# An Efficient Approach for the Synthesis of 1,2,3-Triazole Moiety to Generate Uracil Molecular Architectures Through Cu-Catalyzed Azide–Alkyne Cycloaddition

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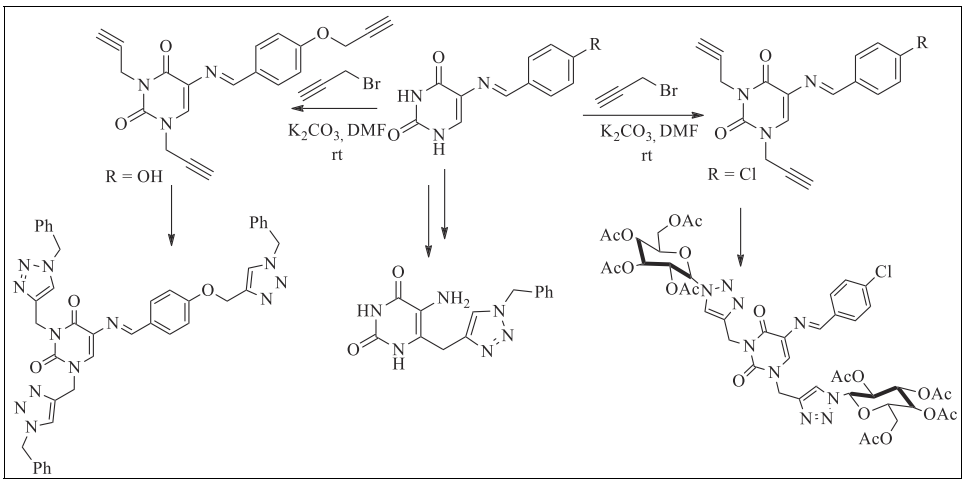


A simple and efficient pathway to tether conjugates of monosaccharides or aromatic moieties to uracil establishing a 1,2,3-triazole linker *via* click chemistry was reported. The reaction of arylimines of 5-amino uracil with propargyl bromide in a basic medium gave a di-propargylated uracil. The latter compound was converted into molecular architectures containing bis-1,2,3-triazole rings through Cu-catalyzed 1,3-cycloaddition reaction with different azides. The same arylimine of 5-amino uracil yielded different products under reflux with propargyl bromide in acetonitril with the majority to 6-propargylated-5-amino uracil.

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## INTRODUCTION

The synthesis and biological evaluation of modified nucleoside analogues have been a very active research area for a number of years [1]. In particular, several acyclonucleosides analogues are presently known as potent antiviral agents, among these are HBG, ACV, DHPG,[2,3] PMEA, and HPMPA[4] derivatives. Furthermore, the importance of side-chain conformation in the interaction of acyclic nucleosides with enzymes has been noted,[5] and differences in affinities for the viral thymidine kinase appear to be because of conformational factors.

Efforts have been focused on the development of supramolecular materials featuring biological units by the chemical combination of biological molecules such as nucleic acids,[6–8] amino acids,[9] peptides,[10–13] or sugar[14–16] with lipids, which remains an amazing approach to create new hybrid amphiphilic structures. Because of their potential biomedical applications as low molecular weight gelators,[17–24] amphiphiles combining sugar, nucleic acid, and lipid moieties, namely, glycosyl-nucleoside lipids, have emerged as biocompatible materials of particular interest due to their intrinsic properties, in particular, the non-covalent nature of the molecular interactions at work (π–π stacking between the nucleobases and/or the triazole moieties, intermolecular hydrogen bond, etc.) [25].

Most of the glycosyl-nucleoside lipid amphiphiles exhibit the ability to form gels with either water or organic solvents giving rise to vesicles, nanofibers networks, or nanoparticles as evidenced by transmission electron microscopy studies [26,27]. Likewise, nucleobases or their modified analogues have been found to be excellent structural motifs in medicinal chemistry, and a number of nucleoside-type and nucleotide-type drugs are currently on the market [28].

The design and synthesis of dendritic architectures through the click chemistry approach have been gaining great attention during the recent years [29–32]. Click chemistry refers to Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azide and alkyne to obtain 1,4-disubstitued 1,2,3-triazole under mild reaction conditions with excellent chemoselectivity and good yield [33,34].

Moreover, 1,2,3-triazoles can be attractive as linker units,[35] which could connect two pharmacophores to give an innovative bifunctional drug, and have become increasingly useful and important in constructing bioactive molecules [36,37]. Also, their derivatives find industrial applications as fluorophores, chemosensors, and charge-transfer agents. They make attractive bridging units, because they are stable under oxidative/reductive and metabolic degradation conditions and actively participate in dipole–dipole interactions and hydrogen bonding [38–40].

In the context of our ongoing effort directed towards the click chemistry of N-propargylated carbazole,[41] we turned our attention to new classes of N-propargylated uracil and explore the synthesis of some new 1,2,3-triazole uracil targets.

## RESULTS AND DISCUSSION

The uracil ring has a high potential to form polar intermolecular and hydrogen bond interactions and offers several possible hydrogen bond sites [3]. The electrophilic attack at uracil ring involves nitrogen ($N^1$ and $N^3$), oxygen ($O^2$ and $O^4$), or ($C^6$), so the formation of compounds **3** and **4** were possible when we studied the propargylation of compound **1a** with propargyl bromide (**2**) in the presence of potassium carbonate at room temperature. The position of the propargyl groups at the heterocyclic core was elucidated by $^{13}C$ NMR spectroscopy (δ = 30.96, 38.78, 73.76, 77.00 and 78.44, 79.22 ppm for ($2H_2C{-}CCH$) with the presence of 2C═O signal, which appeared at δ = 158.77 and 159.16 ppm. In addition, the structure was elucidated by $^1H$ NMR spectroscopy, which showed absence of amino groups and appearance of a doublet signals at δ = 4.62 and 4.69 for $2N{-}CH_2$ and triplet signals at δ = 3.17 and 3.51 ppm for 2C−CH of the propargyl groups (see Supporting Information). IR spectra showed peaks at 1702 and 1663 $cm^{-1}$ and 1567 $cm^{-1}$ for two carbonyl groups and C═N, respectively; these facts allowed us to discard compound **3** and approved the correct structure as shown by compound **4** (Scheme 1).

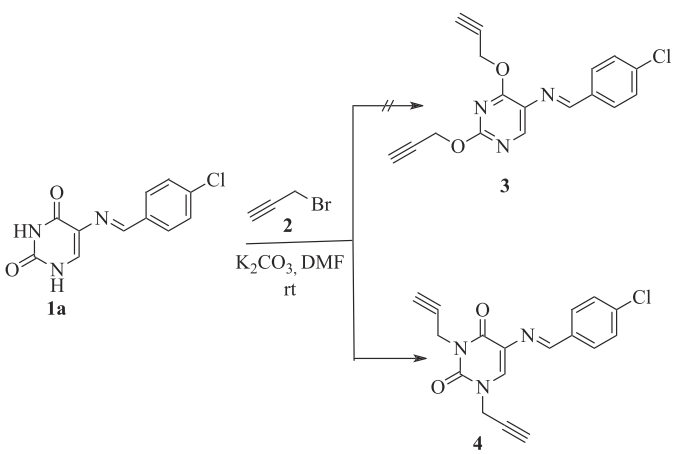
In a pilot experiment, we tethered compound **4** as an alkyne core, together with different monosaccharides and different aromatic compounds *via* 1,2,3-triazoles. Under Cu-catalyzed azide/alkyne click reaction conditions, reacting compound **4** with 1-azido-1-deoxy-2,3,4,6-tetraacetyl-*β*-D-hexoses (glucose and galactose) using $THF/H_2O$ (1:1) as a solvent mixture produced compounds **6** and **8** in excellent yields (Scheme 2). Compounds **6** and **8** showed the first designed target products in which two sugar units were attached to di-propargyled uracil **4**.

Based on these results, we applied a similar methodology to produce compounds **10** and **12** by reacting with compound **4** with 5-azido-1,2,3-trimethoxybenzene (**9**) and (azidomethyl)benzene (**11**) to tether aromatic moiety to alkyne **4** as shown in Scheme 3. The bis-1,2,3-triazole compounds were isolated in excellent yields. The $^1H$ and $^{13}C$ NMR spectra and mass spectrometry confirmed the suggested structures of compounds **10** and **12** (Figs S11, S14, and S16).

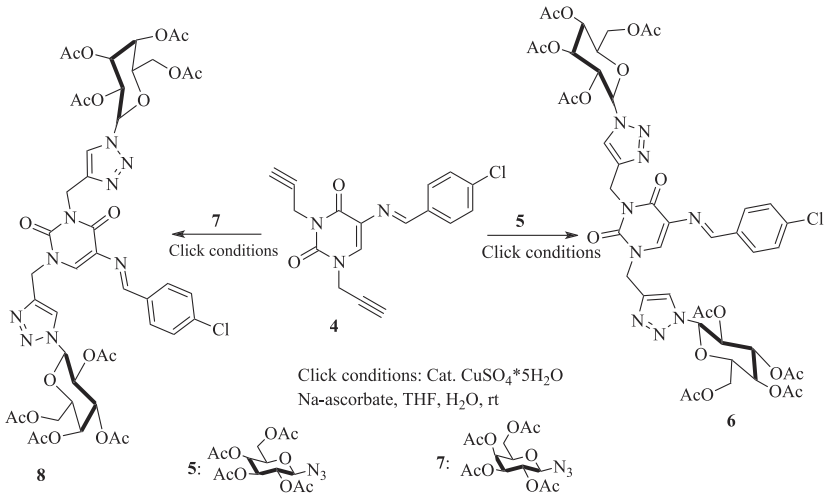
According to what has been previously reported,[42] a reasonable mechanism for the formation of clicked products **6**, **8**, **10**, and **12** involves deprotonation of the triple bond forming Cu-acetylide followed by 1,3-dipolar cycloaddition of azide.

Encouraged by this result and to gain more insight into the reaction, we have synthesized the new library of tri(1-phenyl-1*H*-1,2,3-triazole) **16** by treatment of compound **13** with (azidomethyl)benzene. The tri-

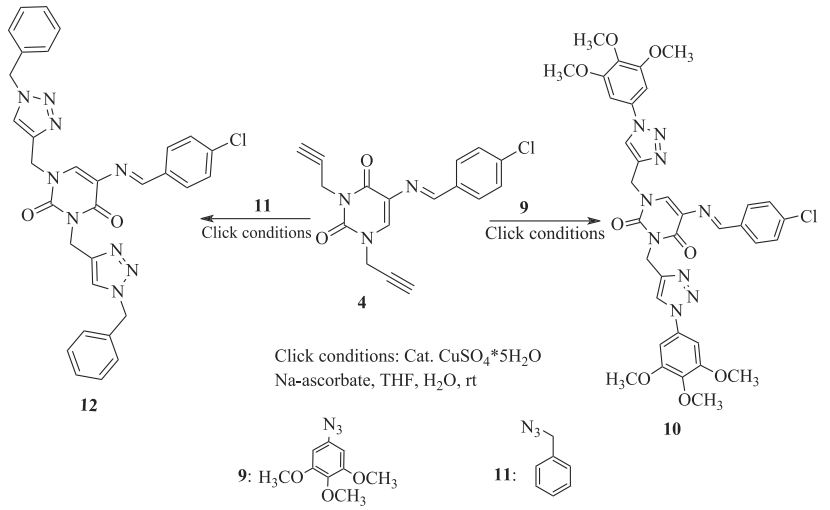
**Scheme 1.** Synthesis of 1,3-di(prop-2-yn-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione **4**.



**Scheme 2.** Synthesis of compounds **6** and **8** under click conditions.



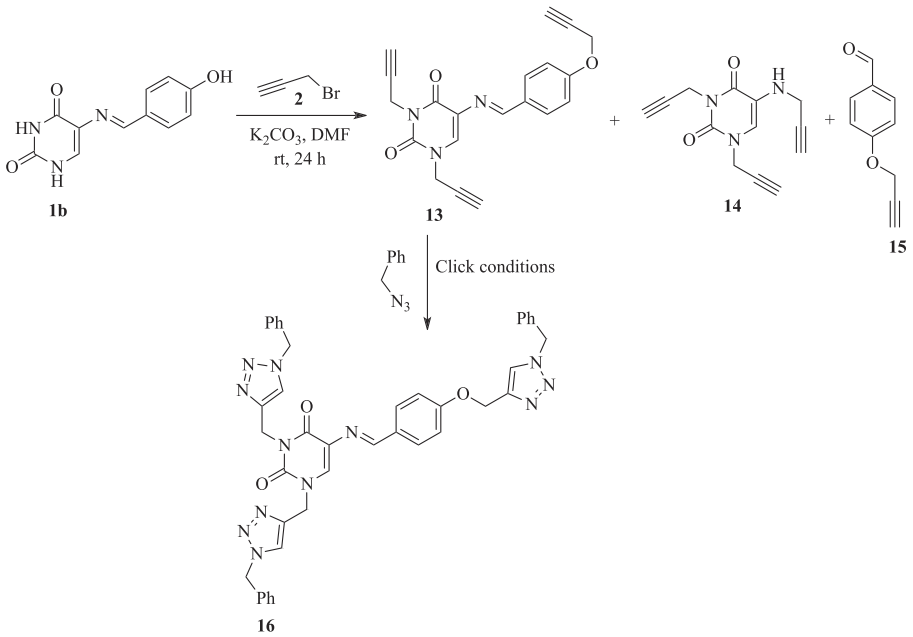

**Scheme 3.** Synthesis of 1,3-bis((1-(aryl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione **10** and **12**.



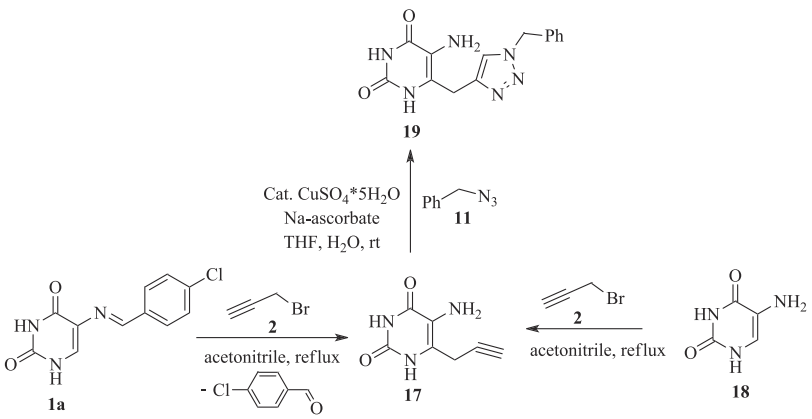

propargylated Schiff base **13**, tetra-propargyl uracil **14**, and the known 4-(prop-2-yn-1-yloxy)benzaldehyde (**15**)[43] were obtained by the reaction of compound **1b** with excess of propargyl bromide under basic conditions at room temperature. The desired products **13**, **14**, and **15** were separated and purified by plate chromatography (silica gel) (Scheme 4). The structure of all compounds was confirmed by examining their $^{1}$H and $^{13}$C NMR spectra, IR, and mass spectra. For compound **13**, the $^{1}$H NMR showed absence of amino groups and presence of two singlet signals at δ = 9.23 and 8.01 ppm for HC═N and 6CH; in addition, the signals assigned to $CH_2$ and CH groups for propargyl groups were at 4.61–4.89 ppm and 3.16–3.62 ppm, respectively. $^{13}$C NMR exhibited two carbonyl groups at δ = 160.11 and 154.65 ppm, three methylene groups at δ = 30.94, 38.66, and 56.06 ppm, and three ─CCH of alkyne groups at 73.69, 76.84, 78.57, 78.96, 79.32, and 79.36 ppm. The mass spectrum of **13** showed a molecular ion peak at *m/z* = 345 (see Supporting Information).

We also investigated another route for the synthesis of the target mono-1,2,3-triazole, which involved treatment of compound **1a** with an excess of propargyl bromide under reflux in acetonitrile as a solvent giving a new propargylated uracil **17** by breaking down of the Schiff base in compound **1a** as known reversible reaction because many Schiff bases can be hydrolyzed back to their aldehydes and amines. As an alternative synthesis

**Scheme 4.** Treatment of compound **1b** with propargyl bromide.




**Scheme 5.** Synthesis of mono-(1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione **19**.




for this compound, we also performed propargylation of 5-aminouracil (**18**) at the same previous conditions and gave the same product **17**. The desired product was isolated in an excellent yield 82%, and the structure of compound **17** was confirmed by spectral data. The $^1$H NMR showed four singlet signals for 2NH, $NH_2$ groups, and CH alkyne at $\delta$ = 11.18, 10.65, 6.94, and 3.21 ppm, respectively, and a doublet signal at $\delta$ = 3.82 ppm for $CH_2$ group. The alkyne product **17** and (azidomethyl)benzene as coupling partner were reacted together, under CuAAC click reaction conditions to deliver mono-triazole compound **19** in good yield (Scheme 5). The structure of compound **19** was supported by spectral data (see Supporting Information).

## CONCLUSION

In summary, we have prepared an interesting class of heterocyclic compounds from easily available starting materials opening a new synthetic way to obtain these substances. We carried out a straightforward convenient

methodology for the synthesis of novel architectures by using the Cu(I)-catalyzed alkyne–azide cycloaddition reaction.

## EXPERIMENTAL

**General remarks.** All reagents were purchased from Alfa Aesar or Fluka and were used without further purification. Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. IR spectra were measured using a Bruker Tensor 27 instrument. $^1$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra were recorded in DMSO-$d_6$ on Bruker Avance DRX-400 spectrometers with tetramethylsilane (for $^1$H) or the solvent (for $^{13}$C, δC = 77.01 ppm) as the internal standards. Mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

***Synthesis of (E)-N-(4-chloro-benzylidene)-2,4-bis(prop-2-yn-1-yloxy)pyrimidin-5-amine (4).*** Propargyl bromide (1.4 g, 12 mmol) was added to a suspension of compound **1a** (0.748 g, 3 mmol) and $K_2CO_3$ (0.828 g, 6 mmol) in dimethylformamide (DMF) (15 mL), and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was poured into 50-mL cold water, a pale yellow precipitate was formed and filtered to give compound **4**, which was recrystallized by using ethanol.

Yellow crystals; mp 186–188°C; yield (1.45 g, 76%); IR (film): $v$ = 1702 (CO), 1663 (C═N), 1567 ($CH_2$) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.17–3.16 (t, 1H, $J$ = 4.8 Hz, C─C$H$), 3.51–3.50 (t, 1H, $J$ = 4.8 Hz, C─C$H$), 4.62–4.61 (d, 2H, $J$ = 2.4 Hz, C$H_2$), 4.69 (d, 2H, $J$ = 2.4 Hz, C$H_2$), 7.56–7.54 (d, 2H, $J$ = 8.8 Hz, C$H$─Ar), 7.87–7.85 (d, 2H, $J$ = 8.8 Hz, C$H$─Ar), 8.12 (s, 1H, C$H$), 9.37 (s, 1H, N═C$H$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 30.96 (N$C$H$_2$), 38.78 (N$C$H2), 73.76 (≡$C$H), 77.00 (≡$C$H), 78.44 (≡$C$), 79.22 (≡$C$), 122.59 ($C$H─Ar), 129.41 ($C$H─Ar), 130.09 ($C$H─Ar), 135.84 ($C$H─Ar), 136.20 ($C$─Ar), 139.87 (C$_6$─Ar), 149.03 ($C$═N), 158.77 ($C$═O), 159.16 ($C$═O). MS (EI, 70 eV): $m/z$ (%) = 329 [M$^{+4}$, 10], 327 [M$^{+2}$, 38], 325 [M$^+$, 100], 286 (50), 243 (11), 188 (90), 150 (30), 89 (40), 79 (48). *Anal.* for $C_{17}H_{12}ClN_3O_2$ (325.75): Calcd C, 62.68; H, 3.71; N, 12.90; found C, 62.79; H, 3.75; N, 13.01.

**General procedure for the synthesis of compounds 6–12.** Azido compounds (2 mmol) were added to the alkyne substrate **4** (0.325 g, 1 mmol) in THF/H2O (1:1) (25 mL), and then sodium ascorbate (0.158 g, 0.8 mmol) and $CuSO_4.5H_2O$ (0.063 g, 0.4 mmol) were added. After sonication, the mixture was stirred at room temperature for the specified time 10–14 h. The mixture was concentrated and poured into 30-mL $H_2O$.

***(2S,4S,5S,6S)-2-(Acetoxymethyl)-6-(4-((5-((E)-(4-chlorobenzylidene)amino)-2,4-dioxo-3-((1((3R,4R,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-3,4-dihydropyrimidin-1(2H)-yl) methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (6).*** Yellow crystals; mp 206–208°C; yield (1.18 g, 71%); IR (film): $v$ = 1698 (CO), 1668 (CO), 1656 (C═N) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.76 (s, 6H, 2COC$H_3$), 1.96, 1.99, 2.03 (s, 18H, 6COC$H_3$), 4.14–4.10 (m, 4H, 2C$_5$H─CH$_2$─OCO, C$_5$H─CH$_2$OCO), 4.35 (2H, s, C$_5$H─CH$_2$─OCO), 5.20–5.16 (m, 4H, 2NC$H_2$), 5.55–5.52 (m, 2H, 2C$_3$$H$), 5.65–5.63 (m, 4H, 2C$_2$$H$, 2C$_4$$H$), 6.36–6.29 (m, 2H, 2C$_1$$H$─N$_{triazole}$), 7.56–7.54 (d, 1H, $J$ = 8 Hz, C$H$─Ar), 7.70–7.68 (d, 1H, $J$ = 8 Hz, CH─Ar), 7.86–7.84 (d, 1H, $J$ = 8 Hz, C$H$─Ar), 7.95–7.93 (d, 1H, $J$ = 8 Hz, C$H$─Ar), 8.17 (s, 1H, C$H_{Ar\text{-}triazole}$), 8.32 (s, 1H, C$H_{Ar\text{-}triazole}$), 8.49 (s, 1H, C$_6$$H$), 9.42 (s, 1H, N═C$H$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 20.26, 20.28, 20.64, 20.70, 20.78, 20.90 (8$C$H$_3$), 44.20 (2N$C$H$_2$), 62.14 (2$C_4$H), 67.95 (2C$_5$H─CH$_2$─OCO), 70.45 ($C_5$H), 70.57 ($C_5$H), 72.56 ($C_3$H), 72.67 ($C_3$H), 73.81 ($C_2$H), 73.86 ($C_2$H), 84.23 ($C_1$H$_{N\text{-}triazole}$), 84.34 ($C_1$H$_{N\text{-}triazole}$), 122.37 ($C_5$), 123.20 (2$C$H$_{Ar\text{-}triazole}$), 129.42 ($C$H─Ar), 129.81 ($C$H─Ar), 129.97 ($C$H─Ar), 131.63 ($C$H─Ar), 135.26 ($C$─Ar), 136.09 ($C$─Ar), 139.88 (2$C_{4\text{-}triazole}$), 149.80 ($C$═N), 140.90 ($C_6$), 158.35 ($C$═O), 159.77 ($C$═O), 168.94, 168.98, 169.87, 170.08, 170.55 (8$C$OCH$_3$). *Anal.* for $C_{45}H_{50}ClN_9O_{20}$ (1072.38): Calcd C, 50.40; H, 4.70; N, 11.76; found C, 50.55; H, 4.75; N, 11.91.

***(2S,3R,4S,5S,6S)-2-(Acetoxymethyl)-6-(4-((5-((E)-(4-chlorobenzylidene)amino)-2,4-dioxo-3-((1 ((3R,4R,5S,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)-1H-1,2,3-triazol-4-yl)methyl)-3,4-dihydropyrimidin-1(2H)-yl) methyl)-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (8).*** Pale yellow crystals; mp 214–216°C; yield (1.25 g, 76%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.70 (s, 6H, 2COC$H_3$), 1.95, 1.99, 2.01 (s, 18H, 6COC$H_3$), 4.14–4.06 (m, 4H, 2C$_5$H─CH$_2$─OCO, C$_5$H─CH$_2$OCO), 4.35 (s, 2H, C$_5$H─CH$_2$─OCO), 5.22–5.16 (m, 4H, 2NCH$_2$), 5.56–5.51 (m, 2H, 2C$_3$H), 5.61–5.59 (m, 4H, 2C$_2$$H$, 2C$_4$$H$), 6.36–6.30 (m, 2H, 2C$_1$$H$─N$_{triazole}$), 7.62–7.60 (d, 1H, $J$ = 8.8 Hz, C$H$─Ar), 7.69–7.67 (d, 1H, $J$ = 8.8 Hz, CH─Ar), 7.86–7.84 (d, 1H, $J$ = 8.8 Hz, C$H$─Ar), 7.94–7.92 (d, 1H, $J$ = 8.8 Hz, CH─Ar), 8.20 (s, 1H, CH$_{Ar\text{-}triazole}$), 8.38 (s, 1H, CH$_{Ar\text{-}triazole}$), 8.52 (s, 1H, C$_6$$H$), 9.38 (s, 1H, N═C$H$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 20.25, 20.28, 20.66, 20.72, 20.88, 20.75 (8$C$H$_3$), 42.10 (2N$C$H$_2$), 60.94 (2$C_4$H), 68.99 (2C$_5$H─CH$_2$─OCO), 70.58 ($C_5$H), 70.64 ($C_5$H), 72.68 ($C_3$H), 72.88 ($C_3$H), 74.25 ($C_2$H), 74.44 ($C_2$H), 82.77 ($C_1$H$_{N\text{-}triazole}$), 82.90 ($C_1$H$_{N\text{-}triazole}$), 118.20 ($C_5$), 127.23 (2$C$H$_{Ar\text{-}triazole}$), 128.56 ($C$H─Ar), 128.95 ($C$H─Ar), 130.84 ($C$H─Ar), 133.78 ($C$H─Ar), 135.14 ($C$H─Ar), 138.78 ($C$─Ar), 140.56 ($C$─Ar), 142.98 (2$C_{4\text{-}triazole}$),

143.45 ($C_6$), 149.66 (*C*═N), 159.44 (*C*═O), 159.86 (*C*═O), 168.82, 168.88, 169.89, 171.21, 171.45 (8*C*$OCH_3$). *Anal.* for $C_{45}H_{50}ClN_9O_{20}$ (1072.38): Calcd C, 50.40; H, 4.70; N, 11.76; found C, 50.56; H, 4.75; N, 11.91.

***(E)-5-((4-chlorobenzylidene)amino)-1,3-bis((1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1H,3H)-dione (10).*** Yellow crystals; mp >300°C; yield (0.73 g, 70%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.70, 3.71 (s, 6H, 2OC$H_3$), 3.84, 3.85 (s, 12H, 4$CH_3$), 5.23, 5.25 (s, 4H, 2NC$H_2$), 7.17–7.14 (d, 4H, *J* = 12 Hz, C*H*─Ar), 7.57–7.54 (d, 2H, *J* = 8.4 Hz, C*H*─Ar), 7.87–7.85 (d, 2H, *J* = 8 Hz, C*H*─Ar), 8.28 (s, 1H, C$H_{Ar\text{-}triazole}$), 8.67 (s, 1H, C$H_{arom\text{-}triazole}$), 8.86 (s, 1H, $C_6H$), 9.45 (s, 1H, N═C*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 44.41 (2NC$H_2$), 56.74 (4OC$H_3$), 60.65 (2OC$H_3$), 98.64 (4*C*H─Ar), 122.37 (2*C*$H_{Ar-N\text{-}triazole}$), 122.85 (2*C*$H_{Ar-N\text{-}triazole}$), 129.46 (2*C*H─Ar), 130.02 (2*C*─Ar), 132.93 ($C_{4\text{-}triazole}$), 136.10 (*C*─Ar), 137.82 (*C*─Ar), 137.92 (*C*─Ar), 149.80 ($C_6$), 153.92 (4O*C*─Ar), 153.96 (*C*═N), 158.37 (*C*═O), 159.89 (*C*═O). MS (*m/z*) (%): 745 [$M^{+1}$, 20], 744 [$M^+$, 10], 540 (20), 510 (54), 496 (100), 479 (40), 440 (30), 428 (50), 402 (30), 383 (18), 219 (12), 94 (18), 77 (50). *Anal.* for $C_{35}H_{34}ClN_9O_8$ (744.15): Calcd C, 56.49; H, 4.61; N, 16.94; found C, 56.63; H, 4.67; N, 17.08.

***(E)-1,3-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-((4–chloro-benzylidene)amino)-pyrimidine-2,4(1H,3H)-dione (12).*** Yellow crystals; mp 288–290°C; yield (0.55 g, 72%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 5.10 (s, 4H, 2NC$H_2$), 5.57 (s, 4H, 2NC$H_2$), 7.01–6.99 (d, 4H, *J* = 8 Hz, C*H*─Ar), 7.27–7.16 (m, 6H, C*H*─Ar), 7.46 (s, 1H, $CH_{Ar\text{-}triazole}$), 7.71–7.67 (m, 4H, $CH_{Ar\text{-}triazole}$), 8.52 (s, 1H, $C_6H$), 9.48 (s, 1H, N═C*H*); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 49.05 (NC$H_2$), 53.34 (NC$H_2$), 57.82 (2NC$H_2$), 115.49 ($C_5$), 124.39 (2$C_5H_{triazol}$), 128.45 (3*C*H─Ar), 128.67 (3*C*H─Ar), 129.23 (3*C*H─Ar), 129.44 (4*C*H─Ar), 130.00 ($C_{5\text{-}triazole}$), 131.66 (2*C*─Ar), 136.31 (2*C*─Ar), 140.50 ($C_6$), 149.90 (*C*═N), 158.60 (*C*═O), 162.22 (*C*═O). MS (*m/z*) (%): 592 [$M^+$, 20], 469 (30), 387 (18), 90 (100). *Anal.* for $C_{31}H_{26}ClN_9O_2$ (592.05): Calcd C, 62.89; H, 4.43; N, 21.29; found C, 63.03; H, 4.49; N, 21.42.

**General procedure for the synthesis of compounds 13–15**. Propargyl bromide (**2**) (2.12 g, 18 mmol) was added to a suspension of compound **1b** (0.693 g, 3 mmol) and $K_2CO_3$ (1.24 g, 9 mmol) in DMF (15 mL), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was poured into 50-mL cold water, and a pale yellow precipitate was formed, filtered, and dried. The formed solid was purified by dissolving it in dry acetone (5 mL) and then subjected to preparative plate chromatography (silica gel) and toluene/acetone (5:1) to give the compounds **13–15**.

***(E)-1,3-di(prop-2-yn-1-yl)-5-((4-(prop-2-yn-1-yloxy) benzylidene)amino)pyrimidine-2,4(1H,3H)-dione (13).*** Yellow crystals; mp 178–180°C, yield (2.15 g, 75%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.16 (s, 1H, C─C*H*), 3.49 (s, 1H, C─C*H*), 3.62 (s, 1H, C─C*H*), 4.617–4.612 (d, 2H, *J* = 2.4 Hz, C$H_2$), 4.68–4.67 (d, 2H, *J* = 2.4 Hz, C$H_2$), 4.896–4.890 (d, 2H, *J* = 2.4 Hz, C$H_2$), 7.09–7.11 (d, 1H, *J* = 8.8 Hz, C*H*─Ar), 7.19–7.17 (d, 1H, *J* = 8.8 Hz, C*H*─Ar), 7.57–7.55 (d, 1H, *J* = 8.8 Hz, C*H*─Ar), 7.83–7.80 (d, 1H, *J* = 8.8 Hz, C*H*─Ar), 8.01 (s, 1H, C*H*), 9.23 (s, 1H, N═C*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 30.94 (NC$H_2$), 38.66 (NC$H_2$), 56.06 (OC$H_2$), 73.69 (≡*C*H), 76.84 (≡*C*H), 78.57 (≡*C*H), 78.96 (≡*C*), 79.32 (≡*C*), 79.36 (≡*C*), 115.60 ($C_5$), 123.54 (*C*H─Ar), 126.59 (*C*H─Ar), 130.27 (*C*─Ar), 132.17 (*C*─Ar), 137.96 ($C_5$), 149.11 (*C*═N), 154.65 (*C*═O), 160.11 (*C*═O). MS (*m/z*) (%): 347 [$M^{+2}$, 20], 345 (100) [M+]. *Anal.* for $C_{20}H_{15}N_3O_3$ (345.35): Calcd C, 69.56; H, 4.38; N, 12.17; found C, 69.72; H, 4.42; N, 12.32.

***1,3-Di(prop-2-yn-1-yl)-5-(prop-2-yn-1-ylamino)pyrimidine-2,4(1H,3H)-dione1,3-di (prop-2-yn-1-yl)-5-(prop-2-yn-1-ylamino)pyrimidine-2,4(1H,3H)-dione (14).*** Yellow crystals; mp 168–170°C; yield (1.00 g, 57%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.10–3.09 (t, 1H, *J* = 2.4 Hz, C─C*H*), 3.35 (s, 1H, C─C*H*), 3.42–3.40 (t, 1H, *J* = 2.4 Hz, C─C*H*), 4.37 (s, 2H, C$H_2$), 4.556–4.550 (d, 2H, *J* = 2.4 Hz, C$H_2$), 4.578–4.572 (d, 2H, *J* = 2.4 Hz, C$H_2$), 6.94 (s, 1H, $C_6H$), 8.15 (s, 1H, N*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 30.86 (NH─*C*$H_2$), 37.71 (N─*C*H2), 73.47 (2H*C*≡), 76.39 (≡*C*H), 79.02 (2*C*≡), 79.56 (≡*C*), 117.99 ($C_5$), 123.23 ($C_6$), 148.51 (*C*═O), 159.64 (*C*═O). MS (*m/z*) (%): 241 [$M^+$, 16], 202 (5), 163 (14), 92 (18), 66 (100). *Anal.* for $C_{13}H_{11}N_3O_2$ (241.25): Calcd C, 64.72; H, 4.60; N, 17.42; found C, 64.90; H, 4.65; N, 17.57.

***Synthesis of (E)-5-((4-((1-benzyl-1H-1,2,3-triazol-4-yl) methoxy)benzylidene)amino)-1,3-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1H,3H)-dione (16).*** (Azidomethyl)benzene (**11**) (0.399 g, 3 mmol) was added to the alkyne substrate **13** (0.345 g, 1 mmol) in THF/$H_2O$ (1:1) (25 mL), and then sodium ascorbate (0.158 g, 0.8 mmol) and $CuSO_4.5H_2O$ (0.063 g, 0.4 mmol) were added. After sonication, the mixture was stirred at room temperature for the specified time of 18 h. The mixture was concentrated and poured into 30-mL $H_2O$. A pale yellow precipitate was formed and filtered to give the product **16**. Yellow crystals; mp 102–104°C; yield (0.88 g, 76%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 4.82 (s, 4H, 2NC$H_2$), 5.28 (s, 2H, OC$H_2$), 5.62 (s, 6H, 3NC$H_2$), 7.24–7.22 (d, 3H, *J* = 7.6 Hz, C*H*─Ar), 7.38–7.32 (m, 10H, C*H*─Ar + C$H_{Ar\text{-}triazole}$), 7.88–7.87 (d, 3H, *J* = 7.6 Hz, C*H*─Ar), 8.33 (s, 1H, $C_6H$), 9.88 (s, 1H, N═C*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 53.34 (2NC$H_2$), 57.14 (3C$H_2$Ph), 61.93 (OC$H_2$), 115.69 ($C_5$),

122.45 ($3C_{5\text{-triazole}}$), 125.43 (5*C*H—Ar), 128.45 (4*C*H—Ar), 128.66 (5*C*H—Ar), 129.25 (5*C*H—Ar), 130.34 ($3C_{4\text{-triazole}}$), 132.24 (*C*—Ar), 136.43 (*C*—Ar), 142.81 ($C_6$), 149.31 (*C*═N), 158.00 (*C*═O), 163.40 (*C*═O). MS (*m/z*) (%): 744 [$M^+$, 14], 292 (12), 171 (18), 144 (32), 90 (100), 64 (48). *Anal*. for $C_{41}H_{36}N_{12}O_3$ (744.80): Calcd. C, 66.12; H, 4.87; N, 22.57; found C, 66.32; H, 4.91; N, 22.76.

***Synthesis of 5-amino-6-(prop-2-yn-1-yl)pyrimidine-2,4(1H,3H)-dione (17).*** An excess of propargyl bromide (5 mL, 2) was added to a suspension of compound **1a** (0.498 g, 2 mmol) or compound **18** (0.254 g, 2 mmol) in acetonitrile as a solvent, and the reaction mixture was refluxed for 10 h. The formed precipitate was filtered and recrystallized from DMF/EtOH. Pale yellow crystals; mp 242–244°C; yield (0.126 g, 76%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 2.89 (2H, s, $CH_2$), 3.21 (s, 1H, C—C*H*), 8.17 (s, 2H, N$H_2$), 10.65 (s, 1H, N*H*), 11.18 (s, 1H, N*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 34.88 (*C*$H_2$), 76.50 (≡*C*H), 79.43 (≡*C*), 122.29 (*C*5), 130.68 (*C*6), 150.75 (*C*═O), 161.91 (*C*═O). MS (*m/z*) (%): 165 [$M^+$, 10], 163 [$M^{+2}$, 100], 131 (18), 120 (22), 92 (40), 65 (70). *Anal*. for $C_7H_7N_3O_2$ (165.15): Calcd. C, 50.91; H, 4.27; N, 25.44; found C, 51.07; H, 4.32; N, 25.62.

***Synthesis of 5-amino-6-((1-benzyl-1H-1,2,3-triazol-4-yl) methyl)pyrimidine-2,4(1H,3H)-dione (19).*** (Azidomethyl) benzene (**11**) (0.133 g, 1 mmol) was added to the alkyne substrate **17** (0.165 g, 1 mmol) in THF/$H_2O$ (1:1) (25 mL), and then sodium ascorbate (0.079 g, 0.4 mmol) and $CuSO_4.5H_2O$ (0.031 g, 0.2 mmol) were added. After sonication, the mixture was stirred at room temperature for the specified time of 12 h. The mixture was concentrated and poured into 30-mL $H_2O$. A pale yellow precipitate was formed and filtered to give the product **19**. Pale yellow crystals; mp 240–242°C; yield (0.228 g, 76%); $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 4.16 (s, 2H, C$H_2$), 5.58 (s, 2H, NC$H_2$), 7.21–7.20 (m, 3H, C*H*—Ar), 7.36–7.34 (m, 3H, C*H*—Ar + $CH_{\text{Ar-triazole}}$), 8.04 (s, 2H, N$H_2$), 10.39 (s, 1H, N*H*), 11.06 (s, 1H, N*H*). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 46.21 (*C*$H_2$), 53.14 (N*C*$H_2$), 122.63 (*C*5), 124.82 (*C*6 + $CH_{\text{Ar-triazole}}$), 127.93 (*C*—Ar), 128.46 (*C*—Ar), 129.19 ($C_{4\text{-triazole}}$), 136.69 (*C*—Ar), 150.85 (*C*═O), 162.42 (*C*═O). MS (*m/z*) (%): 298 ($M^+$, 30), 206 (5), 90 (100). *Anal*. for $C_{14}H_{14}N_6O_2$ (298.30): Calcd. C, 56.37; H, 4.73; N, 28.17; found C, 56.54; H, 4.77; N, 28.32.

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