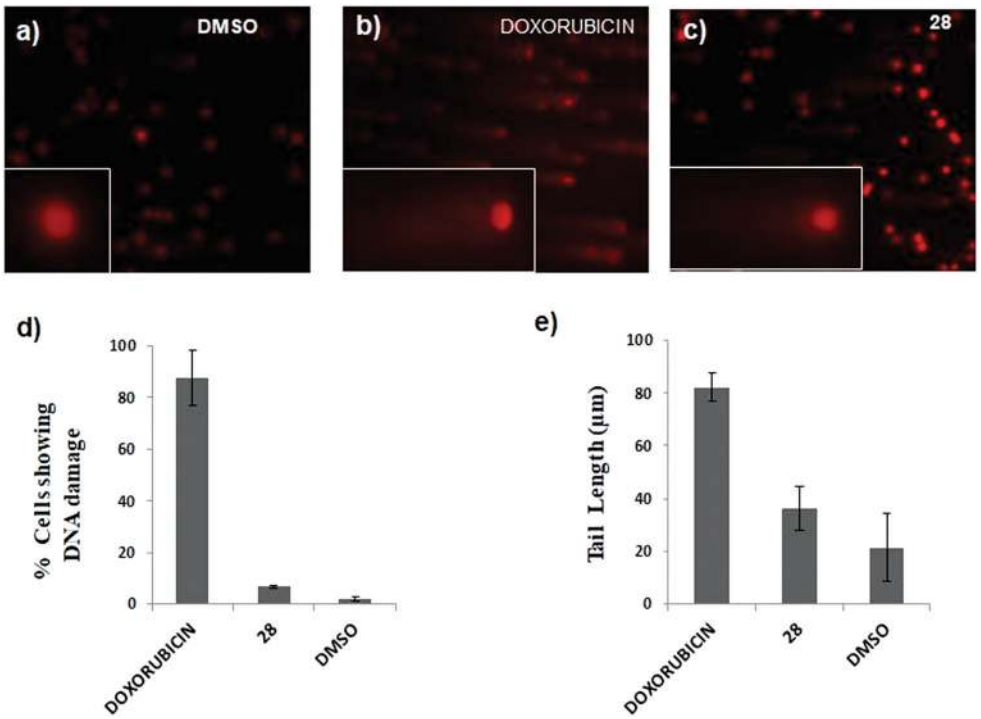


Fig. 2 Effect of compound **28** on DNA damage (comet assay). MCF-7 cells were treated with (a) DMSO (control), (b) **doxorubicin** (10 μM) and (c) compound **28** (10 μM) for 48 h. Lysed and electrophoresed cells were stained with EtBr and observed in the red fluorescent channel (TRITC) of a Nikon-Ti Microscope, using a 10× and 40× objective lens. (d) Percent DNA damage and (e) Tail length generated was calculated manually using the Nikon-Ti Software. No significant DNA damage was observed in cells treated with compound **28**.

High resolution mass spectra were obtained from a quadrupole/TOF mass spectrometer with an ESI source. Solvents were distilled by standard distillation procedures and stored in 4 Å and 3 Å molecular sieves. ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using Bruker AMX-400 MHz and JNM-ECZ500R/S1 instruments. ^{1}H and ^{13}C chemical shifts are referenced to the solvent residual signals $CDCl_3$ ^{1}H NMR δ 7.26 and δ 77.16 for ^{13}C NMR, CD_3OD, ^{1}H NMR δ 4.87, 3.31 and ^{13}C δ 49 and DMSO ^{1}H NMR δ 2.50 and δ 39.52 for ^{13}C reported in parts per million (ppm) at 25 °C. Coupling constants are expressed in hertz (Hz). Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254), and spots were visualized by phosphomolybdic acid and 10% H_2SO_4 in ethanol. 1-Azido-2,3,4,6-tetra-*O*-acetyl β-D-glucose and 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-galactose were prepared in the laboratory. 4-*O*-Propargyl coumarins and 4-*O*-propargyl quinolones were freshly prepared in the laboratory by reported methods. All reagents were purchased from TCI, Merck, Sigma Aldrich, *etc.*

4.2. General experimental procedure for the synthesis of triazole linked *N*-glycosides of coumarins and quinolone carbohybrids 25–44

In a microwave vial, 100 mg (0.268 mmol) of 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-glucose **23** and 53.6 mg (0.268 mmol) of 4-*O*-propargyl coumarin **11** were taken in 2 mL (a 1 : 1 mixture of H_2O : ^{t}BuOH) of the solvent. $CuSO_4{\cdot}5H_2O$ (1.245 mg, 0.005 mmol) and sodium ascorbate (2.28 mg, 0.011 mmol) were added to the above reaction mixture. The resulting reaction mixture was heated under stirring for 15 min at 50 °C (100 W) under microwave conditions. Completion of the reaction was confirmed by TLC. After completion, 5 mL of water was added and the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine, then dried over Na_2SO_4 and evaporated on a rotary evaporator to get a crude product. The crude residue was purified by flash column chromatography and pure compound **25** (138 mg) was isolated in a 90% isolated yield. Other 1,2,3-triazole linked *N*-glucosides **26–34** were also prepared using the above reaction protocol in good to very good yields (67–90%) using 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-glucose **23** and 4-*O*-propargyl coumarin and quinolones **12–20** (Table 1), and adopting the above protocol, we synthesized compounds **26–44**. Similarly, 1,2,3-triazole linked *N*-galactosides **35–44** were prepared in very good to excellent yields (71–94%) using 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-galactose **24** and 4-*O*-propargyl-coumarin and quinolones **12–20** (Table 2).

4.2.1. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (25). Off white amorphous solid, R_f = 0.44 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 5.2 Hz, 1H), 5.93–5.91 (m, 1H), 5.83 (s, 1H), 5.44–5.42 (m, 2H), 5.28–5.22 (m, 1H) 5.15–5.07 (m, 1H), 4.32 (dd, J = 4.4 Hz, J = 12.8 Hz, 1H), 4.17–4.09 (m, 2H), 4.04 (dd, J = 5.2 Hz, J = 10.0 Hz, 1H), 2.16 (s, 3H, CH_3 of $COCH_3$), 2.05

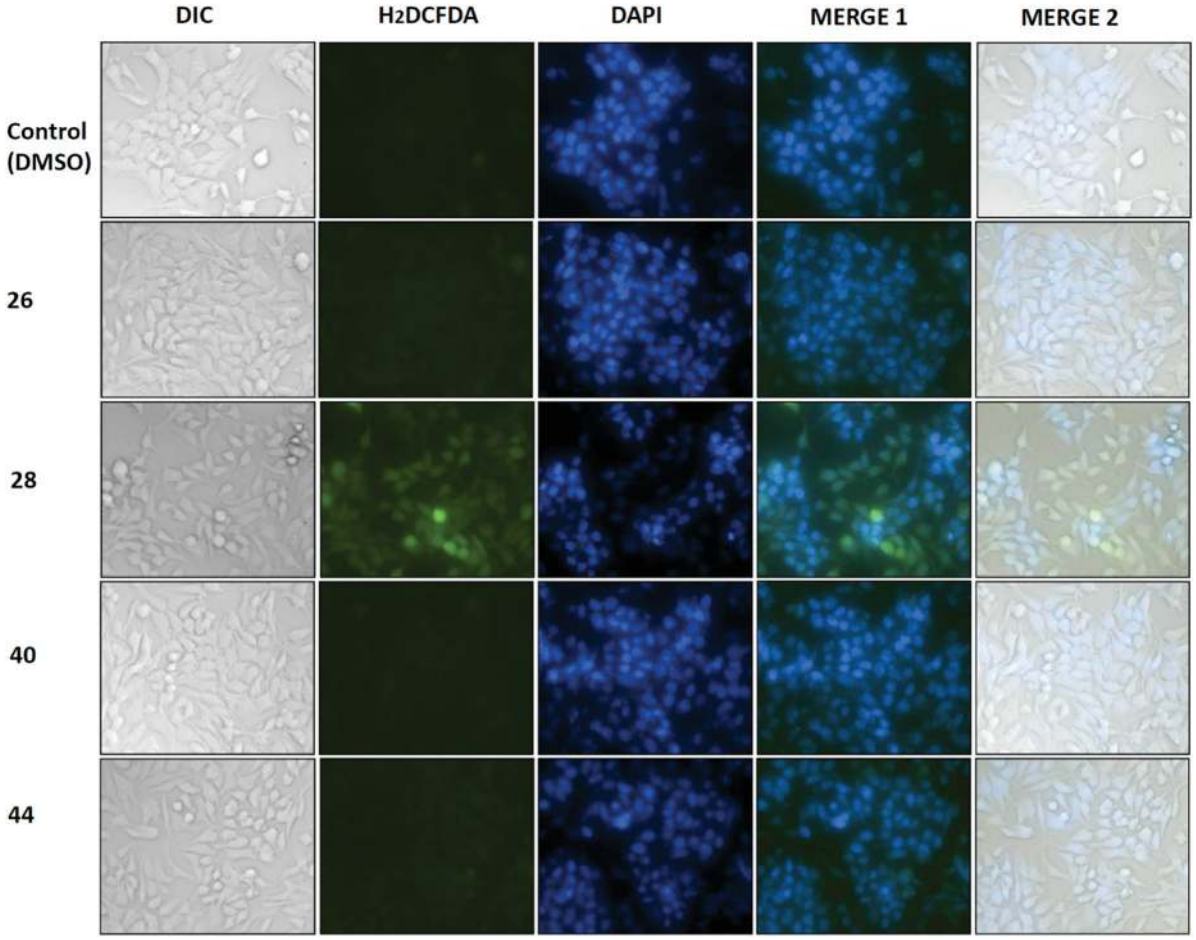


Fig. 3 Effect of selected compounds **26**, **28**, **40** and **44** on ROS generation (H_2DCFDA assay): MCF-7 cells treated with compound **28** show cell death due to the formation of reactive oxygen species (ROS), which were detected as green fluorescence. Cells were treated with DMSO (control) and compounds **26**, **28**, **40** and **44** for 48 h followed by treatment with H_2DCFDA. Live treated cells were observed in DIC and H_2DCFDA mediated ROS generation was detected in the green fluorescent channel (FITC) of a Nikon-Ti Microscope under a 40× objective lens. DAPI was used for nuclear staining of cells.

(s, 3H, CH_3 of $COCH_3$), 2.02 (s, 3H, CH_3 of $COCH_3$), 1.86 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.8, 169.3, 168.9, 164.8, 162.6, 153.2, 142.3, 132.5, 124.0, 123.1, 122.0, 116.7, 115.3, 91.3, 85.8, 75.2, 72.4, 70.3, 69.7, 67.6, 62.4, 61.5, 20.6, 20.5, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{27}N_3O_{12}$ $[M + H]^+$ 574.1667; found: 574.1730.

4.2.2. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-methoxy-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (26). White amorphous solid, R_f = 0.35 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.38–7.33 (m, 2H), 7.26 (brs, 1H), 6.06 (s, 1H), 5.96 (s, 1H), 5.56 (brs, 2H), 5.48 (brs, 2H), 5.38 (brs, 1H), 4.44 (brs, 1H), 4.31–4.18 (m, 2H), 3.95 (s, 3H, CH_3 of OCH_3), 2.20 (brs, 6H, CH_3 of $COCH_3$), 2.15 (s, 3H, CH_3 of $COCH_3$), 1.99 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 169.3, 168.9, 164.5, 162.7, 155.9, 147.8, 142.3, 121.9, 120.5, 117.8, 115.7, 105.2, 91.6, 85.9, 75.3, 72.4, 70.3, 67.6, 62.4, 61.4, 55.9, 20.6, 20.5, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{29}N_3O_{12}$ $[M + H]^+$ 604.1773; found: 604.1819.

4.2.3. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-chloro-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (27). Off white amorphous solid, R_f = 0.48 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.75 (s, 1H), 7.49 (d, J = 3.6 Hz, 1H), 7.26 (s, 1H), 5.92 (d, J = 8.4 Hz, 1H), 5.85 (s, 1H), 5.45–5.41 (m, 2H), 5.34 (s, 2H), 5.27–5.24 (m, 1H), 4.33 (d, J = 4.4 Hz, J = 12.8 Hz, 1H), 4.18 (d, J = 4.8 Hz, 1H), 4.04 (d, J = 8.4 Hz, 1H), 2.08 (s, 3H, CH_3 of $COCH_3$), 2.07 (s, 3H, CH_3 of $COCH_3$), 2.04 (s, 3H, CH_3 of $COCH_3$), 1.88 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.7, 169.3, 159.0, 168.9, 151.7, 142.0, 129.5, 122.7, 122.0, 118.2, 116.5, 92.1, 85.9, 75.4, 72.3, 70.3, 67.7, 62.6, 61.4, 20.6, 20.5, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{26}ClN_3O_{12}$ $[M + H]^+$ 608.1278; found: 608.1344.

4.2.4. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-methyl-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (28). Off white amorphous solid, R_f = 0.44 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.58 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 5.93 (brs, 1H), 5.80 (s, 1H), 5.45 (brs, 2H), 5.33 (s, 2H), 5.29–5.25 (m, 1H), 4.34–4.32 (m, 1H), 4.19–4.14 (m, 1H), 4.04 (s, 1H), 2.39 (s, 3H, CH_3) 2.08 (s, 3H, CH_3 of $COCH_3$), 2.07 (s, 3H, CH_3 of $COCH_3$), 2.03 (s, 3H, CH_3 of $COCH_3$), 1.88 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.7, 169.3,

168.9, 164.8, 162.7, 151.5, 142.4, 133.6, 133.5, 122.7, 121.8, 116.5, 115.0, 91.2, 85.9, 75.3, 72.4, 70.3, 67.7, 62.4, 61.4, 20.8, 20.6, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{29}N_3O_{12}$ $[M + H]^+$ 588.1824; found: 588.1875.

4.2.5. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-bromo-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (29). Off white amorphous solid, R_f = 0.53 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.89 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.85 (s, 1H), 5.47–5.39 (m, 2H), 5.34 (s, 2H), 5.25 (t, *J* = 9.2 Hz, 1H), 4.33 (dd, *J* = 4.4 Hz, *J* = 12.4 Hz, 1H), 4.17 (d, *J* = 12.4 Hz, 1H), 4.04 (d, *J* = 6.4 Hz, 1H), 2.08 (s, 3H, CH_3 of $COCH_3$), 2.06 (s, 3H, CH_3 of $COCH_3$), 2.02 (s, 3H, CH_3 of $COCH_3$), 1.88 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.7, 169.3, 168.9, 163.5, 161.7, 152.2, 135.3, 125.7, 122.1, 118.5, 117.0, 116.7, 92.1, 85.9, 75.4, 72.3, 70.3, 67.6, 62.6, 61.4, 20.6, 20.5, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{26}BrN_3O_{12}$ $[M + H]^+$ 652.0773; found: 652.0832.

4.2.6. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((7-fluoro-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (30). Off white amorphous solid, R_f = 0.65 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.77 (dd, *J* = 6.4 Hz, *J* = 8.4 Hz, 1H), 7.01–6.99 (m, 1H), 6.97–6.94 (m, 1H), 5.93 (d, *J* = 8.4 Hz, 1H), 5.78 (s, 1H), 5.44–5.40 (m, 2H), 5.32 (s, 2H), 5.27–5.21 (m, 1H), 4.32–4.28 (m, 1H), 4.16–4.13 (m, 1H), 4.05–4.02 (m, 1H), 2.05 (s, 3H, CH_3 of $COCH_3$), 2.05 (s, 3H, CH_3 of $COCH_3$), 2.00 (s, 3H, CH_3 of $COCH_3$), 1.85 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.7, 169.3, 168.9, 164.4, 163.7, 162.2, 142.1, 125.1, 125.0, 122.0, 112.2, 111.9, 104.3, 104.0, 90.3, 85.8, 75.3, 72.3, 70.3, 67.6, 62.5, 61.5, 20.6, 20.49, 20.45, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{26}FN_3O_{12}$ $[M + H]^+$ 592.1573; found: 592.1631.

4.2.7. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (31). Off white amorphous solid R_f = 0.15 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.05 (s, 1H), 5.97 (d, *J* = 8.8 Hz, 1H), 5.49–5.42 (m, 2H), 5.27 (brs, 3H), 4.31 (dd, *J* = 6.0 Hz, *J* = 12.4 Hz, 1H), 4.16 (d, *J* = 11.6 Hz, 1H), 4.04 (dd, *J* = 2.80 Hz, *J* = 10.0 Hz, 1H), 2.04–2.00 (brs, 9H, CH_3 of $COCH_3$), 1.85 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.8, 169.3, 168.9, 165.7, 163.2, 143.2, 138.4, 131.3, 122.7, 122.1, 121.7, 116.0, 115.2, 97.0, 85.8, 75.2, 72.5, 70.3, 67.7, 62.1, 61.5, 20.6, 20.5, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{28}N_4O_{11}$ $[M + H]^+$ 573.1827; found: 573.1889.

4.2.8. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((8-fluoro-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (32). Off white amorphous solid, R_f = 0.2 (7 : 3, ethyl acetate : hexane v/v), ^{1}H NMR (400 MHz, CD_3OD): δ 8.52 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.37 (ddd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 5.2 Hz, *J* = 8.0 Hz, 1H), 6.20 (d, *J* = 3.6 Hz, 1H), 6.19 (s, 1H) 5.65 (t, *J* = 9.6 Hz, 1H), 5.56 (t, *J* = 9.2 Hz, 1H), 5.41 (s, 2H), 5.30 (t, *J* = 10.0 Hz, 1H), 4.34 (dd, *J* = 4.8 Hz, *J* = 12.4 Hz, 1H), 4.27 (ddd, *J* = 1.6 Hz, *J* = 4.8 Hz, 1H), 4.20 (dd, *J* = 2.0 Hz, *J* = 12.4 Hz, 1H), 2.06 (s, 3H, CH_3 of $COCH_3$), 2.04 (s, 3H, CH_3 of $COCH_3$), 2.00 (s, 3H, CH_3 of $COCH_3$), 1.82 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (CD_3OD, 100 MHz) δ 170.8, 170.0, 169.7, 168.9, 164.7, 162.4, 142.6, 123.6, 121.8, 118.3, 115.9, 97.4, 85.2, 74.6, 72.6, 70.5, 67.8, 61.8, 61.5, 19.15, 19.1, 19.0, 18.6: δ HRMS (ESI), *m*/*z* calcd for $C_{26}H_{27}FN_4O_{11}$ $[M + H]^+$ 591.1733; found: 591.1785.

4.2.9. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((8-nitro-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (33). Yellow colour amorphous solid, R_f = 0.24 (7 : 3, ethyl acetate : hexane, v/v) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (dd, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H), 8.25 (dd, *J* = 1.2 Hz, *J* = 8.5 Hz, 1H), 7.96 (s, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 6.14 (d, *J* = 2.0 Hz, 1H), 5.91 (d, *J* = 9.0 Hz, 1H), 5.45–5.40 (m, 2H), 5.33 (s, 2H), 5.25–5.21 (m, 1H), 4.32 (dd, *J* = 4.0 Hz, *J* = 13.0 Hz, 1H), 4.16 (dd, *J* = 2.5 Hz, *J* = 12.5 Hz, 1H), 4.03 (ddd, *J* = 1.6 Hz, *J* = 4.0 Hz, 1H), 2.06 (s, 3H, CH_3 of $COCH_3$), 2.05 (s, 3H, CH_3 of $COCH_3$), 2.01 (s, 3H, CH_3 of $COCH_3$), 1.87 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.8, 169.4, 169.1, 162.9, 161.7, 142.4, 133.7, 133.1, 131.3, 128.8, 121.9, 120.9, 118.1, 98.6, 86.0, 75.4, 72.4, 70.4, 67.7, 62.5, 61.5, 20.7, 20.6, 20.5, 20.2. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{27}N_5O_{13}$ $[M + H]^+$ 618.1678; found: 618.1728.

4.2.10. (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-oxo-8-(trifluoromethoxy)-1,2dihydro-quin-olin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (34). Pinkish white amorphous solid, R_f = 0.35 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (brs, 1H, NH), 8.03 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.10 (s, 1H), 5.95 (d, *J* = 7.6 Hz, 1H), 5.46–5.44 (m, 2H), 5.29 (s, 2H), 5.26–5.24 (m, 1H), 4.31–4.28 (m, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 4.06–4.04 (m, 1H), 2.04 (brs, 6H, CH_3 of $COCH_3$), 1.98 (s, 3H, CH_3 of $COCH_3$), 1.83 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.8, 169.3, 168.9, 163.5, 162.3, 142.7, 135.0, 130.9, 122.0, 121.9, 121.8, 121.6, 121.4, 119.2, 117.1, 98.3, 85.7, 75.2, 72.4, 70.3, 67.7, 62.3, 61.5, 50.5, 20.6, 20.47, 20.4, 20.0. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{27}F_3N_4O_{12}$ $[M + H]^+$ 657.165; found: 657.1710.

4.2.11. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (35). Off white amorphous solid, R_f = 0.47 (7 : 3, ethyl acetate : hexane, v/v) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 5.92 (d, *J* = 9.6 Hz, 1H), 5.82 (s, 1H), 5.54–5.50 (m, 2H), 5.36–5.32 (m, 2H), 5.30–5.27 (m, 1H), 4.31–4.28 (m, 1H), 4.20–4.13 (m, 2H), 2.17 (s, 3H, CH_3 of $COCH_3$), 1.99 (s, 3H, CH_3 of $COCH_3$), 1.96 (s, 3H, CH_3 of $COCH_3$), 1.84 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.9, 169.7, 169.1, 164.8, 162.5, 153.2, 142.1, 132.5, 123.9, 123.1, 122.2, 116.6, 115.4, 91.2, 86.2, 74.1, 70.5, 67.9, 66.9, 62.4, 61.2, 20.59, 20.54, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{27}N_3O_{12}$ $[M + H]^+$ 574.1667; found: 574.1730.

4.2.12. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(4-(((6-methoxy-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyltriacetate (36). Light yellow amorphous solid, R_f = 0.39 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.19 (s, 1H), 7.17 (d, *J* = 4.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.90 (d, *J* = 9.2 Hz, 1H), 5.81 (s, 1H), 5.53–5.48

(m, 2H), 5.31 (s, 2H), 5.29–5.26 (m, 1H), 4.28 (brs, 1H), 4.17–4.13 (m, 2H), 3.77 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3 of $COCH_3$), 1.99 (s, 3H, CH_3 of $COCH_3$), 1.96 (s, 3H, CH_3 of $COCH_3$), 1.83 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.8, 169.6, 169.0, 164.5, 162.6, 155.8, 147.7, 142.1, 122.3, 120.4, 117.7, 115.7, 105.2, 91.5, 86.3, 74.2, 70.5, 67.9, 66.9, 62.4, 61.1, 55.8 (OCH_3), 20.9, 20.5, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{29}N_3O_{12}$ $[M + H]^+$ 604.1773; found: 604.1819.

4.2.13. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-chloro-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (37). Light yellow amorphous solid R_f = 0.54 (7 : 3, ethyl acetate : hexane, v/v) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 3.2 Hz, 1H), 5.91 (s, 1H), 5.89 (d, *J* = 4.0 Hz, 1H), 5.58 (d, *J* = 3.2 Hz, 1H), 5.53 (d, *J* = 9.6 Hz, 1H), 5.36 (s, 2H), 5.30 (d, *J* = 3.2 Hz, 1H), 5.28 (d, *J* = 3.2 Hz, 1H), 4.29–4.24 (m, 1H), 4.23–4.17 (m, 1H), 2.22 (s, 3H, CH_3 of $COCH_3$), 2.05 (s, 3H, CH_3 of $COCH_3$), 2.01 (s, 3H, CH_3 of $COCH_3$), 1.91 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 170.2, 169.8, 169.6, 169.1, 163.6, 161.7, 151.7, 141.8, 132.5, 129.5, 122.8, 122.2, 118.2, 116.6, 92.1, 86.4, 74.3, 70.5, 67.9, 66.8, 62.6, 61.1, 20.6, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{26}ClN_3O_{12}$ $[M + H]^+$ 608.1278; found: 608.1344.

4.2.14. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-methyl-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (38). White amorphous solid, R_f = 0.49 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.55 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 5.91 (d, *J* = 9.2 Hz, 1H), 5.79 (s, 1H), 5.54–5.51 (m, 2H), 5.31 (s, 2H), 5.29–5.26 (m, 1H), 4.28–4.26 (m, 1H), 4.21–4.12 (m, 2H), 2.34 (s, 3H, CH_3), 2.18 (s, 3H, CH_3 of $COCH_3$), 2.01 (s, 3H, CH_3 of $COCH_3$), 1.98 (s, 3H, CH_3 of $COCH_3$), 1.86 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 169.8, 169.7, 169.0, 164.8, 162.7, 151.4, 142.2, 133.6, 133.5, 122.8, 122.2, 115.0, 91.2, 86.3, 74.2, 70.6, 67.9, 66.9, 62.3, 61.1, 20.8, 20.5, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{27}H_{29}N_3O_{12}$ $[M + H]^+$ 588.1824; found: 588.1875.

4.2.15. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((6-bromo-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (39). Light yellow solid, R_f = 0.55 (7 : 3, ethyl acetate : hexane, v/v) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.89 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 5.90 (d, *J* = 9.2 Hz, 1H), 5.85 (s, 1H), 5.55–5.00 (m, 2H), 5.33 (brs, 2H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.27 (d, *J* = 5.6 Hz, 1H), 4.22–4.16 (m, 1H), 4.09 (m, 1H), 2.19 (s, 3H, CH_3 of $COCH_3$), 2.02 (s, 3H, CH_3 of $COCH_3$), 1.98 (s, 3H, CH_3 of $COCH_3$), 1.88 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.8, 169.6, 169.1, 163.5, 161.7, 152.1, 141.8, 135.3, 125.8, 122.3, 116.7, 92.0, 86.4, 74.2, 70.5, 67.9, 66.8, 62.6, 61.1, 20.6, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{26}BrN_3O_{12}$ $[M + H]^+$ 652.0773; found: 652.0832.

4.2.16. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((8-fluoro-2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (40). Colourless amorphous solid, R_f = 0.54 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.79 (dd, *J* = 6.4 Hz, *J* = 8.4 Hz, 1H), 6.99 (dd, *J* = 8.8 Hz, 2H), 5.89 (d, *J* = 9.2 Hz, 1H), 5.79 (s, 1H), 5.56–5.49 (m, 2H), 5.34 (s, 2H), 5.28 (dd, *J* = 2.8 Hz, *J* = 10.4 Hz, 1H), 4.28–4.25 (m, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 2.20 (s, 3H, CH_3 of $COCH_3$), 2.03 (s, 3H, CH_3 of $COCH_3$), 1.99 (s, 3H, CH_3 of $COCH_3$), 1.87 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.8, 169.6, 169.1, 166.3, 164.4, 163.7, 162.1, 154.6, 154.5, 142.0, 125.1, 125.0, 122.1, 112.1, 111.9, 104.3, 104.0, 90.3, 86.4, 74.3, 70.5, 68.0, 66.8, 62.5, 61.1, 20.5, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{26}FN_3O_{12}$ $[M + H]^+$ 592.1573; found: 592.1631.

4.2.17. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (41). Off white amorphous solid, R_f = 0.3 (ethyl acetate), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.52 (dd, *J* = 1.2 Hz, *J* = 14.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.13 (s, 1H), 5.90 (d, *J* = 9.6 Hz, 2H), 5.60–5.56 (m, 2H), 5.35 (s, 2H), 5.28 (dd, *J* = 3.2 Hz, *J* = 10.4 Hz, 1H), 4.26–4.24 (m, 1H), 4.20–4.17 (m, 1H), 2.21 (s, 3H, CH_3 of $COCH_3$), 2.04 (s, 3H, CH_3 of $COCH_3$), 2.00 (s, 3H, CH_3 of $COCH_3$), 1.90 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.9, 169.7, 169.1, 165.5, 163.3, 143.0, 138.3, 131.3, 122.9, 122.2, 121.7, 115.9, 115.3, 97.1, 86.4, 74.2, 70.7, 67.9, 66.8, 62.2, 61.1, 20.62, 20.60, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{28}N_4O_{11}$ $[M + H]^+$ 573.1827; found: 573.1889.

4.2.18. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((8-fluoro-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (42). Light yellow solid, R_f = 0.32 (ethyl acetate), ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (brs, 1H), 8.01 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.11 (td, *J* = 5.2 Hz, *J* = 8.0 Hz, 1H), 6.10 (s, 1H), 5.89 (d, *J* = 9.2 Hz, 1H), 5.58–5.53 (m, 2H), 5.32 (s, 2H), 5.29–5.25 (m, 1H), 4.27–4.24 (s, 1H), 4.20–4.11 (m, 2H), 2.21 (s, 3H, CH_3 of $COCH_3$), 2.05 (s, 3H, CH_3 of $COCH_3$), 2.01 (s, 3H, CH_3 of $COCH_3$), 1.90 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 170.3, 169.9, 169.7, 169.1, 164.2, 162.5, 150.6, 148.2, 142.7, 127.5, 127.4, 122.0, 121.5, 118.5, 117.2, 116.2, 116.0, 98.2, 86.3, 74.1, 70.6, 67.9, 66.9, 62.2, 61.2, 20.6, 20.6, 20.4, 20.1. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{27}FN_4O_{11}$ $[M + H]^+$ 591.1733; found: 591.1785.

4.2.19. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((8-nitro-2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (43). Yellow amorphous solid R_f = 0.25 (7 : 3, ethyl acetate : hexane, v/v) ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (dd, *J* = 1.5 Hz, *J* = 8.0 Hz, 1H), 8.24 (dd, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H), 8.00 (s, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 6.13 (s, 1H), 5.86 (d, *J* = 7.2 Hz, 1H), 5.54 (dd, *J* = 1.0 Hz, *J* = 3.0 Hz, 1H), 5.52–5.48 (m, 1H), 5.31 (s, 2H), 5.25–5.23 (m, 1H), 4.25–4.22 (m, 1H), 4.19–4.12 (m, 2H), 2.18 (s, 3H, CH_3 of $COCH_3$), 2.02 (s, 3H, CH_3, of $COCH_3$), 1.98 (s, 3H, CH_3 of $COCH_3$), 1.87 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.9, 169.8, 169.3, 142.2, 133.7, 131.3, 128.8, 122.1, 120.9, 118.1, 98.6, 86.5, 74.3, 70.6, 68.0, 66.8, 62.5, 61.2, 20.7, 20.5, 20.3. HRMS (ESI), *m*/*z* calcd for $C_{26}H_{27}N_5O_{13}$ $[M + H]^+$ 618.1678; found: 618.1728.

4.2.20. (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(((2-oxo-8-(trifluoromethoxy)-1,2-dihydro-quinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (44). Light brown solid, R_f = 0.27 (7 : 3, ethyl acetate : hexane, v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.34 (s, 1H, NH), 8.03 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.11 (s, 1H),

5.90 (d, J = 9.2 Hz, 1H), 5.58–5.53 (m, 2H), 5.32 (s, 2H), 5.30–5.26 (m, 1H), 4.28–4.25 (m, 1H), 4.26–4.18 (m, 1H), 4.16–4.09 (m, 1H), 2.20 (s, 3H, CH_3 of $COCH_3$), 2.03 (s, 3H, CH_3 of $COCH_3$), 1.99 (s, 3H, CH_3 of $COCH_3$), 1.88 (s, 3H, CH_3 of $COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 169.8, 169.7, 169.1, 163.2, 162.4, 142.5, 134.9, 130.8, 121.9, 121.6, 121.5, 117.2, 98.3, 86.4, 74.2, 70.6, 67.9, 66.8, 62.3, 61.1, 20.6, 20.4, 20.1. HRMS (ESI), m/z calcd for $C_{27}H_{27}F_3N_4O_{12}$ $[M + H]^+$ 657.165; found: 657.1710.

4.3. General experimental procedure for the global deacetylation of triazole linked *N*-glycosides

In a 50 mL round bottomed flask, 50 mg (0.087 mmol) of acetylated compound **27** was taken in methanol, and then NaOMe (1.41 mg, 0.0261 mmol) was added and the mixture was stirred for 2 h at room temperature. The methanol was evaporated *in vacuo* using a rotary evaporator to a get crude residue. The crude residue was purified by flash column chromatography which furnished the pure compound **45** (28.9 mg) in 80% isolated yield. A similar reaction protocol was adopted for the removal of acetate groups on compounds **27–28**, **33**, and **35–39**, and deacetylated products **45–51** were obtained in good to very good isolated yields (79–91%).

4.3.1. 6-Chloro-4-((1-((2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one (45). Off white amorphous solid, R_f = 0.61 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.72–7.70 (m, 1H), 7.69–7.67 (m, 1H), 7.13–6.96 (m, 1H), 5.50 (d, J = 9.6 Hz, 1H), 4.51 (s, 2H), 4.13 (dd, J = 3.2 Hz, J = 5.6 Hz, 1H), 4.02 (dd, J = 7.2 Hz, J = 14.0 Hz, 1H), 3.77–3.72 (m, 2H), 3.69–3.66 (m, 2H), 3.25–3.18 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.5, 167.4, 148.2, 132.0, 129.1, 123.6, 122.3, 87.8, 80.3, 77.4, 72.5, 70.0, 67.8, 63.2, 61.2. HRMS (ESI), m/z calcd for $C_{18}H_{18}ClN_3O_8$ $[M + Na]^+$ 463.3043; found: 463.3035.

4.3.2. 6-Methyl-4-((1-((2*R*,3*S*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one (46). Off white amorphous solid, R_f = 0.7 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s 1H), 7.53 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 2.4 Hz, 8.4 Hz, 1H), 6.17 (s, 1H), 5.42 (s, 2H), 3.82–3.78 (m, 1H), 3.71–3.69 (m, 1H), 3.47 (brs, 1H), 3.44–3.43 (m, 1H), 3.38 (brs, 1H), 3.36 (brs, 1H), 3.35 (brs, 1H), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 162.1, 151.4, 146.7, 141.3, 134.1, 133.3, 129.7, 125.1, 116.7, 114.0, 91.7, 80.5, 71.3, 72.5, 70.0, 65.3, 20.7. HRMS (ESI), m/z calcd for $C_{19}H_{21}N_3O_8$ $[M + H]^+$ 420.1401; found: 420.1376.

4.3.3. 4-((1-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one (47). White amorphous solid, R_f = 0.71 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.77 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.65 (dt, J = 1.6 Hz, J = 8.4 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.19 (s, 1H), 5.43 (s, 2H), 4.71–4.66 (m, 2H), 4.09–4.03 (m, 1H), 3.77–3.71 (m, 2H), 3.58–3.43 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6), δ 164.8, 162.0, 153.2, 141.4, 133.2, 124.6, 123.3, 116.9, 115.5, 91.8, 88.6, 79.7, 78.9, 74.1, 63.2, 60.9. HRMS (ESI), m/z calcd for $C_{18}H_{19}N_3O_8$ $[M + Na]^+$ 428.1070; found: 428.1044.

4.3.4. 6-Methoxy-4-((1-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one (48). Brown amorphous solid, R_f = 0.71 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.26 (dd, J = 3.2 Hz, J = 9.2 Hz, 1H), 7.14 (d, J = 3.2 Hz, 1H), 6.19 (s, 1H), 5.53 (d, J = 9.6 Hz, 1H), 5.45 (s, 2H), 4.06 (t, J = 9.6 Hz, 2H), 3.78 (s, 3H, OCH_3), 3.74–3.71 (m, 1H), 3.57–3.53 (m, 2H), 3.51–3.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 162.1, 155.9, 147.6, 141.1, 124.8, 120.7, 118.2, 116.0, 105.5, 92.1, 88.6, 78.9, 74.0, 69.7, 68.9, 63.1, 60.8, 56.2. HRMS (ESI), m/z calcd for $C_{19}H_{21}N_3O_4$ $[M + H]^+$ 436.1351; found: 436.1357.

4.3.5. 6-Methyl-4-((1-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one (49). White amorphous solid, R_f = 0.61 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, CD_3OD): δ 8.47 (s, 1H), 7.57 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.00 (s, 1H), 5.40 (s, 2H), 4.17 (t, J = 9.6 Hz, 1H), 3.97 (d, J = 4.0 Hz, 1H), 3.86–3.82 (m, 1H), 3.78–3.75 (m, 1H), 3.74–3.73 (m, 1H), 3.71–3.70 (m, 1H), 3.69–3.68 (m, 1H), 2.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 165.6, 163.8, 151.3, 134.2, 133.5, 122.4, 116.0, 114.9, 90.3, 88.9, 78.6, 73.8, 70.0, 68.9, 62.2, 61.0, 19.4. HRMS (ESI), m/z calcd for $C_{19}H_{21}N_3O_8$ $[M + H]^+$ 420.1401; found: 420.1376.

4.3.6. 6-Bromo-4-((1-((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one (50). Brown amorphous solid, R_f = 0.62 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 1H), 7.81 (t, J = 1.6 Hz, 1H), 7.41–7.40 (m, 1H), 7.39 (t, J = 2.0 Hz, 1H), 6.26 (s, 1H), 5.54 (d, J = 9.2 Hz, 1H), 5.44 (s, 2H), 4.06 (t, J = 9.2 Hz, 1H), 4.01 (s, 1H), 3.76–3.75 (m, 1H), 3.73–3.71 (m, 1H), 3.56 (dd, J = 3.2 Hz, J = 9.2 Hz, 1H), 3.51 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 161.5, 152.3, 141.3, 135.8, 125.4, 125.3, 124.8, 119.4, 117.4, 116.4, 92.7, 91.5, 88.7, 78.9, 74.0, 69.8, 69.3, 68.9, 63.4, 60.9, 57.7, 54.2. HRMS (ESI), m/z calcd for $C_{18}H_{18}BrN_3O_8$ $[M + Na]^+$ 506.0169; found: 506.0145.

4.3.7. 8-Nitro-4-((1-((2*R*,3*S*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)-quinolin-2(1*H*)-one (51). Yellow amorphous solid, R_f = 0.71 (1 : 9, methanol : ethyl acetate, v/v), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (s, 1H), 8.45 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 8.20 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 6.39 (s, 1H), 5.59 (d, J = 8.8 Hz, 1H), 5.52 (brs, 1H), 5.40 (s, 2H), 5.29 (brs, 1H), 4.73 (brs, 1H), 3.83–3.79 (m, 1H), 3.69 (d, J = 6.8 Hz, 1H), 3.27 (t, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.6, 161.8, 141.6, 134.1, 133.2, 130.9, 128.9, 124.8, 121.7, 117.6, 98.7, 88.0, 80.4, 77.3, 72.5, 69.9, 63.0, 61.1. HRMS (ESI), m/z calcd for $C_{18}H_{19}N_5O_9$ $[M + H]^+$ 450.1256; found: 450.1257.

4.4. Cell culture

HepG2, MCF-7, HCT-116 and Huh-7.5 cell lines were cultured in DMEM (Himedia, India), provided with 5% CO_2, 10% fetal bovine serum (Gibco, USA) and 1% penicillin–streptomycin

(Gibco, USA) at 37 °C under humid conditions. Cells were monitored and cultured every alternate day and cells used for assays are of less than 12 passages.

4.5. Cell viability assay

Cells under healthy conditions were trypsinized using 0.05% trypsin–EDTA (Gibco, USA) and a single cell suspension was prepared. Cells were counted using a hemocytometer and 50 000 cells per well were seeded in a 12 well plate. Cells were allowed to attach properly for 8 h followed by compound treatment and incubation at 37 °C for 48 h. Compounds (**25–51**) dissolved in DMSO were treated at 20 μM concentration and cell viability in HepG2 and MCF-7 cell lines and for selected compounds **26**, **28**, **40** and **44**, cell viability in HCT-116 and Huh-7.5 cell lines was studied through cell counting, after 48 h of treatment. DMSO (vehicle control) and **doxorubicin** (positive control) were used as controls during this assay. The active compound **28** was then checked further in the MCF-7 cell line at 1 μM, 5 μM, 10 μM, 15 μM and 20 μM concentrations for 48 h and viable cells were washed with PBS, trypsinized and resuspended, followed by counting using a hemocytometer. IC_{50} of the compound was calculated using the Origin software. To observe changes in cell morphology, cells treated with different concentrations (1 μM, 5 μM, 10 μM, 15 μM and 20 μM) of compound **28** or DMSO (control) were observed under DIC, using a Nikon-Ti Microscope.

4.6. H_2DCFDA mediated ROS detection assay

Cancer cells (HepG2, MCF-7, HCT-116 and Huh-7.5) were trypsinized and suspended in DMEM. Using a hemocytometer, 50 000 cells were seeded in a 35 mm culture dish and allowed to attach properly for 8 h. Cells were treated with compounds **26**, **28**, **40** and **44** at 10 μM concentration along with the control (DMSO). Cells were then incubated for 48 h and DAPI was added 24 h post compound treatment. After 48 h, the medium of the cells was discarded and the cells were washed twice with phosphate buffer saline (PBS). The medium was added again and the cells were treated with 1 μM H_2DCFDA (Sigma, USA) for 15 minutes in an incubator under dark conditions. After 15 minutes, the cells were again washed with PBS and ROS production was detected using a Nikon-Ti Microscope.

4.7. COMET assay

MCF-7 cells were treated with DMSO (control), compound **28** and **doxorubicin** at 10 μM concentration for 48 h. After 48 h, the cells were washed with PBS, trypsinized and 50 000 cells were seeded in a 35 mm culture dish followed by compound treatment and incubation for 48 h. After 48 h, the cells were again washed and trypsinized. Here 25 000 cells were counted and taken for further assays. Cells were pelleted at 4 °C and resuspended in 50 μL PBS. A primary gel layer was prepared on a glass slide using 1% agarose (Himedia, India). Now suspended cells were mixed with 0.5% low melting agarose and placed on a primary layer uniformly. Slides were then incubated at 4 °C for 10 minutes till proper solidification. These slides were kept in lysis buffer (2.5 M NaCl, 100 mM EDTA, 10 mM Tris base, pH adjusted to 10, 1% Triton X added fresh) for 2 h at 4 °C. After 2 h, the cells were washed once in distilled water and transferred to electrophoresis buffer (300 mM NaOH, 1 mM EDTA, pH adjusted to 13) for unwinding at 4 °C for 20 minutes. Electrophoresis was performed in the same buffer for 35 minutes at 25 V, 400 mA. After electrophoresis, the slides were transferred into 1× EtBr solution (10× stock-20 μg mL^{-1}) for DNA staining. The slides were then transferred to autoclaved distilled water and washed for 10 minutes. Comets were visualized at 10× and 40× magnification, using a Nikon-Ti (U. S. A.) microscope.

Conflicts of interest

There are no conflicts of interest to declare.

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