Accepted Manuscript

Synthesis and Photophysical Studies on N^1-(2′-*O*,4′-*C*-methylene*ribo*furano-nucleoside-3′-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles

Smriti Srivastava, Vipin K. Maikhuri, Rajesh Kumar, Kapil Bohra, Harbansh Singla, Jyotirmoy Maity, Ashok K. Prasad

PII: S0008-6215(18)30493-2

DOI: 10.1016/j.carres.2018.09.007

Reference: CAR 7610

To appear in: *Carbohydrate Research*

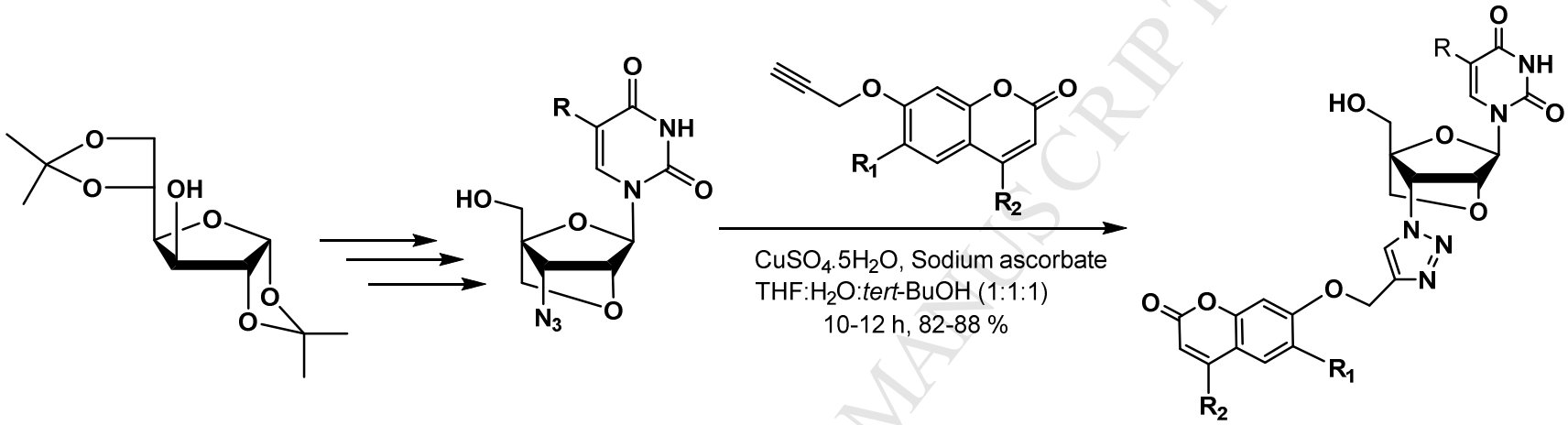
Received Date: 25 August 2018

Revised Date: 27 September 2018

Accepted Date: 27 September 2018

Please cite this article as: S. Srivastava, V.K. Maikhuri, R. Kumar, K. Bohra, H. Singla, J. Maity, A.K. Prasad, Synthesis and Photophysical Studies on N^1-(2′-*O*,4′-*C*-methylene*ribo*furano-nucleoside-3′-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles, *Carbohydrate Research* (2018), doi: https://doi.org/10.1016/j.carres.2018.09.007.

Graphical abstract



Synthesis and Photophysical Studies on N^1-(2'-*O*,4'-*C*-methylene*ribo*furano-nucleoside-3'-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles

Smriti Srivastava,[a] Vipin K. Maikhuri,[a] Rajesh Kumar,[a] Kapil Bohra,[b] Harbansh Singla,[a] Jyotirmoy Maity[a] and Ashok K. Prasad[a]

[a]*Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi-110 007*
[b]*Department of Chemistry, DDU College, University of Delhi, Dwarka, Sect. 3, Delhi-110 078*

Abstract

A series of eight N^1-(2'-*O*,4'-*C*-methylene-β-D-*ribo*furanonucleoside-3'-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles have been synthesized by Cu(I)-catalyzed azide-alkyne cycloaddition reaction of 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methyleneuridine and 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridine with 7-propargyloxy coumarins in 82-88% yields. The synthesized coumarintriazolyl-bicyclonucleoside conjugates possess an extra bridge between 2'-*O* and 4'-*C* in the nucleoside moiety, which facilitates its pre-organization into *N*-type sugar puckering. This was confirmed by X-ray crystal structure studies on one of the conjugates, *i.e.* on N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-C^4-(4-phenylcoumarin-7-oxymethyl)-1,2,3-triazole. Photophysical studies carried out on the synthesized compounds demonstrate that they possess useful level of fluorescence with Stokes shift of approximately 70 nm.

1. Introduction

Modified nucleosides have shown their importance in the field of bio-medical science[1] as antibacterial,[2,3] antifungal,[2a] antiviral[4,5] and anticancer agents.[6] Efficient and facile synthetic methodologies have been developed for synthesis of triazole-linked modified nucleosides in view of their unique biological and photophysical profiles.[7,8] For the synthesis of substituted triazoles Huisgen has pioneered azide-alkyne 1,3-dipolar cycloaddition reactions under thermal condition. The Cu(I)-catalyzed version of the Huisgen [3+2] cycloaddition reaction between a terminal alkyne and an azide regioselectively produces 1,4-disubstituted 1,2,3-triazoles.[9] This reaction has been used to introduce fluorescent moiety on less fluorescent or non-fluorescent nucleosides among other class of molecules *via* a triazole linker.[10,11]

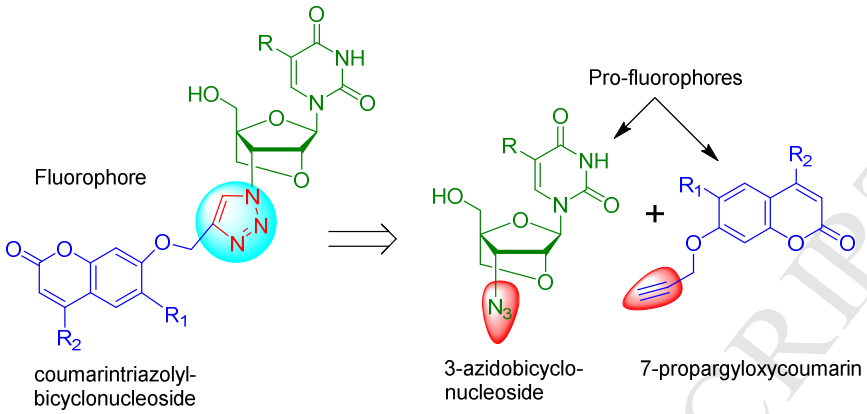
The bicyclonucleosides, in particular 2'-*O*,4'-*C*-methylene*ribo*nucleosides (LNA monomers) have attracted the spotlight of nucleoside chemists worldwide due to their *N*-type sugar ring

conformation, which make them RNA mimic. When incorporated into an oligonucleotide, conformational restriction of LNA monomers provides a preorganized backbone of the oligonucleotide and increase base stacking interactions, leading to an energetically favorable duplex formation.[12] Coumarin-nucleoside conjugates have been synthesized by Kosiova, *et al.*[13] and Seela, *et al.*[14] for the determination of their fluorescent properties. Olomolo, *et al.*[15] synthesized coumarin triazolyl-conjugated nucleosides and evaluated their potential against dual action HIV I protease and non-nucleoside reverse trancriptase. Coumarins and their derivatives have shown sufficient fluorescence in the visible light range to be used in laser dyes and organic light-emitting diodes. Intense fluorescent triazol-linked sugar coumarin derivatives were synthesized by Rajaganesh *et al.*,[16] whereas fluorescent coumarin-triazolylglycosides were synthesized by Nyuchev *et al.*[17] for their application in surface imaging. He, *et al.*[18] synthesized 3,4-bis-triazolocoumarin-sugar conjugates and studied their quenching specificity with silver (I) in aqueous media and Xue, *et al*.[19] synthesized triazolyl bidentate glycoligands and performed optical studies with them. The current developments in the field of bicyclic-nucleosides as well as in triazole-linked fluorescent nucleoside conjugates encouraged us to synthesize coumarintriazolyl-bicyclonucleosides, *viz.* N^1-(2'-*O*,4'-*C*-methylene*ribo*furanosyl-nucleoside-3'-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles and evaluate their photo-physical properties.

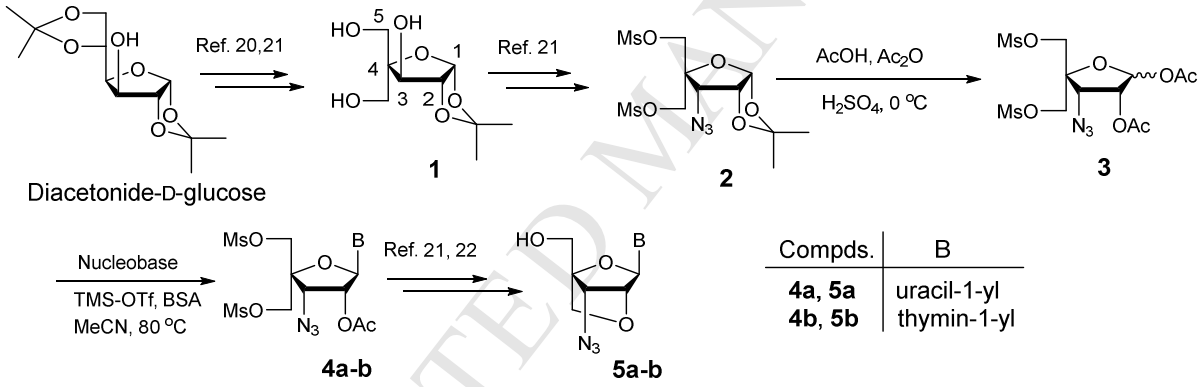
2. Results and Discussion

The retrosynthetic analysis of the desired coumarintriazolyl-bicyclonucleoside conjugate revealed that Cu(I)-catalyzed Huisgen [3+2] cycloaddition reaction between 3'-azidobicyclonucleoside and 7-propargyloxycoumarin should lead to the desired compound (**Scheme 1**). Two 3-azidobicyclonucleosides, *i.e*. 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methyleneuridine (**5a**) and 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridine (**5b**) were synthesized by Vorbrüggen coupling of uracil and thymine, respectively, with the common glycosyl donor 3-azido-3-deoxy-1,2-*O*-diacetyl-5-*O*-methanesulfonyl-4-*C*-methanesulfonyloxymethyl-α-D-*ribo*furanose (**3**), which in turn was synthesized from the commercially available diacetone-D-glucose through intermediate compounds **1** and **2** following literature procedure in an overall yields of 15-20% (**Scheme 2**).[20,21,22]

Scheme 1: Retrosynthetic analysis of coumarintriazolyl-bicyclonucleoside conjugates.



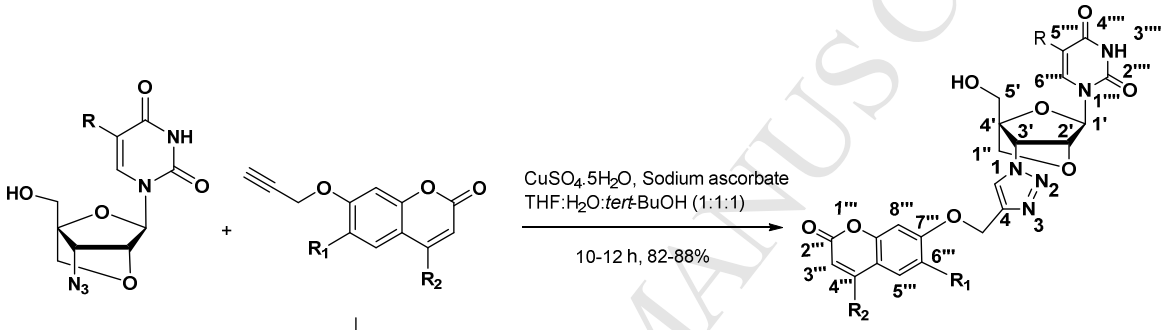
Scheme 2: Synthesis of 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methylene-β-D-*ribo*furanosyl pyrimidines.



The other key precursor, 7-propargyloxycoumarin (**6**), 4-methyl-7-propargyloxycoumarin (**7**), 6-chloro-4-methyl-7-propargyloxycoumarin (**8**) and 4-phenyl-7-propargyloxycoumarin (**9**) were synthesized by propargylation of 7-hydroxycoumarin, 7-hydroxy-4-methylcoumarin, 6-chloro-7-hydroxy-4-methylcoumarin and 7-hydroxy-4-phenylcoumarin, respectively using propargyl bromide in acetone in the presence of potassium carbonate in 80-85% yields.[23,24] Each of the two 3-azidobicyclonucleoside, **5a** and **5b** were subjected to Cu(I)-catalyzed azide-alkyne cycloaddition reaction with 7-propargyloxycoumarins **6-9** in the presence of $CuSO_4.5H_2O$-sodium ascorbate as a coupling reagent in mixture of THF:*tert*-BuOH:H_2O (1:1:1) to afford N^1-(3'-deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazole (**10**), N^1-(3'-deoxy-2'-*O*,4'-C-methyleneuridin-3'-yl)-C^4-(4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (**11**), N^1-(3'-deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-C^4-(6-chloro-4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (**12**), N^1-(3'-deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-C^4-(4-phenylcoumarin-7-

oxymethyl)-1,2,3-triazole (**13**), N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazole (**14**), N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-C^4-(4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (**15**), N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-C^4-(6-chloro-4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (**16**) and N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-C^4-(4-phenylcoumarin-7-oxymethyl)-1,2,3-triazole (**17**) in 82-88% yields (**Scheme 3**).

Scheme 3: Synthesis of coumarintriazolyl-bicyclonucleoside conjugates **10**-**17**.



5a; R = H
5b; R = CH_3

Compds.	R_1	R_2
6	H	H
7	H	CH_3
8	Cl	CH_3
9	H	Ph

Compds.	R	R_1	R_2
10	H	H	H
11	H	H	CH_3
12	H	Cl	CH_3
13	H	H	Ph
14	CH_3	H	H
15	CH_3	H	CH_3
16	CH_3	Cl	CH_3
17	CH_3	H	Ph

The structures of all the synthesized compounds **1**-**17** were unambiguously established on the basis of their spectral (IR, ^{1}H-, ^{13}C NMR and HRMS) data analysis. The structures of known compounds **1**-**9** were further confirmed on the basis of comparison of their physical and spectral data with those reported in the literature.[20-24] The synthetic procedure and experimental details of 2'-*O*-acetyl-3'-azido-3'-deoxy-5'-*O*-methanesulfonyl-4'-*C*-methanesulfonyloxymethyl-uridine (**4a**), 3'-azido-3'-deoxy-5'-*O*-methanesulfonyl-2'-*O*,4'-*C*-methyleneuridine, 3'-azido-5'-*O*-benzoyl-3'-deoxy-2'-*O*,4'-*C*-methyleneuridine and 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methyleneuridine (**5a**) are reported in a patent only.[22] Herein, we have provided their synthesis and characterization data in the supporting information.

The single crystal X-ray diffraction studies was performed on N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-C^4-(4-phenylcoumarin-7-oxymethyl)-1,2,3-triazole (**17**), which revealed its important structural features. The crystal structure of compound **17** showed that the nucleoside moiety of the compound is locked in the *N*-type conformation due to the presence of 2'-*O*,4'-*C*-methylene bridge (**Figure 1**). Further, we report herein the crystal structures of compounds **1** and **2** for the first time, which clearly reveal the opposite configuration of C-3 hydroxy group in compound **1** with respect to the C-3 azido group in compound **2** (**Scheme 2** and **Figure 2**). The detailed crystallographic data of compounds **1**, **2** and **17** were deposited in the Cambridge Crystallographic Data Centre with CCDC nos. **1535099**, **1535166** and **1547973**, respectively (**Figure 2**).

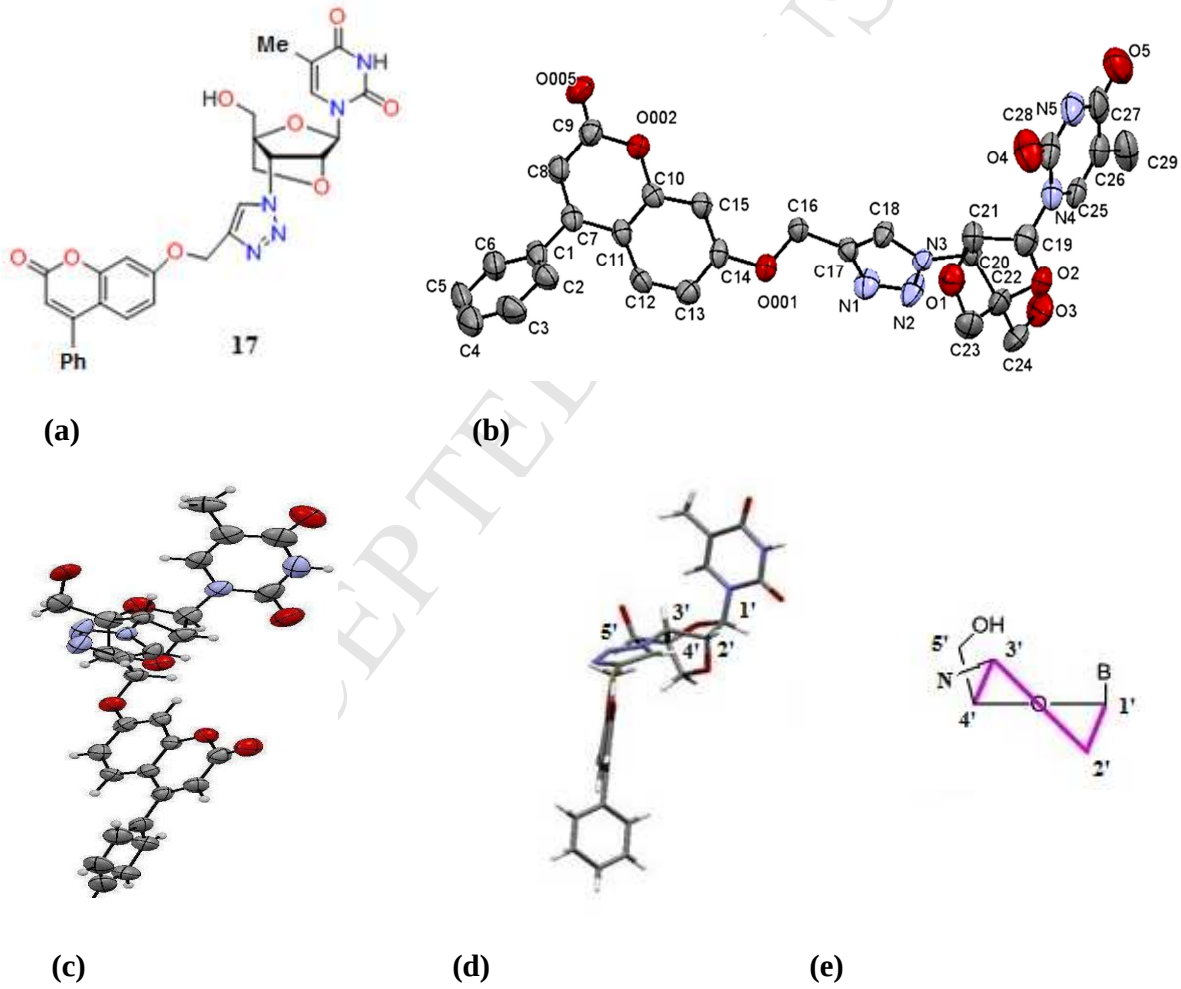
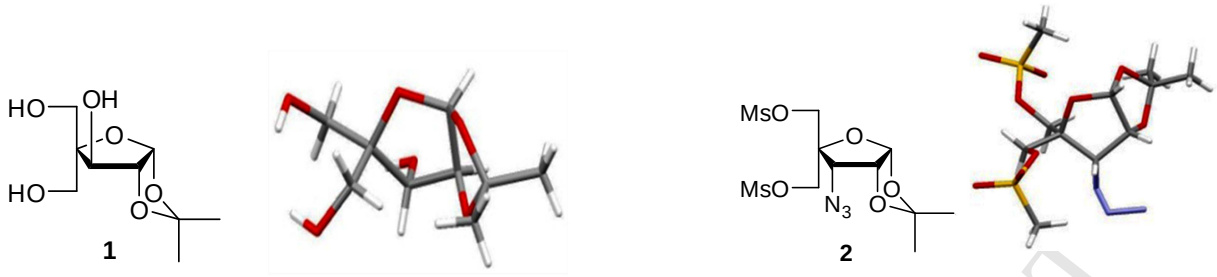


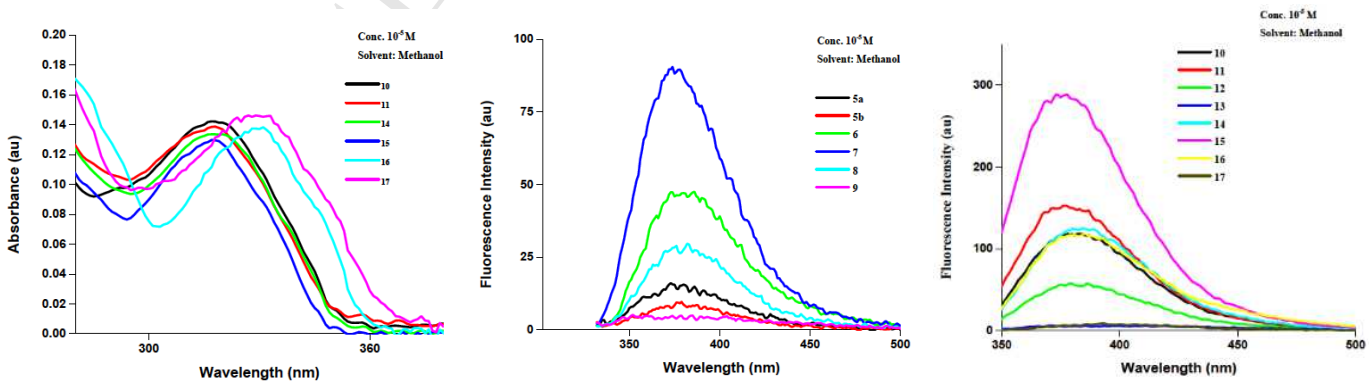
Figure 1: (a) Molecular structure of compound **17**; (b) and (c) ORTEP diagram of compound **17** drawn in 50% thermal probability ellipsoids. Solvent molecules are omitted for clarity; (d) Preferred *N*-type sugar ring puckering in compound **17**; (e) Representative *N*-type sugar puckering in nucleosides.



(a) **(b)** **(c)** **(d)**

Figure 2: (a) and (c) Molecular structures of compounds **1** and **2**; (b) and (d) Mercury diagram of compounds **1** and **2** drawn in 20% thermal probability ellipsoids showing inversion of configuration at C-3 carbon on chemical conversion of compound **1** to **2**.

Photophysical Studies: The photophysical properties of all the synthesized N^1-(3'-deoxy-2'-*O*,4'-*C*-methylene-β-D-*ribo*furanosylnucleoside-3'-yl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles **10-17** and their precursors, *i.e.* azidosugars **5a-5b** and propargyloxy coumarins **6-9** were determined in methanol at 10^{-5} M concentration. The absorbance spectra of six coumarintriazolyl-bicyclonucleoside conjugates **10**, **11**, **14**, **15**, **16** and **17** have been shown in **Figure 3a**. The fluorescence spectra of the two azidonucleoside precursors **5a-5b** and four propargyloxycoumarin derivatives **6-9** have been shown in **Figure 3b** and fluorescence spectra of all eight synthesized coumarintriazolyl-bicyclonucleoside conjugates **10-17** have been shown in **Figure 3c**. All coumarintriazolyl-bicyclonucleoside conjugates showed absorbance at approximately 320-330 nm and emission at around 400 nm (**Table 1**). Fluorescence intensities of conjugates **10-17** have been compared with the corresponding coumarin alkynes **6-9** and azides **5a-5b**, and has been found higher than both the precursors. All studied compounds have shown maximum fluorescence intensity when excited at 320 nm.



(a) (b) (c)

Figure 3: (a) Absorption spectra of compounds **10**-**11** and **14**-**17**; (b) Emission spectra of azidonucleosides **5a** and **5b** and alkynyloxy-compounds **6**-**9**; (c) Emission spectra of coumarintriazolyl-bicyclonucleoside conjugates **10**-**17**. All spectra were recorded in methanol at 10^{-5} M concentration.

Table 1: Photophysical data of eight synthesized coumarintriazolyl-bicyclonucleosides **10**-**17**

Compd No.	Absorbance λ_{abs} (nm)	Excitation λ_{ex} (nm)	Emission λ_{em} (nm)/ Intensity (au)	Stoke Shift (nm)
10	322	320	390/118	70
11	322	320	395/153	75
12	324	320	391/55	71
13	326	320	397/6	77
14	323	320	390/123	70
15	321	320	394/288	74
16	330	320	390/118	70
17	325	320	398/8	78

Further, structure-fluorescence intensity relationship of the synthesized conjugates **10**-**17** has been studied. The electron donating methyl group on C-4 position of coumarin increases the fluorescence intensity. The electron withdrawing phenyl moiety and chloro-group at C-4 / C-6 positions of coumarin moiety decreases the extent of conjugation by decreasing the electron density on the coumarin and so the fluorescence emission intensity was decreased. Conjugates having 5-methyluracil nucleobase were possessing slightly higher fluorescence intensity than conjugates having uracil nucleobase. The results of spectral studies demonstrate the importance of these triazole-linked analogues, as the starting sugar azides and alkynyloxy-coumarins possesses lesser fluorescence intensity than the conjugates.

3. Conclusion

A small library of novel coumarintriazolyl-bicyclonucleosides **10**-**17** has been synthesized by using very simple and efficient, Cu(I)-catalyzed azide-alkyne cycloaddition reaction between 3'-azido-3'-deoxy-2'-*O*,4'-*C*-methylene-nucleosides and 7-propargyloxy coumarins in 82-88% yields. The X-ray crystal structure studies on one of the coumarintriazolyl-bicyclonucleoside conjugates **17** revealed that the sugar moiety is puckered in *N*-type conformation. This pre-organization may have resulted due to the presence of the bridging methylene group between C-2' oxygen and C-4'

carbon in these coumarintriazolyl-bicyclonucleoside conjugates **10**-**17**. Photophysical studies of these compounds revealed that they possess useful level of fluorescence properties.

4. Experimental

Melting points were determined on Buchi M-560 instrument and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 2000 FT-IR spectrometer by making KBr disc for solid samples and thin film for oils. The optical rotations were measured with Rudolph autopol II automatic polarimeter using light of 546 nm wavelength. The ^{1}H- and ^{13}C NMR spectra were recorded on a Jeol alpha-400 spectrometer at 400 and 100.6 MHz, respectively, using TMS as internal standard. The chemical shift values are on δ scale and the coupling constants (*J*) are in Hz. Signals from -O*H* groups in ^{1}H NMR spectra recorded in $CDCl_3$ and DMSO-d_6 were verified by removing them by shaking the solution with D_2O. HR-ESI-TOF-MS analyses were recorded on a MicroTOF instrument from Bruker Daltonics, Bremen on ESI positive mode. Analytical TLCs were performed on precoated Merck silica-gel $60F_{254}$ plates; the spots were detected under UV light as well as by charring using 4% H_2SO_4 in ethanol solution. Silica gel (100-200 mesh) was used for column chromatography. Chemicals were obtained from commercial suppliers and were used without any further purification unless otherwise noted.

Absorption spectra were recorded between 250 nm and 600 nm using a Perkin-Elmer UV/Vis spectrometer Lambda 45 at scan speed 240 nm/min. All measurements were carried out in PE-UV/Vis Spectroscopy cells (1 cm). Fluorescence emission spectra were taken on Varian Cary eclipse Fluorescence spectrophotometer at 10 nm slit width with 150 Watt DC powered Xenon lamp. Absorption and fluorescence spectra were developed by Origin 6.0 software. HPLC grade solvents were used for all solution preparation.

4.1 General procedure for the preparation of *N*^{1}-(3'-deoxy-2'-*O*,4'-*C*-methylene-β-D-*ribo*furanosyl-nucleoside-3'-yl)-*C*^{4}-(coumarin-7-oxymethyl)-1,2,3-triazoles (10-17).

Azidobicyclo nucleosides **5a/5b** (0.67 mmol) and 5'-propargylated coumarin **6-9** (0.81 mmol), as desired were suspended in a mixture of THF:*tert*-BuOH:H_2O (1:1:1) (30 mL). Sodium ascorbate (0.54 mmol) was added into the reaction mixture followed by the addition of $CuSO_4.5H_2O$ (0.27 mmol). The heterogeneous mixture was stirred vigorously for 10-12 h. After completion of the

reaction as shown on analytical TLC, excess of solvents was evaporated under reduced pressure and traces of any residual moisture were removed by co-evaporation with toluene. The crude product thus obtained was purified by using silica gel column chromatography to afford the title compounds in pure form.

4.1.1. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-*C*^{4}-(coumarin-7-oxymethyl)-1,2,3-triazole (10). It was obtained as white solid in 85% yield; R_f = 0.45 (10% MeOH in $CHCl_3$); mp: 178-180 ^oC; IR (cm^{-1}, KBr): 3422, 1701, 1400, 1277, 1128, 1053, 1014, 836, 761; $[\alpha]_D^{28}$ = + 4.64 (*c* 0.05, MeOH);^{1}H NMR (400 MHz, DMSO-d_6): δ 3.60 (1H, d, *J* = 8.4 Hz), 3.88 (1H, d, *J* = 8.4 Hz), 3.97-4.09 (2H, m), 4.83 (1H, s), 5.13 (1H, s), 5.28 (2H, s), 5.68 (2H, s), 6.30 (1H, d, *J* = 2.3 Hz), 7.02 (1H, dd, *J* = 2.0 & 8.4 Hz), 7.16 (1H, d, *J* = 3.2 Hz), 7.64 (1H, d, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 8.4 Hz), 7.99 (1H, d, *J* = 9.2 Hz), 8.44 (1H, s), 11.43 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 56.61, 59.53, 61.47, 71.00, 79.24, 86.23, 90.30, 101.14, 101.55, 112.62, 112.72, 112.89, 125.52, 129.82, 138.82, 141.91, 144.16, 149.94, 155.29, 160.09, 161.36, 163.33; HR-ESI-TOF-MS: *m/z* 504.1137 ($[M+Na]^+$), calcd. for $[C_{22}H_{19}N_5O_8+Na]^+$ 504.1126.

4.1.2. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-*C*^{4}-(4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (11). It was obtained as white solid in 86% yield; R_f = 0.45 (10% MeOH in $CHCl_3$); mp: 166-168 ^oC; IR (cm^{-1}, KBr): 3424, 2345, 1701, 1389, 1275, 1146, 1054, 848, 567; $[\alpha]_D^{28}$ = + 0.46 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (3H, s), 3.61 (1H, d, *J* = 9.2 Hz), 3.88 (1H, d, *J* = 8.4 Hz), 3.96-4.10 (2H, m), 4.83 (1H, s), 5.14 (1H, s), 5.29 (2H, s), 5.46 (1H, *t*, *J* = 6.0 Hz), 5.68 (2H, s), 6.22 (1H, s), 7.05 (1H, dd, *J* = 2.4 and 8.2 Hz), 7.14 (1H, d, *J* = 2.4 Hz), 7.69 (1H, d, *J* = 9.2 Hz), 7.85 (1H, d, *J* = 7.6 Hz), 8.44 (1H, s), 11.43 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 18.14, 56.61, 59.54, 61.46, 71.01, 79.25, 86.24, 90.30, 101.14, 101.58, 111.17, 112.59, 113.57, 125.49, 126.51, 138.93, 141.95, 149.62, 153.03, 154.58, 159.82, 161.23, 163.65. HR-ESI-TOF-MS: *m/z* 518.1292 ($[M+Na]^+$), calcd. for $[C_{23}H_{21}N_5O_8+Na]^+$ 518.1282.

4.1.3. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-*C*^{4}-(6-chloro-4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (12). It was obtained as off white solid in 82% yield; R_f = 0.45 (10% MeOH in $CHCl_3$); mp: 165-167 ^oC; IR (cm^{-1}, KBr): 3448, 2345, 1707, 1605, 1387, 1279, 1163, 1047, 826; $[\alpha]_D^{28}$ = + 3.99 (*c* 0.05, MeOH);^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (3H, s), 3.62 (1H, d, *J* = 8.4 Hz), 3.89 (1H, d, *J* = 8.8 Hz) 3.98-4.11 (2H, m), 4.85 (1H, s), 5.15 (1H, s), 5.39 (2H, s), 5.47 (1H, t, *J* = 5.6 Hz), 5.68 (2H, s), 6.29 (1H, s), 7.47 (1H, s), 7.82 (1H, s), 7.85 (1H, s),

8.47 (1H, s), 11.43 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 18.13, 56.62, 59.58, 62.44, 71.03, 79.27, 86.23, 90.31, 101.13, 102.15, 112.26, 113.80, 117.73, 125.75, 125.97, 138.92, 141.28, 150.13, 152.75, 153.12, 155.74, 159.72, 163.41. HR-ESI-TOF-MS: *m/z* 552.0897 ([M+Na]$^+$), calcd. for [$C_{23}H_{20}ClN_5O_8$+Na]$^+$ 552.0893.

4.1.4. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methyleneuridin-3'-yl)-*C*^{4}-(4-phenylcoumarin-7-oxymethyl)-1,2,3-triazole (13). It was obtained as off white solid in 84% yield; R_f = 0.45 (10% MeOH in $CHCl_3$); mp: 169-171 ^{o}C; IR (cm^{-1}, KBr): 3422, 2345, 1701, 1458, 1376, 1274, 1153, 1052, 822, 700 cm^{-1}; $[\alpha]_D^{28}$ = + 4.30 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.59 (1H, d, *J* = 9.2 Hz), 3.86 (1H, d, *J* = 8.8 Hz), 3.95-4.08 (2H, m), 4.81 (1H, s), 5.12 (1H, s), 5.29 (2H, s), 5.45 (1H, t, *J* = 4.4 Hz), 5.66 (2H, s), 6.24 (1H, s), 6.98 (1H, dd, *J* = 2.0 and 8.9 Hz), 7.24 (1H, d, *J* = 2.0 Hz), 7.34 (1H, d, *J* = 9.2 Hz), 7.49- 7.56 (5H, m), 7.84 (1H, d, *J* = 7.6 Hz), 8.43 (1H, s), 11.42 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 56.61, 59.54, 61.54, 70.01, 79.25, 86.25, 90.31, 101.15, 102.06, 111.54, 112.06, 112.98, 125.54, 127.87, 128.88, 129.70, 134.95, 138.94 , 141.70 , 150.14, 155.11, 155.40, 159.98, 161.12, 163.42; HR-ESI-TOF-MS: *m/z* 580.1443 ([M+Na]$^+$), calcd. for [$C_{28}H_{23}N_5O_8$+Na]$^+$ 580.1439.

4.1.5. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-*C*^{4}-(coumarin-7-oxymethyl)-1,2,3-triazole (14). It was obtained as white solid in 86% yield; R_f = 0.5 (10% MeOH in $CHCl_3$); mp: 170-172 ^{o}C; IR (cm^{-1}, KBr): 3422, 2118, 1701, 1458, 1278, 1125, 1057, 835, 759; $[\alpha]_D^{28}$ = + 4.24 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78 (3H, s), 3.58 (1H, d, *J* = 9.2 Hz), 3.86 (1H, d, *J* = 9.2 Hz), 3.97-4.11 (2H, s), 4.87 (1H, s), 5.10 (1H, s), 5.27 (2H, s), 5.46 (1H, t, *J* = 5.2 Hz), 5.66 (1H, s), 6.28 (1H, d, *J* = 11.2 Hz), 6.99 (1H, dd, *J* = 2.4 and 6 Hz), 7.14 (1H, d, *J* = 2.4 Hz), 7.62 (1H, d, *J* = 8.4 Hz), 7.70 (1H, s), 7.97 (1H, d, *J* = 9.2 Hz), 8.42 (1H, s), 11.40 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 12.65, 57.37, 59.68, 62.27, 71.95, 79.84, 86.71, 90.80, 102.11, 108.88, 112.99, 113.21, 113.54, 125.81, 130.57, 134.93, 142.29, 145.03, 150.61, 155.82, 160.97, 161.50; HR-ESI-TOF-MS: *m/z* 495.1473 ([M+H]$^+$), calcd. for [$C_{23}H_{21}N_5O_8$+H]$^+$ 495.1463.

4.1.6. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-*C*^{4}-(4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (15). It was obtained as white solid in 88% yield; R_f = 0.5 (10% MeOH in $CHCl_3$); mp: 166-168 ^{o}C; IR (cm^{-1}, KBr): 3154, 2372, 1701, 1458, 1389, 1277, 1145, 1057, 850, 760; $[\alpha]_D^{28}$ = + 3.83 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (3H, s), 2.34 (3H, s), 3.57 (1H, d, *J* = 9.2 Hz), 3.84 (1H, d, *J* = 8.4 Hz), 3.96-4.09 (2H, m), 4.85 (1H, s), 5.08 (1H, s), 5.24 (2H, s), 5.47 (1H , *t*, *J* = 6.0 Hz), 5.63 (1H, s), 6.16 (1H, s), 6.97 (1H, dd, *J* = 2.0 and

9.2 Hz), 7.07 (1H, d, *J* = 2.4 Hz), 7.62 (1H, d, *J* = 9.2 Hz), 7.67 (1H, s), 8.39 (1H, s), 11.38 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 12.50, 18.21, 56.82, 59.71, 61.53, 71.06, 79.37, 86.21, 90.39, 101.62, 108.76, 111.38, 112.68, 113.46, 125.56, 126.57, 134.73, 141.88, 150.16, 153.51, 154.70, 160.25, 161.02, 164.10; HR-ESI-TOF-MS: *m/z* 510.1620 ($[M+H]^+$), calcd. for $[C_{24}H_{23}N_5O_8+H]^+$ 510.1619.

4.1.7. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-*C*^{4}-(6-chloro-4-methylcoumarin-7-oxymethyl)-1,2,3-triazole (16). It was obtained as white solid in 82% yield; R_f= 0.45 (10% MeOH in $CHCl_3$); mp: 165-167 ^oC; IR (cm^{-1}, KBr): 3454, 2345, 1704, 1459, 1388, 1055, 840, 765; $[\alpha]_D^{28}$ = + 0.38 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (3H, s), 2.36 (3H, s), 3.56 (1H, d, *J* = 8.4 Hz), 3.84 (1H, d, *J* = 8.8 Hz) 3.95-4.09 (2H, m), 4.85 (1H, s), 5.09 (1H, s), 5.34 (2H, s), 5.45 (1H, t, *J* = 5.6 Hz), 5.63 (1H, s), 6.25 (1H, d, *J* = 1.2 Hz), 7.43 (1H, s), 7.67 (1H, s), 7.79 (1H, s), 8.41 (1H, s), 11.37 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 12.30, 17.97, 56.54, 59.83, 62.58, 71.22, 79.07, 86.25, 90.46, 108.90, 112.28, 113.75, 118.06, 125.65, 126.30, 134.54, 141.50, 150.09, 153.00, 153.24, 155.61, 159.95, 163.71; HR-ESI-TOF-MS: *m/z* 544.1225 ($[M+H]^+$), calcd. for $[C_{24}H_{22}ClN_5O_8+H]^+$ 544.1230.

4.1.8. *N*^{1}-(3'-Deoxy-2'-*O*,4'-*C*-methylene-5-methyluridin-3'-yl)-*C*^{4}-(4-phenylcoumarin-7-oxymethyl)-1,2,3-triazole (17). It was obtained as white solid in 85% yield; R_f = 0.55 (10% MeOH in $CHCl_3$); IR (cm^{-1}, KBr): 3422, 2345, 1702, 1458, 1376, 1275, 1152, 1055, 859, 757; $[\alpha]_D^{28}$ = + 4.84 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (3H, s), 3.59 (1H, d, *J* = 8.8 Hz), 3.86 (1H, d, *J* = 9.2 Hz), 3.97-4.11 (2H, m), 4.87 (1H, s), 5.11 (1H, s), 5.29 (2H, s), 5.47 (1H, t, *J* = 5.2 Hz), 5.66 (1H, s), 6.23 (1H, s), 6.97 (1H, dd, *J* = 2.4 and 9.6 Hz), 7.24 (1H, d, *J* = 2.4 Hz), 7.33 (1H, d, *J* = 9.2 Hz), 7.49- 7.56 (5H, m), 7.70 (1H, s), 8.43 (1H, s), 11.41 (1H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 12.44, 56.76, 59.64, 61.56, 71.00, 79.18, 85.90, 90.31, 102.07, 108.79, 111.33, 112.08, 113.00, 125.34, 127.88, 128.45, 128.89, 129.56, 134.66, 134.85, 141.71, 150.10, 155.05, 155.40, 159.80, 161.35, 164.01; HR-ESI-TOF-MS: *m/z* 572.1763 ($[M+H]^+$), calcd. for $[C_{29}H_{25}N_5O_8+H]^+$ 572.1776.

4.2. X-Ray diffraction studies on *N*^{1}-(3'-deoxy-2'-*O*,4'-*C*-methylene-5-methyluridine-3'-yl)-*C*^{4}-(4-phenylcoumarin-7-oxymethyl)-1,2,3-triazole (**17**), 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-β-L-threo-pentofuranose (**1**) and 3-azido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-4-*C*-methanesulfonyloxymethyl-α-D-*ribo*furanose (**2**).

Single crystals suitable for X-ray diffraction studies were grown by dissolving compounds **1** and **2** in methanol and chloroform mixture, compound **17** in DMSO and by allowing slow evaporation of the solutions at room temperature. The X-ray diffraction data were collected with graphite-monochromated Mo Ka radiation (l ¼0.71073Å) at temperature 293 K. The structures were solved by direct methods using SHELXS-97 and refined by the full-matrix least-squares method on F2 (SHELXL-97).[25] All calculations were carried out using the WinGX package of the crystallographic programs.[26] For the molecular graphics, the program Mercury[27] was used. Molecular structures were drawn as given in **Figures 1** and **2**, using Mercury software. The selected bond lengths, bond angles, etc. are given in Table 2.

Table 2: X-ray crystal data and structure refinement for compounds **17**, **1** and **2**

Compounds	**17**	**1**	**2**
Empirical formula	$C_{29}H_{25}N_5O_8$	$C_9H_{16}O_6$	$C_{11}H_{19}N_3O_9S_2$
Formula weight	571.17	220.22	401.41
Temperature	293(2) K	293(2) K	298(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P 21	P 21	P 21
Unit cell dimensions	a = 7.8521(15) Å, α = 90°	a = 5.6443(5) Å, α = 90°	a = 5.6530 (4) Å, α = 90°
	b = 14.5640(7) Å, β = 78.99(6)°	b = 9.4753(6) Å, β = 90°	b = 15.0897(5) Å, β = 95.92°
	c = 14.4304(9) Å, γ = 90°	c = 9.7937(2) Å, γ = 90°	c = 10.141(3) Å, γ = 90°
Volume	1619.88(17) $Å^3$	519.33(6) $Å^3$	860.42(6) $Å^3$
Z	2	2	2
Density (calculated)	1.367 mg / m^3	1.408 mg / m^3	1.549 mg / m^3
Absorption coefficient	0.164 mm^{-1}	0.119 mm^{-1}	0.361 mm^{-1}
F(000)	698.0	236.0	420.0

Theta range for data collection	2.99 to 24.99°.	3.64 to 24.99°	3.86 to 28.46°
Index ranges	-9≤h≤9, -17≤k≤17, -17≤l≤1	-6≤h≤6, -11≤k≤11, -11≤l≤7	-6≤h≤6, -17≤k≤17, -12≤l≤12
Reflections collected	5047	3215	9811
Independent reflections	99.8%	99.8%	99.8%
Reflections collected / unique	19474 / 5694 [R(int) = 0.0326]	3215 / 1468 [R(int) = 0.0126]	9811 / 3019 [R(int) = 0.0195]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	5694 / 1 / 432	2650 / 1 / 136	3019 / 1 / 226
Goodness-of-fit on F^2	1.053	1.206	0.867
Final R indices [I>2σ(I)]	R1 = 0.0752, wR2 = 0.2159	*R1* = 0.0405, *wR2* = 0.1236	*R1* = 0.0568, *wR2* = 0.1605
R indices (all data)	R1 = 0.0918, wR2 = 0.2300	*R1* = 0.0412, *wR2* = 0.1247	*R1* = 0.0589, *wR2* = 0.1644
Absolute structure parameter	-0.04(8)	1.5(13)	0.04(2)
Largest diff. peak and hole	-0.749 e.Å^{-3}	0.332 and -0.242 e.Å^{-3}	1.719 and -0.741 e.Å^{-3}
CCDC No.	**1547973**	**1535099**	**1535166**

5. Acknowledgements:

We are grateful to University of Delhi for providing financial support under DU-DST Purse Grant and under scheme to strengthen research and development. We are also thankful to CIF-USIC University of Delhi, Delhi for providing crystallographic data and NMR spectral recording facility. S.S. thanks CSIR for the award of Junior/Senior Research Fellowships. V.K.M. thanks

CFEES-DRDO for his research fellowship. R.K. thanks UGC for the award of Junior/Senior Research Fellowships.

6. References

1. K. Upadhyaya, A. Ajay, R. Mahar, R. Pandey, B. Kumar, S.K. Shukla, R.P. Tripathi, Tetrahedron 69 (2013) 8547–8558.
2. (a) M.M. El-Sadek, N.S.A. El-Dayem, S.Y. Hassan, G.A. Yacout Int. Res. J. Microbiol. 4 (2013) 204–219; (b) M.M. El-Sadek, S.Y. Hassan, N.S.A. El-Dayem, G.A. Yacout, Molecules 17 (2012) 7010–7027.
3. K.C. Nicolaou, S.P. Ellery, F. Rivas, K. Saye, E. Rogers, T.J. Workinger, M. Schallenberger, R. Tawatao, A. Montero, A. Hessell, F. Romesberg, D. Carson, D. Burton, Bioorg. Med. Chem. 19 (2011) 5648–5669.
4. (a) A. Cho, O.L. Saunders, T. Butler, L. Zhang, J. Xu, J.E. Vela, J.Y. Feng, A.S. Ray, A.S.C.U. Kim, Bioorg. Med. Chem. Lett. 22 (2012) 2705–2707; (b) A. Cho, L. Zhang, J. Xu, D. Babusis, T. Butler, R. Lee, O.L. Saunders, T. Wang, J. Parrish, J. Perry, J.Y. Feng, A.S. Ray, C.U. Kim, Bioorg. Med. Chem. Lett. 22 (2012) 4127–4132.
5. (a) J. Wu, W. Yu, L. Fu, W. He, Y. Wang, B. Chai, C. Song, J. Chang, Eur. J. Med. Chem. 63 (2013) 739–745; (b) S.K.V. Vernekar, L. Qiu, J. Zacharias, R.J. Geraghty, Z. Wang, Med. Chem. Commun. 5 (2014) 603–608.
6. (a) M.M. Kamel, H.I. Ali, M.M. Anwar, N.A. Mohamed, A.M. Soliman, Eur. J. Med. Chem. 45 (2010) 572–580; (b) M.M. El Sadek, N.S. Abd El-Dayem, S.Y. Hassan, M.A. Mostafa, G.A. Yacout, Molecules 19 (2014) 5163-5190; (c) M. Wang, Y. Xia, Y. Fan, P. Rocchi, F. Qu, J.L. Iovanna, L. Peng, Bioorg. Med. Chem. Lett. 20 (2010) 5979–5983.
7. (a) I. Kosiova, S. Kovackova, P. Kois, Tetrahedron 63 (2007) 312–320; (b) T.O. Olomola, R. Klein, K.A. Lobb, Y. Sayed, P.T. Kaye, Tetrahedron Letts. 51 (2010) 6325–6328; (c) M.M. Haque, H. Sun, S. Liu, Y. Wang, X. Peng, Angew. Chem. Int. Ed. 53 (2014) 7001–7005.
8. (a) R. Rajaganesh, P. Ravinder, V. Subramanian, T.M. Das, Carbohydrate Res. 346 (2011) 2327–2336; (b) X.-P. He, Z. Song, Z.-Z. Wang, X.-X. Shi, K. Chen, G.-R. Chen, Tetrahedron 67 (2011) 3343–3347; (c) J-L. Xue, X-P. He, J.-W. Yang, D.-T. Shi, C.-Y. Cheng, J. Xie, G.-R. Chen, K. Chen, Carbohydrate Res. 363 (2012) 38–42.
9. V. Rostovtsev, L. Green, V. Fokin, B. Sharpless, Angew. Chem Int. Ed. 41 (2002) 2596–2599.

10. (a) S.S. Bag, S. Talukdar, S.K. Das, M.K. Pradhan, S. Mukherjee, Org. Biomol. Chem. 14 (2016) 5088–5108; (b) S.S. Bag, R. Kundu, J. Org. Chem. 76 (2011) 3348–3356.
11. K. Sivakumar, F. Xie, B.M. Cash, S. Long, H.N. Barnhill, Q. Wang, Org. Lett. 6 (2004) 4603–4606.
12. H. Kaur, B.R. Babu, S. Maiti, Chem. Rev. 107 (2007) 4672–4697.
13. I. Kosiova, S. Kovackova, P. Kois, Tetrahedron 63 (2007) 312–320.
14. Seela, V.R. Sirivolu, Org. Biomol. Chem. 6 (2008) 1674–1687.
15. T.O. Olomola, R. Klein, K.A. Lobb, Y. Sayed, P.T. Kaye, Tetrahedron Letters 51 (2010) 6325-6328.
16. R. Rajaganesh, P. Ravinder, V. Subramanian, T.M. Das, Carbo. Res. 346 (2011) 2327-2335.
17. A.N. Nyuchev, E.A. Sharonova, N.A. Lenshina, A.S. Shavyrin, M.A. Lopatin, I.V. Balalaeva, I.P. Beletskaya, A.Y. Fedorov, Tetrahedron Letters 52 (2011) 4196–4199.
18. X.P. He, Z. Song, Z.Z. Wang, X.X. Shi, K. Chen, G.R. Chen, Tetrahedron 67 (2011) 3343-3347.
19. J.L. Xue, X.P. He, J.W. Yang, D.T. Shi, C.Y. Cheng, J. Xie, G.R. Chen, K. Chen, Carbo. Res. 363 (2012) 38–42.
20. R.D. Youssefyeh, J.P.H. Verheyden, J.G. Moffatt, J. Org. Chem. 44 (1979) 1301–1309.
21. V.K. Sharma, S.K. Singh, K. Bohra, C.S.L. Reddy, V. Khatri, C.E. Olsen, A.K. Prasad, Nucleosides, Nucleotides and Nucleic Acids 32 (2013) 256–272.
22. B.A. Mayes, A.M. Moussa, A.J. Stewart, PCT Int. Appl. 2014, 2014066239A1.
23. (a) A.N. Brubaker, J.D. Ruiter, W.L. Whitmer, J. Med. Chem. 29 (1986) 1094–1099; (b) P. Srivastava, V.K. Vyas, B. Variya, P. Patel, G. Qureshi, M. Ghate, Bioorg. Chem. 67 (2016) 130–138.
24. H.-M. Chen, Z. Armstrong, S.J. Hallam, S.G. Withers, Carbohydrate Res. 421 (2016) 33–39; (b) C. Krishna, M.V. Bhargavi, C.P. Rao, G.L.D. Krupadanam, Med. Chem. Res. 24 (2015) 3743–3751.
25. G.M. Sheldrick, Acta Crystallogr. Sect. A: Found. Crystallogr. 64 (2008) 112–122.
26. L.J. Farrugia, J. Appl. Crystallogr. 32 (1999) 837–838.
27. C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J.vanDe. Streek, J. Appl. Crystallogr. 39 (2006) 453–457.

Highlights:

1. A series of novel coumarintriazolyl-bicyclonucleosides have been synthesized.
2. Crystal structure of one coumarintriazolyl-bicyclonucleoside has been reported.
3. Synthesis of nucleoside monomers with *N*-configuration.
4. Photo-physical studies of eight coumarintriazolyl-bicyclonucleoside conjugates.