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Expedient synthesis of coumarin-coupled triazoles via 'click chemistry' leading to the formation of coumarin–triazole–sugar hybrids

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ABSTRACT

Coumarin-based triazoles were synthesized from 3-azidomethylcoumarin and a terminal acetylenic compound. Uncatalysed thermal conditions result in a mixture of both 1,4- and 1,5-regioisomers or the thermodynamically more stable 1,4-regioisomer, whereas the Cu(I)-catalysed reaction affords only the favourable 1,4-regioisomer. B3LYP/6-31G(d) level of theory has been used to calculate geometry and frequency features of the reactants, transition states (**TS**s) and products. Computational studies further reveal that 1,4-regioisomeric products are more favourable and also thermodynamically more stable compared to the 1,5-regioisomers.

1. Introduction

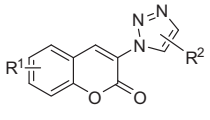
N-Heterocyclic compounds are broadly distributed in nature and include amino acids, purines, pyrimidines and many other natural products. *N*-Heterocyclic compounds, such as [1,2,3]-triazoles, benzimidazoles and benzothiazoles, display a wide range of biological activities[1] and have also found extensive industrial applications, such as dyes, corrosion inhibitors, photo stabilizers, photographic materials and agrochemicals.[2]

Some of the heterocyclic glycoconjugates, such as nucleosides and nucleotides, act as primary building blocks of nucleic acids and are widespread in nature. Certain heterocyclic-based carbohydrates of natural and unnatural origins containing exocyclic nitrogen atoms exhibit valuable biological activities.[3,4] In general the carbohydrate derivatives reported in the literature[5] are known to possess good therapeutic profiles of solubility, in vivo stability, target-binding affinity and cell permeability. Due to an increasing need to decipher the information contained in complex carbohydrates, simple and readily accessible methods for high-throughput analysis must be developed. 'Click chemistry' has been reported to be one of the most frequently used approaches in glycochemistry[6] where libraries of compounds can be quickly synthesized. Ferrieres and co-workers[7] have employed a mild uncatalysed 1,3-DCR (1,3-dipolar cycloaddition reaction) to generate a series of saccharidyl 1,4,5-trisubstituted-1,2,3-triazoles as heterocyclic analogues.

As a privileged scaffold, coumarin is an ubiquitous subunit in many natural products with remarkable biological activities and unique physical properties.[8–10] Recently Wang and co-workers[11] have synthesized a coumarin-containing triazole structure where the triazole ring is directly linked to the third position of the coumarin moiety (Fig. 1).

It is to be noted that 1,2,3-triazoles, can be prepared through two possible pathways in which the catalysed route affords 1,4-disubstituted-1,2,3-triazoles, and the non-catalysed route affords a mixture of 1,4- and 1,5-disubstituted-1,2,3-triazoles (Fig. 2). Regioselectivity is influenced in a complicated manner by the presence of substituents on the acetylenic and azido compounds as well as on the reaction conditions.

The present investigation focuses on the effect of the reaction conditions, either the thermal or Cu(I)-catalysed pathway chosen by alkyne moieties to synthesize 1,2,3-triazoles from 3-azidomethylcoumarin. As a guide to the present work, we chose the alkyne moieties in such a way that the regioselectivity is explained by both experimental and DFT calculations. Thus, in this report we



R^1 = H, OH, Et_3N, Br, OCH_3
R^2 = C_6H_5, C_7H_7, $C_7H_4F_3$, C_6H_4F, C_6H_4Cl, C_6H_4Br

Figure 1. Coumarin triazole compounds known in the literature.[11]

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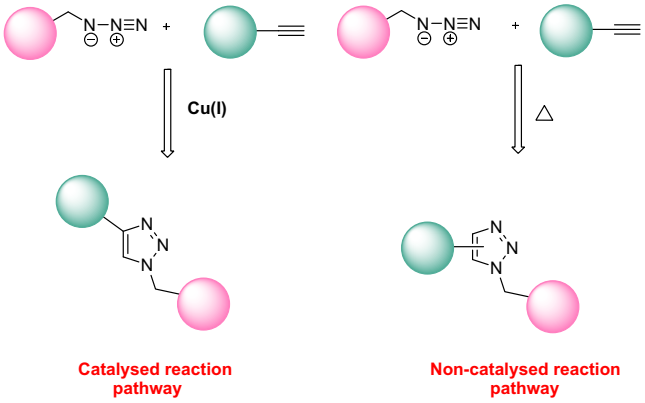
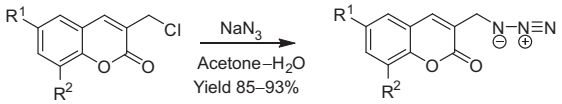


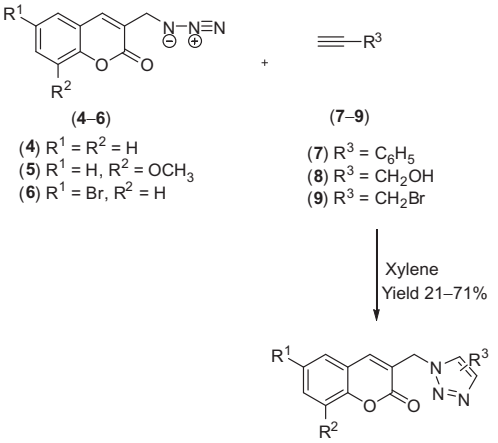
Figure 2. Two possible pathways in the synthesis of triazole compounds.



(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = H$, $R^2 = OCH_3$
(**3**) $R^1 = Br$, $R^2 = H$

(**4**) $R^1 = R^2 = H$
(**5**) $R^1 = H$, $R^2 = OCH_3$
(**6**) $R^1 = Br$, $R^2 = H$

Scheme 1. Synthesis of 3-azidomethyl coumarin (**4**–**6**).



(**4**–**6**)
(**4**) $R^1 = R^2 = H$
(**5**) $R^1 = H$, $R^2 = OCH_3$
(**6**) $R^1 = Br$, $R^2 = H$

(**7**–**9**)
(**7**) $R^3 = C_6H_5$
(**8**) $R^3 = CH_2OH$
(**9**) $R^3 = CH_2Br$

(**10**–**18**)
(**10**) $R^1 = R^2 = H$, $R^3 = 4\text{-}C_6H_5$, $5\text{-}C_6H_5$
(**11**) $R^1 = R^2 = H$, $R^3 = 4\text{-}CH_2OH$
(**12**) $R^1 = R^2 = H$, $R^3 = 5\text{-}CH_2OH$
(**13**) $R^1 = R^2 = H$, $R^3 = 4\text{-}CH_2Br$
(**14**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = 4\text{-}C_6H_5$, $5\text{-}C_6H_5$
(**15**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = 4\text{-}CH_2OH$
(**16**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = 5\text{-}CH_2OH$
(**17**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = 4\text{-}CH_2Br$
(**18**) $R^1 = Br$, $R^2 = H$, $R^3 = 4\text{-}CH_2Br$

Scheme 2. Synthesis of coumarin-coupled triazole compounds (**10**–**18**).

have demonstrated that the use of these conditions provides a simple and general method for the synthesis of coumarin-coupled triazole compounds. In order to obtain further insight into the structure–function relationships among the triazoles, we have generated a library of triazole derivatives linked via a methylene group to coumarin. Although there exist several reports on triazoles in the recent literature,[12] to our knowledge this is the first report on sugar-containing coumarin-triazole derivatives substituted at the 3-position of coumarin via a methylene group.

2. Results and discussion

In this study we employed 3-azidomethyl coumarin and acetylenic derivatives to prepare coumarin-coupled triazole compounds linked via a methylene group. 3-Chloromethylcoumarins (**1**–**3**) were synthesized and characterized by adopting the literature procedure.[13] Reaction of **1**–**3** with sodium azide in acetone gave the corresponding 3-azidomethyl coumarin derivatives (**4**–**6**) in 85–93% yields (Scheme 1), and these compounds were characterized by NMR spectroscopy, mass spectrometry and elemental analysis.

6-Bromo-3-azidomethylcoumarin (**6**) crystallizes from chloroform in an orthorhombic lattice in a monoclinic space group $P2_1/c$. An ORTEP view and crystal packing diagram are shown in Figure 3. The coumarin moiety is nearly planar with atom C10, which shows only a minimal deviation (0.026(1) Å) from the mean plane. The molecule and its centre of inversion along with $(a + c)$ translations form a one-dimensional π–π stacking arrangement. The normal distance between the molecule and its (stacking) translational equivalents (sym: $-x, -y, 1 - z$) are 3.463 (3) Å and 3.551 (3) Å (sym: $1 - x, 1 - y, 2 - z$), respectively.

As shown in Scheme 2, reaction of 3-azidomethylcoumarin derivatives (**4**–**6**) with propargyl bromide (**9**) in xylene under thermal conditions furnishes primarily 1,4-disubstituted triazole products **13**, **17** and **18** in 61–71% yields. Reaction of propargyl alcohol (**8**) with 3-azidomethylcoumarins **4** and **5** affords 1,4- (**11** and **15**) and 1,5-triazole (**12** and **16**) compounds that were separated through column chromatography in 45–59% and 21–23% yields, respectively. Reaction of phenylacetylene (**7**) with 3-azidomethylcoumarin derivatives **4** and **5** affords an inseparable mixture of 1,4- and 1,5-isomers **10** and **14** in a ratio of 1:0.8 and 1:0.25, respectively, as determined from NMR studies. However, the ratio of these isomers depends upon the electronic and steric effects as has been reported with a similar kind of derivatives.[14]

Synthesis of compounds containing a coumarin triazole moiety was further extended to carbohydrate derivatives. The propargyl glycosides **19**, **20**, **21** and **22** were synthesized from readily available sugars, viz., D-glucose, D-galactose, 4,6-*O*-ethylidene-D-glucopyranose and 4,6-*O*-butylidene-D-glucopyranose, from the corresponding acetylated sugars by treatment with propargyl alcohol in the presence of borontrifluoride etherate.[15]

Attempts to couple 3-azidomethylcoumarins **4**–**6** with the propargyl glycoside of D-glucose did not result in the expected products under thermal conditions. Though few literature reports are focussed on cycloaddition reactions of propargylglycosides under thermal conditions,[16] the same strategy seemed to be

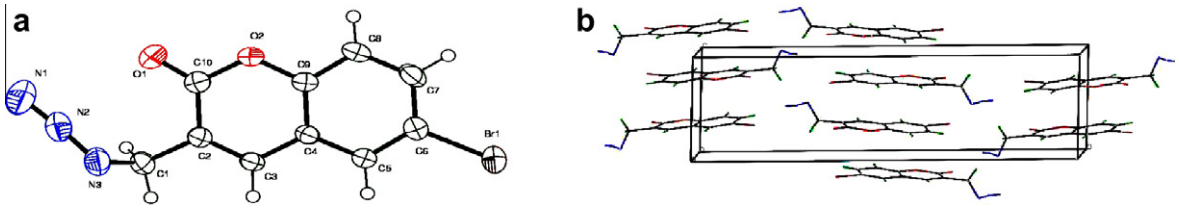


Figure 3. (a) Single-crystal XRD and (b) crystal-packing diagram of compound **6**.

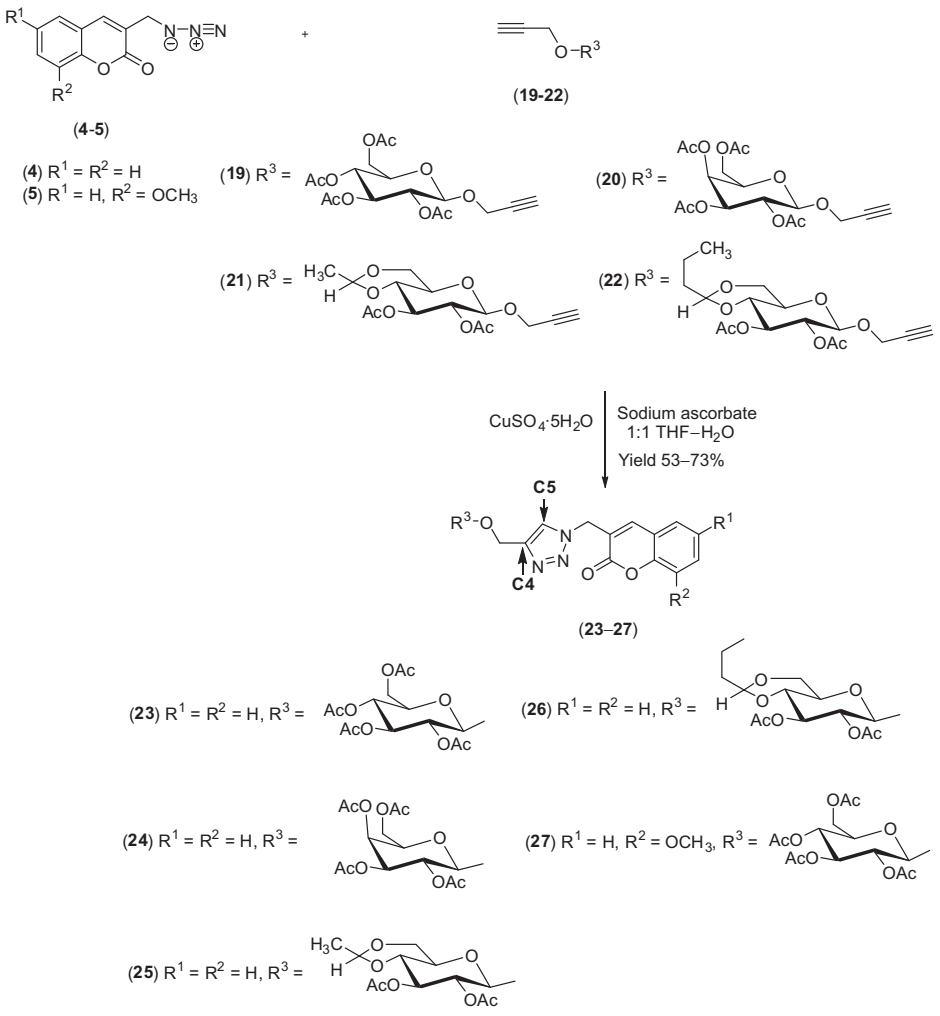
unappealing for our molecules, since these labile molecules do not survive at elevated temperature. Therefore, an alternate strategy has been chosen, and the present investigations revealed a mild and efficient method for synthesizing [1,2,3]-triazoles using Cu(I) as catalyst. To our expectations, Cu(I)-catalysed reaction conditions resulted in the formation of the expected products **23**–**27** in 53–73% yield (Scheme 3). The Cu(I)-catalysed reaction results in the thermodynamically more favourable 1,4-regioisomer and not the 1,5-regioisomer.

In the ^{1}H NMR spectra of both non-sugar (**10**–**18**) and sugar-hybrid (**23**–**27**) coumarin triazole derivatives, the triazole proton appears as singlet in the range 6.94–8.07 ppm, while the allylic methylene resonances were observed at 3.9 ppm. In their ^{13}C NMR spectra the triazole carbons appear in the range 144.2–151.7 and 122.8–124.6 ppm. The triazole proton in 1,4-regioisomeric compounds **11** and **15** was found at 7.05 and 7.88 ppm, respectively, whereas in the case of 1,5-regioisomeric compounds **12** and **16**, it was shifted upfield to 6.94 and 7.67 ppm, respectively. Similar observations were reported in the literature for 1,4- and 1,5-substituted triazoles.[17] Moreover, the $\Delta(\delta_{C4}-\delta_{C5})$ values of compounds **11** and **15** were calculated as 25.7 and 27.1 ppm, respectively, whereas for compounds **12** and **16** the $\Delta(\delta_{C4}-\delta_{C5})$ values were 22.3 and 23.2, respectively. These results further support our observations that $\Delta(\delta_{C4}-\delta_{C5})$ values of 1,4-regioisomeric compounds are comparatively larger than those for 1,5-regioisomers, which is in accordance with the values reported in the literature.[18] ^{1}H NMR spectra of coumarin triazole phenyl hybrids **10** and **14** reveal the presence of a mixture of both 1,4- and 1,5-isomers in a ratio of 1:0.8 and 1:0.25, respectively. In contrast to phenylacetylene **7** and propargyl alcohol **8**, propargyl bromide **9** results only in the favourable 1,4-regioisomers **13**, **17** and **18** as confirmed by NMR studies.

Compounds **23**–**27** were shown to be in the β-anomeric form as evidenced by a wide doublet for H-1 (δ 4.6 ppm, J = 7.8 Hz). The ^{13}C NMR spectra of triazole compounds **23**–**27** confirmed the presence of conjugated products as the anomeric carbon was identified at 99.7–100.1 ppm. ^{13}C NMR analyses of compounds **23**–**27** were also carried out: the relatively large $\Delta(\delta_{C4}-\delta_{C5})$ values for the different triazoles, ranging from 19.3 to 21.5 ppm, indicate that these compounds are 1,4-regioisomers, since much smaller values would be expected for 1,5-regioisomers.[18] (Table 1)

2.1. Computational studies

Earlier studies reveal that the B3LYP hybrid functional in density functional theory (DFT)[19,20] is a reliable method for studying Diels–Alder reactions.[21] Hence, geometry optimization and frequency calculations were carried out on the reactants, transition states (**TS**s) and products using the B3LYP/6-31G(d) level of theory. All gas-phase-optimized stationary points were verified as minima or first-order saddle points by the frequency calculations. All calculations were performed with the GAUSSIAN 03[22] program package. The geometries of the **TS** are depicted in Figure 4.



Scheme 3. Synthesis of coumarin-coupled triazole saccharide compounds (**23**–**27**).

Table 1
^{13}C NMR analysis of triazole compounds **23–27**

Compd No.	C-4	C-5	$\Delta(\delta_{C4} - \delta_{C5})$ ppm
23	144.4	124.9	19.5
24	144.2	124.9	19.3
25	145.1	125	20.1
26	144.4	124.9	19.5
27	144.3	122.8	21.5

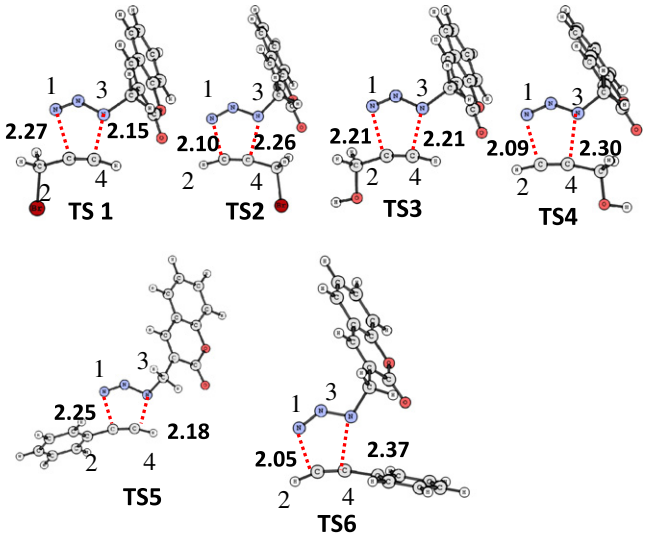


Figure 4. B3LYP/6-31G(d)-optimized geometries of concerted transition states of 3-methylazidocoumarin with propargyl bromide (**TS 1** and **2**), propargyl alcohol (**TS 3** and **4**) and phenyl acetylene (**TS 5** and **6**) along with distances in Å.

All geometries of all transition states namely propargyl bromide (**TS 1** and **2**), propargyl alcohol (**TS 3** and **4**) and phenyl acetylene (**TS 5** and **6**) are depicted in Figure 4. Analysis of the geometries of the **TS** reveals that all **TSs** are nearly synchronous and concerted in nature. Calculated activation and reaction energies for various reactions are presented in Table 2 along with the calculated dipole moments. Examination of the results shows that the reaction free-energy of 1,4-products is higher than that of the 1,5-products. Thus 1,4-products are thermodynamically favourable, whereas the formation of 1,5-products is kinetically controlled. These findings are in accordance with the experimental observations. It can be noted from Table 2 that the substituent marginally influences the formation of the products, and Figure 4 illustrates the effect of substitution on the reactivity of 1,3-dipolar compounds with acetylene. Upon substitution the synchronicity is lost, and the steric hindrance from coumarin plays an important role in the regioselectivity. Moreover, the substitution of various functional groups on acetylene affects the bond lengths in **TS**. For example, the calculated distances (1–2 and 3–4) in **TS5** are different due to substitution of the phenyl group. In the case of **TS6** these distances are 2.05 and 2.34 Å, respectively. The trend obtained in this study is akin to that of a recent study on the unsubstituted 1,3-dipolar compounds with acetylene and ethylene carried out by Houk and co-workers. A new distortion/interaction energy model has been proposed for the 1,3-dipolar cycloaddition reactivity. The qualitative comparison of the present results with those of an earlier finding indicates that the origin of regioselectivity in these systems is mainly due to the substitution of various functional groups.

It can be noted from Figure 5 that the steric hindrance between coumarin and substituent groups destabilizes the structure of 1,5-**TSs** when compared to that of the 1,4-product. This effect is also reflected in the corresponding energies. As a result, the exothermicities of the 1,4-reactions are higher than those of the 1,5-reactions as evidenced from the reaction energies. Therefore, the 1,4-products are thermodynamically more favourable in comparison with the 1,5-products, which are kinetically controlled. These observations are also in accordance with the results of higher temperature studies.[23]

3. Conclusion

In summary, the Cu(I)-catalysed reaction pathway is the more efficient route for propargyl glycosides to undergo cycloaddition with azidomethylcoumarin. The non-catalysed reaction pathway chosen by the acetylenic derivatives seems to be unsuitable for propargyl glycosides. Studies further suggest that 1,4-products are thermodynamically controlled processes, and it is consistent with experimental observations that 1,4-products are the major products in all cases. However, the introduction of 1-methyltriazole is expected to result in analogues with improved bioactivity and pharmacokinetic profiles. For future applications the present results should provide caution on the use of thermal reaction conditions in connection with propargyl glycosides. Alternatively Cu(I)-catalysed reaction conditions offer a clear promise for the synthesis of coumarin–triazole–sugar hybrids.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 300 NMR spectrometer using tetramethylsilane (Me_4Si) as the internal standard. High-resolution mass spectra (HRMS) were carried out on a Jeol GC mate mass spectrometer in the electrospray-ionization (ESI) mode at IIT Madras (Chennai, India). Elemental analysis was carried out using an Eager 300 C,H,N analyser at IIT Bombay (Mumbai, India). Single-crystal XRD studies were performed using a Bruker axs (kappa apex 2) analyser at IIT Madras (Chennai, India). Thin-layer chromatography (TLC) was performed on manually coated plates (Acme) with detection by UV light or iodine vapour. Column chromatography was performed using SiO_2 (Acme 100–200 mesh). Earlier studies reveal that B3LYP[20,21] is a reliable method for studying Diels–Alder reactions.[22] Hence, geometry optimization and frequency calculations were carried out on the reactants, transition states (**TS**s) and products using B3LYP/6-31G* level of theory. All gas-phase-optimized stationary points

Table 2
Activation enthalpies, free energies and reaction energies (given in the brackets) at 298 K for the addition of an azido compound to an acetylenic compound[a]

S. No.	1,4-Product			1,5-Product		
	$\Delta^{\ddagger}H°$ [ΔHrxn]	$\Delta^{\ddagger}G°$ [ΔGrxn]	Dipole moment(D)	$\Delta^{\ddagger}H°$ [ΔHrxn]	$\Delta^{\ddagger}G°$ [ΔGrxn]	Dipole moment (D)
1	15.19 (−71.57)	27.98 (−57.04)	7.30	14.73 (−70.60)	27.68 (−54.73)	3.89
2	15.33 (−71.72)	28.00 (−57.63)	5.63	12.77 (−70.32)	25.6 (−55.82)	5.74
3	18.87 (−69.38)	31.48 (−54.52)	5.94	16.98 (−66.03)	29.63 (−50.78)	4.06

[a] Energies in kcal/mol at 298 K, B3LYP/6-31G* geometry and ZPVE corrections are included.

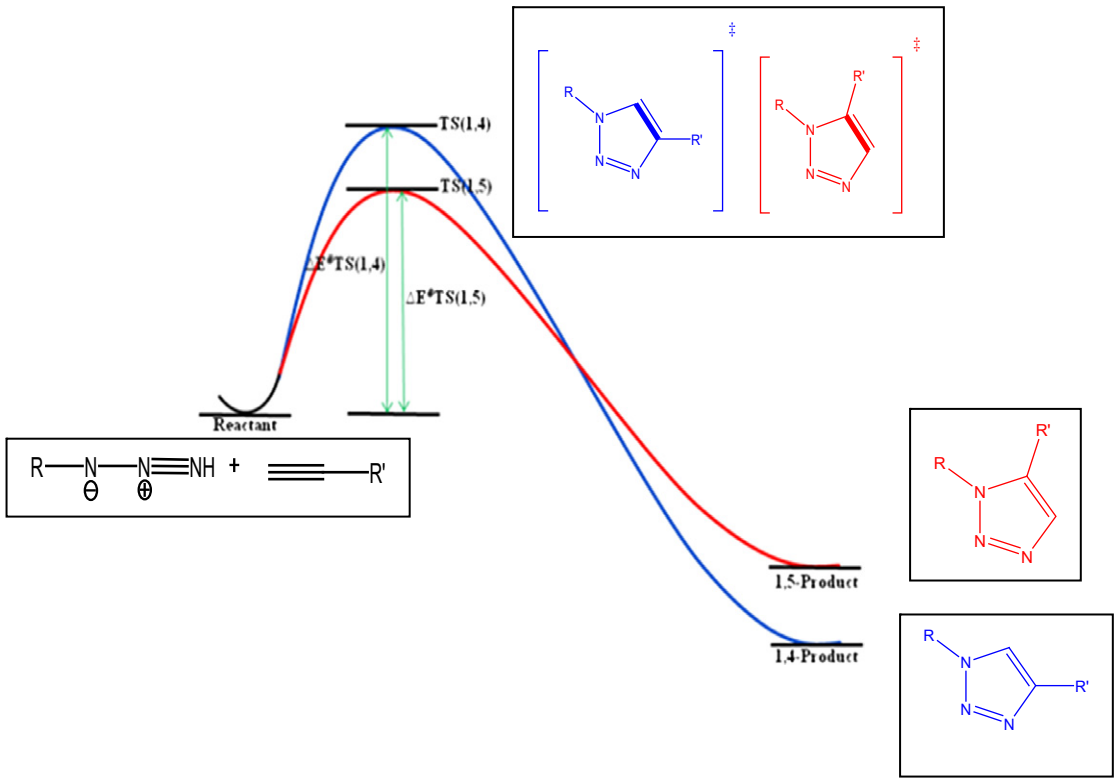


Figure 5. Energy profile of cycloaddition reaction.

were verified as minima or first-order saddle points by frequency calculations. All calculations were performed with the GAUSSIAN 03[23] program package. While assigning the spectral data, several abbreviations were used and these include 'Trz' for triazole, 'Cou' for coumarin, 'Phe' for phenyl, 'Sacc' for saccharide, 'Ace' for acetyl, 'Eth' for 4,6-*O*-ethylidene, 'But' for 4,6-*O*-butylidene and 'Ano' for anomeric.

4.2. General procedure for the synthesis of coumarin-coupled triazole compounds (10–18)

A mixture of 3-azidomethylcoumarin **4** (0.5 g, 2.5 mmol) and phenylacetylene (**7**, 0.27 mL, 2.5 mmol) in xylene (5 mL) was stirred overnight, and then the reaction mixture was refluxed for 7–9 h. The reaction mixture was cooled to room temperature, whereby a solid separated. The crude product was then filtered off and purified by column chromatography using a 1:9 MeOH–$CHCl_3$ as eluant, which afforded the expected compound **10**. Yellow solid (0.4 g, 53%); mp 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.07 (s, 2 × 1H, Trz-*H*), 7.85–7.73 (s, 2 × 1H, Cou-*H*), 7.58–7.41 (m, 2 × 4H, Cou-*H*), 7.4–7.27 (m, 2 × 3H, Phe-*H*), 5.53–5.48 (s, 2 × 2H, Cou-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 160–159.9 (2 × 1C, Cou-*C*═O), 153.3–148.2 (2 × 1C, Cou-*C*), 142.3–140.3 (2 × 1C, Trz-*C*), 133.3–124.8 (2 × 12C, Phe-*C*, Cou-*C*), 123.6–122.9 (2 × 1C, Trz-*C*), 120.9–116.7 (2 × 1C, Phe-*C*), 49.2–46.7 (2 × 1C, Cou-*C*H_2). HRESIMS: calcd for $C_{18}H_{13}N_3O_2$ ([M+1]), 303.1008, found: 303.1005. Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32, N, 13.85. Found: C, 71.51; H, 4.18, N, 13.25.

4.2.1. 3-((4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)coumarin (11) and 3-((5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-methyl)coumarin (12)

A mixture of 3-azidomethyl coumarin **4** (0.5 g, 2.5 mmol) and propargyl alcohol **8** (0.14 mL, 2.5 mmol) in xylene (5 mL) afforded compounds **11** and **12** on subsequent purification by column chromatography.

4.2.1.1. Data for 11. White solid (0.29 g, 45%); mp 182–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.05 (s, 1H, Trz-*H*), 6.99 (s, 1H, Cou-*H*), 6.81–6.86 (m, 2H, Cou-*H*), 6.55–6.6 (m, 2H, Cou-*H*), 4.73 (s, 2H, Cou-CH_2), 3.92 (s, 2H, Trz-CH_2), 1.84 (s, 1H, Trz-CH_2–O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.2 (1C, Cou-*C*═O), 158.3 (1C, Cou-*C*), 153.4 (1C, Trz-*C*), 147.2–128.2 (5C, Cou-*C*), 127.7 (1C, Trz-*C*), 123.5 (1C, Cou-*C*), 121.2 (1C, Cou-*C*), 60.5 (1C, Cou-*C*H_2), 53.8 (1C, Trz-*C*H_2): Anal. Calcd for $C_{13}H_{11}N_3O_3$ 257.24: C, 60.70; H, 4.31; N, 16.33. Found: C, 61.12; H, 4.57; N, 16.64.

4.2.1.2. Data for 12. White solid (0.14 g, 21%); mp 176–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.94 (s, 1H, Trz-*H*), 6.89 (s, 1H, Cou-*H*), 6.88–6.83 (m, 2H, Cou-*H*), 6.64–6.57 (m, 2H, Cou-*H*), 4.78 (s, 2H, Cou-CH_2), 4.01 (s, 2H, Trz-CH_2), 1.86 (s, 1H, Trz-CH_2-*OH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 160.7 (1C, Cou-*C*═O), 153.7 (1C, Cou-*C*), 144.7 (1C, Trz-*C*), 142.8–124.2 (5C, Cou-*C*), 122.4 (1C, Trz-*C*), 118.5 (1C, Cou-*C*), 116.6 (1C, Cou-*C*), 49.3 (1C, Cou-*C*H_2), 21.4 (1C, Trz-*C*H_2): Anal. Calcd for $C_{13}H_{11}N_3O_3$ 257.24: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.45; H, 4.21; N, 16.64.

4.2.2. 3-((4-(Bromomethyl)-1*H*-1,2,3-triazol-1-yl)methyl)-coumarin (13)

A mixture of 3-azidomethylcoumarin (**4**, 0.5 g, 2.5 mmol) and propargyl bromide (**9**, 0.3 mL, 2.5 mmol) in xylene (5 mL) afforded compound **13**. Brown solid (0.5 g, 62%); mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.9 (s, 1H, Trz-*H*), 7.77 (s, 1H, Cou-*H*), 7.60–7.48 (m, 2H, Cou-*H*), 7.37–7.29 (m, 2H, Cou-*H*), 5.46 (s, 2H, Cou-CH_2), 4.58 (s, 2H, Trz-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 160.7 (1C, Cou-*C*═O), 153.8 (1C, Cou-*C*), 144.9 (1C, Trz-*C*), 142.8–124.13 (5C, Cou-*C*), 122.5 (1C, Trz-*C*), 118.5 (1C, Cou-*C*), 116.8 (1C, Cou-*C*), 49.3 (1C, Cou-*C*H_2), 21.4 (1C, Trz-*C*H_2): Anal. Calcd for

$C_{13}H_{10}BrN_3O_2$ 320.14: C, 48.77; H, 3.15; N, 13.13. Found: C, 48.21; H, 2.87; N, 13.36.

4.2.3. 3-(4-(Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-8-methoxycoumarin (14)

A mixture of 8-methoxy-3-azidomethylcoumarin (**5**, 0.57 g, 2.5 mmol) and phenylacetylene (**7**, 0.3 mL, 2.5 mmol) in xylene (5 mL) afforded compound **14**. White solid (0.47 g, 66%); mp 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.06 (s, 2 × 1H, Trz-*H*), 7.85–7.82 (s, 2 × 1H, Cou-*H*), 7.68–7.17 (m, 2 × 3H, Cou-*H*), 7.11–6.96 (m, 2 × 3H, Phe-*H*), 5.53–4.86 (s, 2 × 2H, Cou-CH_2), 3.96 (s, 2 × 3H, Cou-OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 160.2–159.4 (2 × 1C, Cou-*C*=*O*), 148.1–147.0 (2 × 1C, Cou-*C*), 143.3–142.9 (2 × 1C, Trz-*C*), 142.4–124.8 (2 × 10C, Phe-C, Cou-*C*), 123.8–123.1 (2 × 1C, Trz-*C*), 121.0–113.9 (2 × 3C, Phe-*C*), 49.2–46.7 (2 × 1C, Cou-CH_2), 56.26 (2 × 1C, Cou-OCH_3). HRESIMS: calcd for $C_{19}H_{15}N_3O_3$ ([M+1]), 333.3407, found: 333.3405. Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 67.55; H, 4.17; N, 12.17.

4.2.4. 3-((4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)-8-methoxycoumarin (15) and 3-((5-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)-8-methoxycoumarin (16)

A mixture of 8-methoxy-3-azidomethylcoumarin (**5**, 0.57 g, 2.5 mmol) and propargyl alcohol (**8**, 0.14 mL, 2.5 mmol) in xylene (5 mL) afforded compounds **15** and **16** on subsequent purification by column chromatography.

4.2.4.1. Data for 15. White solid (0.37 g, 59%); mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.88 (s, 1H, Trz-*H*), 7.66 (s, 1H, Cou-*H*), 7), 7.29–7.23 (m, 1H, Cou-*H*), 7.16–7.08 (m, 2H, Cou-*H*), 5.48 (s, 2H, Cou-CH_2), 4.73 (s, 2H, Trz-CH_2), 3.97 (s, 3H, Cou-OCH_3) 2.6 (s, 1H, Trz-CH_2–O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.7 (1C, Cou-*C*=O), 153.5 (1C, Cou-*C*), 151.7 (1C, Trz-*C*), 147.8–128 (5C, Cou-*C*), 124.6 (1C, Trz-*C*), 124.1–119.1 (2C, Cou-*C*), 61.1 (1C, Cou-OCH_3), 60.6 (1C, Cou-CH_2), 53.7 (1C, Trz-CH_2): Anal. Calcd for $C_{14}H_{13}N_3O_4$ 287.27: C, 58.53; H, 4.56; N, 14.63. Found: C, 59.21; H, 4.96; N, 14.84.

4.2.4.2. Data for 16. White solid (0.15 g, 23%); mp 172–175 °C; ^{1}H NMR (300 MHz,$CDCl_3$): δ_H 7.67 (s, 1H, Trz-*H*), 7.34 (s, 1H, Cou-*H*), 7.25–7.21 (m, 1H, Cou-*H*), 7.14–7.01 (m, 2H, Cou-*H*), 5.54 (s, 2H, Cou-CH_2), 4.75 (d, *J* = *4.5 Hz*, 2H, Trz-CH_2), 3.97 (s, 3H, Cou-OCH_3), 2.6 (s, 1H, Trz-CH_2-O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.5 (1C, Cou-*C*=O), 151.7 (1C, Cou-*C*), 147.6 (1C, Trz-*C*), 145.8–128.3 (5C, Cou-*C*), 124.4 (1C, Trz-*C*), 124.1–118.8 (2C, Cou-*C*), 61 (1C, Cou-OCH_3), 57.3 (1C, Cou-CH_2), 51.58 (1C, Trz-CH_2): Anal. Calcd for $C_{14}H_{13}N_3O_4$ 287.27: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.17; H, 4.24; N, 14.15.

4.2.5. 3-((4-(Bromomethyl)-1*H*-1,2,3-triazol-1-yl)methyl)-8-methoxycoumarin (17)

A mixture of 8-methoxy-3-azidomethylcoumarin (**5**, 0.57 g, 2.5 mmol) and propargyl bromide (**9**, 0.3 mL, 2.5 mmol) in xylene (5 mL) afforded compound **17**. Brown solid (0.46 g, 61%); mp 160–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.04 (s, 1H, Trz-*H*), 7.79 (s, 1H, Cou-*H*), 7.3–7.23 (m, 1H, Cou-*H*), 7.18–7.12 (m, 2H, Cou-*H*), 5.5 (s, 2H, Cou-CH_2), 4.62 (s, 2H, Trz-CH_2), 3.98 (s, 3H, Cou-OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8 (1C, Cou-*C*=O), 151.7 (1C, Cou-*C*), 149.1 (1C, Trz-*C*), 147.9–127.5 (5C, Cou-*C*), 124.6 (1C, Trz-*C*), 123.9–119.2 (2C, Cou-*C*), 61.03 (1C, Cou-OCH_3), 54.01 (1C, Cou-CH_2), 26.6 (1C, Trz-CH_2). Anal. Calcd for $C_{14}H_{12}BrN_3O_3$ 350.17: C, 48.02; H, 3.45; N, 12.00. Found: C, 48.29; H, 3.58; N, 11.87.

4.2.6. 6-Bromo-3-((4-(bromomethyl)-1*H*-1,2,3-triazol-1-yl)methyl)coumarin (18)

A mixture of 6-bromo-3-azidomethylcoumarin (**6**, 0.7 g, 2.5 mmol) and propargyl bromide (**9**, 0.3 mL, 2.5 mmol) in xylene (5 mL) afforded compound **18**. White solid (0.53 g, 71%); mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.89 (s, 1H, Trz-*H*), 7.69 (s, 1H, Cou-*H*), 7), 7.65 (s, 1H, Cou-*H*), 7.32–7.25 (m, 2H, Cou-*H*), 5.47 (s, 2H, Cou-CH_2), 4.59 (s, 2H, Trz-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 160 (1C, Cou-*C*=O), 152.6 (1C, Cou-*C*), 145.02 (1C, Trz-*C*), 141.3–124.2 (4C, Cou-*C*), 123.7 (1C, Trz-*C*), 119.9 (1C, Cou-*C*), 118.5–117.6 (2C, Cou-*C*), 49.2 (1C, Cou-CH_2), 21.3 (1C, Trz-CH_2). Anal. Calcd for $C_{13}H_9Br_2N_3O_2$ 399.04: C, 39.13; H, 2.27; N, 10.53. Found: C, 39.67; H, 2.59; N, 10.16.

4.3. General procedure for the synthesis of coumarin-coupled triazole compounds (23–27)

To a vigorously stirring suspension of 2-propyn-1-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**19**, 0.21 g, 0.6 mmol) in 1:1 THF–H_2O was added 3-azidomethylcoumarin (**4**, 0.11 g, 0.6 mmol). The reaction was initiated by the addition of $CuSO_4{\cdot}5H_2O$ (0.014 g, 0.05 mmol) and sodium ascorbate (0.022 g, 0.1 mmol). The suspension was stirred vigorously at 40 °C for 2 h. At this time TLC indicated completion of the reaction. Distilled water was added, and the aqueous layer was extracted with $CHCl_3$ (2 × 25 mL). The combined extracts were dried, filtered and evaporated to afford a brownish oily residue. The product was then purified using column chromatography using 3:7 MeOH–$CHCl_3$ as eluant, which afforded the expected compound **23** as a brownish oil.

4.3.1. 3-((4-((2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-methyl)-1*H*-1,2,3-triazol-1-yl)methyl)coumarin (23)

Brownish oily liquid (0.32 g, 68%); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.84 (s, 1H, Trz-*H*), 7.73 (s, 1H, Cou-*H*), 7.6–7.5 (m, 2H, Cou-*H*), 7.3–7.29 (m, 2H, Cou-*H*), 5.47 (s, 2H, Cou-CH_2), 5.22–4.81 (m, 3H, Sacc-*H*), 4.67 (d, *J* = 7.8 Hz, 1H ano-*H*), 4.3–3.71 (m, 5H, Sacc-*H*), 2.1–1.1 (m, 12H, Ace-*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 170.7–170.2 (2C, Ace-*C*=O), 169.4 (2 × 1C, Ace-*C*=O), 161.1 (1C, Cou-*C*=O), 153.8 (1C, Cou-*C*), 144.4 (1C, Trz-*C*), 142.5–128.4 (3C, Cou-*C*), 124.9 (1C, Trz-*C*), 124.3–116.7 (4C, Cou-*C*), 99.7 (1C, Ano-*C*), 72.8–68.3 (4C, Sacc-*C*), 62.7 (1C, Trz-CH_2), 61.8 (1C, Sacc-*C*), 49.3 (1C, Cou-CH_2), 29.6 (1C, Ace-*C*), 20.7–20.5 (3C, Ace-CH_3). HRESIMS: calcd for $C_{27}H_{29}N_3O_{12}$ ([M+1]), 587.5321, found: 587.5320. Anal. Calcd for $C_{27}H_{29}N_3O_{12}$: C, 55.20; H, 4.98; N, 7.15. Found: C, 54.87; H, 4.59; N, 6.98.

4.3.2. 3-((4-((2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-methyl)-1*H*-1,2,3-triazol-1-yl)methyl)coumarin (24)

A mixture of 3-azidomethylcoumarin (**4**, 0.11 g, 0.6 mmol) and 2-propyn-1-yl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**20**, 0.21 g, 0.6 mmol) in 1:1 THF–H_2O afforded compound **24** (0.30 g, 65%). Brownish oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.82 (s, 1H, Trz-*H*), 7.51 (s, 1H, Cou-*H*), 7.48–7.42 (m, 2H, Cou-*H*), 7.29–7.19 (m, 2H, Cou-*H*), 5.41 (s, 2H, Cou-CH_2), 5.32–4.73 (m, 3H, Sacc-*H*), 4.61 (d, *J* = 7.8 Hz, 1H, Ano-*H*), 4.1–3.9 (m, 5H, Sacc-*H*), 2.1–1.89 (m, 12H, Ace-*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.4–169.6 (4C, Ace-*C*=O), 160.6 (1C, Cou-*C*=O), 157.5–153.6 (2C, Cou-*C*), 144.2 (1C, Trz-*C*), 142.6–128.4 (3C, Cou-*C*), 124.9 (1C, Trz-*C*), 122.6–116.6 (3C, Cou-*C*), 100.1 (1C, Ano-*C*), 70.7–62.5 (4C, Sacc-*C*), 61.3 (1C, Trz-CH_2), 60.9 (1C, Sacc-C), 49.2 (1C, Cou-CH_2), 20.9–20.5 (4C-Ace-CH_3). HRESIMS: calcd for $C_{27}H_{29}N_3O_{12}$ ([M+1]), 587.5321, found: 587.5310. Anal. Calcd for $C_{27}H_{29}N_3O_{12}$: C, 55.20; H, 4.98; N, 7.15. Found: C, 55.39; H, 4.58; N, 7.08.

4.3.3. 3-((4-((2,3-Di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)coumarin (25)

A mixture of 3-azidomethylcoumarin (**4**, 0.11 g, 0.6 mmol) and 2-propyn-1-yl 2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranose (**21**, 0.18 g, 0.6 mmol) in 1:1 THF–H_2O afforded compound **25**. White solid (0.30 g, 73%); mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.79 (s, 1H, Trz-*H*), 7.72 (s, 1H, Cou-*H*), 7.59–7.49 (m, 2H, Cou-*H*), 7.36–7.26 (m, 2H, Cou-*H*), 5.46 (s, 2H, Cou-CH_2), 5.22–4.77 (m, 4H, Sacc-*H*), 4.67 (d, *J* = 7.8 Hz, 1H Ano-*H*), 4.23–3.35 (m, 5H, Sacc-*H*), 2.04 (s, 3H, Ace-CH_3), 1.989 (s, 3H, Ace-CH_3), 1.32 (d, *J* = 5.1 Hz, 3H, Eth-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170–169.5 (2C, Ace-*C*=O), 168.9 (1C, Cou-*C*=O), 153.9 (1C, Cou-*C*), 145.1 (1C, Trz-*C*), 142.8–128.4 (3C, Cou-*C*), 124.99 (1C, Trz-*C*), 124.1–99.8 (5C, Cou-*C*), 92.15 (1C, Ano-*C*), 71.8–66.9 (5C, Sacc-*C*), 49.3 (1C, Trz-CH_2), 29.9 (1C, Cou-CH_2), 20.7–20.6 (2C, Ace-CH_3), 20.1 (1C, Eth-CH_3): Anal. Calcd for $C_{25}H_{27}N_3O_{10}$ 529.50: C, 56.71; H, 5.14; N, 7.94. Found: C, 57.24; H, 5.47; N, 7.66.

4.3.4. 3-((4-((2,3-Di-*O*-acetyl-4,6-*O*-butylidene-β-D-glucopyranosyloxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)coumarin (26)

A mixture of 3-azidomethylcoumarin (**4**, 0.11 g, 0.6 mmol) and 2-propyn-1-yl 2,3-di-*O*-acetyl-4,6-*O*-butylidene-β-D-glucopyranose (**22**, 0.21 g, 0.6 mmol) in 1:1 THF–H_2O afforded compound **26**. White solid (0.31 g, 71%); mp 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.80 (s, 1H, Trz-*H*), 7.73 (s, 1H, Cou-*H*), 7.59–7.49 (m, 2H, Cou-*H*), 7.36–7.29 (m, 2H, Cou-*H*), 5.46 (s, 2H, Cou-CH_2), 5.22–4.77 (m, 4H, Sacc-*H*), 4.67 (d, *J* = 7.8 Hz, 1H Ano-*H*), 4.51–3.37 (m, 5H, Sacc-*H*), 2.04 (s, 3H, Ace-*H*), 1.99 (s, 3H, Ace-*H*), 1.63–1.56 (m, 2H, But-CH_2), 1.40–1.33 (m, 2H, But-CH_2), 0.92–0.87 (m, 3H, But-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.4–169.6 (2C, Ace-*C*=O), 160.6 (1C, Cou-*C*=O), 153.7 (1C, Cou-*C*), 144.4 (1C, Trz-*C*), 142.5–128.4 (3C, Cou-*C*), 124.9 (1C, Trz-*C*), 124.1–102.6 (5C, Cou-*C*), 100.1 (1C, Ano-*C*), 72.1–66.5 (5C, Sacc-*C*), 62.7 (1C, Trz-CH_2), 49.2 (1C, Cou-CH_2), 35.95 (1C, But-CH_2), 20.9–20.5 (2C, Ace-CH_3), 17.7 (1C, But-CH_3), 13.8 (1C, But-CH_2): Anal. Calcd for $C_{27}H_{31}N_3O_{10}$ 557.55: C, 58.16; H, 5.60; N, 7.54. Found: C, 59.23; H, 5.23; N, 7.86.

4.3.5. 3-((4-((2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-8-methoxycoumarin (27)

A mixture of 8-methoxy-3-azidomethylcoumarin (**5**, 0.14 g, 0.6 mmol) and 2-propyn-1-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**19**, 0.21 g, 0.6 mmol) in 1:1 THF–H_2O afforded compound **27** (0.23 g, 53%). Brownish oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.84 (s, 1H, Trz-*H*), 7.69 (s, 1H, Cou-*H*), 7.23–7.1 (m, 3H, Cou-*H*), 5.47 (s, 2H, Cou-CH_2), 5.22–4.81 (m, 3H, Sacc-*H*), 4.67 (d, *J* = 7.8 Hz, 1H Ano-*H*), 4.3–4.14 (m, 3H, Sacc-*H*), 3.96 (s, 3H, Cou-OCH_3), 3.75–3.72 (m, 2H, Sacc-*H*), 2.18–1.99 (m, 12H, Ace-*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.7–170.2 (2C, Ace-*C*=*O*), 169.4 (2 × 1C, Ace-*C*=*O*), 160.2 (1C, Cou-*C*=*O*), 147.2 (1C, Cou-*C*), 144.3 (1C, Trz-*C*), 142.7–124.3 (3C, Cou-*C*), 122.8 (1C, Trz-*C*), 119.7–114.4 (4C, Cou-*C*), 99.6 (1C, Ano-*C*), 72.8–68.3 (4C, Sacc-*C*), 62.6 (1C, Trz-CH_2), 61.8 (1C, Sacc-*C*), 56.3 (1C, Cou-OCH_3), 49.2 (1C, Cou-CH_2), 30.8 (1C, Ace-CH_3), 20.7–20.5 (3C, Ace-CH_3). HR-ESIMS: calcd for $C_{28}H_{31}N_3O_{13}$ ([M+1]), 617.5580, found: 617.5578. Anal. Calcd for $C_{28}H_{31}N_3O_{13}$: C, 54.46; H, 5.06; N, 6.80. Found: C, 54.12; H, 4.98; N, 6.98.

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Supplementary data

Full crystallographic details have been deposited with Cambridge Crystallographic Data Centre for structure **6** (CCDC 723228). These data may be obtained, on request from The Director, CCDC, 12 Union Road, Cambridge CBZ 1EZ, UK (Email: deposit@cdc.cam.ac.uk or http://www.ccdc.cam.ac.uk). Supplementary data (NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.07.037.

References

1. Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194.
2. Fan, W. Q.; Katritzky, A. R.. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 4, pp 1–126.
3. Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385–423.
4. (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–554; (b) Rossi, L. L.; Basu, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3596–3599; (c) Gallos, J. K.; Koumbis, A. E. *Curr. Org. Chem.* **2003**, *7*, 771–797.
5. (a) Santoyo-Gonzalez, F.; Hernandez-Mateo, F. *Top. Heterocycl. Chem.* **2007**, *7*, 133–177; (b) Dedola, S.; Nepogodiev, S. A.; Feild, R. A. *Org. Biomol. Chem.* **2007**, *5*, 1006–1017; (c) Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Poulsen, S.-A. In *Drug Des. Res. Perspectives*; Kaplan, S. P., Ed.; Nova: New York, 2007; pp 57–102.
6. (a) Dondoni, A. *Chem. Asian J.* **2007**, *2*, 700–708; (b) Hanson, S. R.; Greenberg, W. A.; Wong, C.-H. *QSAR Comb. Sci.* **2007**, *26*, 1243–1252; (c) Pieters, R. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *QSAR Comb. Sci.* **2007**, *26*, 1181–1190; (d) Santoyo-Gonzalez, F.; Hernandez-Meteo, F. *Chem. Soc. Rev.* **2009**, *38*, 3449–3462; (e) Sawa, M.; Hsu, T. L.; Itoh, T.; Sugiyama, M.; Hanson, S. R.; Vogt, P. K.; Wong, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12371–12376.
7. Perion, R.; Ferrieres, V.; Garcia Moreno, M. I.; Mellet, C. O.; Duval, R.; Garcia Fernandez, J. M.; Plusquellec, D. *Tetrahedron* **2005**, *61*, 9118–9128.
8. Curir, P.; Galeotti, F.; Dolci, M.; Barile, E.; Lanzotti, V. *J. Nat. Prod.* **2007**, *70*, 1668–1671.
9. Kontogiorgis, C. A.; Hadjipavlou Litina, D. *J. Med. Chem.* **2005**, *48*, 6400–6408.
10. (a) Zhao, Y.; Zheng, Q.; Dakin, K.; Xu, K.; Martinez, M. L.; Li, W. H. *J. Am. Chem. Soc.* **2004**, *126*, 4653–4663; (b) Zhou, Z.; Fahrni, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 8862–8863; (c) Kwon, J. Y.; Singh, N. J.; Kim, H. N.; Kim, S. K.; Kim, K. S.; Yoon, J. *J. Am. Chem. Soc.* **2004**, *126*, 8892–8893; (d) Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642–3645; (e) Schiedel, M. S.; Briehn, C. A.; Bauerle, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4677–4680; (f) Yee, D. J.; Balsanek, V.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 2282–2283.
11. Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603–4606.
12. (a) Ganesh, N. V.; Jayaraman, N. *J. Org. Chem.* **2009**, *74*, 739–746; (b) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412; (c) Zhang, J.; Chang, C.-W. T. *J. Org. Chem.* **2009**, *74*, 4414–4417; (d) Sherman, R. W.; Robins, E. *Carbohydr. Res.* **1968**, *7*, 184–192; (e) Baggett, N.; Marsden, B. J. *Carbohydr. Res.* **1982**, *110*, 11–18; (f) Marino, C.; Cancio, M. J.; Varela, O.; de Lederkremer, R. M. *Carbohydr. Res.* **1995**, *276*, 209–213; (g) Key, J. A.; Koh, S.; Timerghazin, Q. K.; Brown, A.; Cairo, C. W. *Dyes Pigments* **2009**, *82*, 196–203.
13. Kaye, P. T.; Musa, M. A. *Synthesis* **2002**, *18*, 2701–2706.
14. Sustmann, R. *Tetrahedron Lett.* **1971**, *29*, 2717–2720.
15. Mereyala, H. B.; Gurrala, S. R. *Carbohydr. Res.* **1998**, *307*, 351–354.
16. Calvo-Flores, F. G.; Isac-Garcia, J.; Hernandez-Mateo, F.; Perez-Balderas, F.; Calvo-Asin, J. A.; Sanchez-Vaquero, E.; Santoyo-Gonzalez, F. *Org. Lett.* **2000**, *2*, 2499–2502.
17. Torne, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
18. (a) Rodios, N. A. *J. Heterocycl. Chem.* **1984**, *21*, 1169–1173; (b) Gouin, S. G.; Bultel, L.; Falentin, C.; Kovensky, J. *Eur. J. Org. Chem.* **2007**, 1160–1167.
19. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
20. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785–789.
21. Singh, L.; Ishar, M. P. S.; Elango, M.; Subramanian, V.; Gupta, V.; Kanwal, P. *J. Org. Chem.* **2008**, *73*, 2224–2233.
22. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.;

Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. GAUSSIAN *03, Revision E.01*; Gaussian, Inc.: Wallingford, CT, 2004.

23. (a) Ess, D. H.; Jones, G. O.; Houk, K. N. *Org. Lett.* **2008**, *10*, 1633–1636; (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187–10193; (c) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647.