Communication

An Efficient Synthesis of Mono and Bis-1,2,3-triazole AZT Derivatives via Copper(I)-catalyzed Cycloaddition

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An efficient synthesis of novel mono and bis-1,2,3-triazoles 3′-azido-2′-deoxythymidine (AZT) derivatives via copper(I)-catalyzed 1,3-dipolar cycloaddition reaction is described. Starting from AZT and terminal alkyne derivatives, mono and bis-1,2,3-triazole AZT derivatives are regioselectively obtained in good yields under mild conditions using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as a catalyst system, and *t*-BuOH/H_2O (1:1, v/v) as a co-solvent. The structures of these compounds were elucidated by IR, HR MS and NMR.

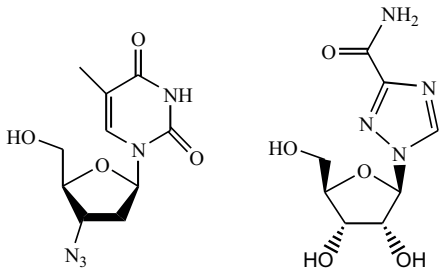
Keywords: 3′-Azido-2′-deoxythymidine (AZT); 1,2,3-Triazole; 1,3-Dipolar cycloaddition.

INTRODUCTION

Nucleoside analogues have long been used to treat various viral-induced tumors. 3′-Azido-2′-deoxythymidine (AZT) (Fig. 1a), as a nucleoside analogue, has been reported to possess high activity against AIDS, owing to its potential inhibiting property to HIV reverse transcriptase.[1] Azoles are the largest class of antifungal agents in clinical use.[2] 1,2,3-Triazole can serve as a suitable moieties in these drugs since it is stable to metabolic degradation and susceptible to hydrogen bonding beneficial for the affinity with molecular targets and solubility.[3,4] Compounds containing a 1,2,3-triazole moiety show various biological activities such as anti-HIV,[5] anti-microbial,[6] anti-allergic,[7] and selective β3 adrenergic receptor agonist.[8] Ribavirin (Fig. 1b) is the first synthetic and so far the only small molecule triazole nucleoside drug for treating viral infections caused by hepatitis C virus (HCV).[9] A number of synthetic methodologies have been developed for the preparation of various nucleoside analogues containing 1,2,3-triazole moiety since then.[10]

With respect to introducing 1,2,3-triazole groups in to organic molecules, copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of azides and terminal alkynes, discovered by the groups of Sharpless and Meldal,[11,12] is a useful approach. This characteristic of the reaction is its complete specificity, biocompatibility of the reactants and high degree of dependability. Cu(I)-catalyzed 1,3-dipolar cycloaddition is premiere example of a click chemistry employed in a wide range of applications within drug discovery, including modification of cell surfaces, specific labeling of virus particles, proteins, oligonucleotides and synthesis of new glycoproteins and dendrimers.[13]

Generation of the 1,2,3-triazoles moiety in the 3′-position of 2′-deoxyribose nucleosides through the 1,3-dipolar cycloaddition of organic azides with alkynes has been



a. AZT **b.** Ribavirin

Fig. 1. The structures of AZT and Ribavirin.

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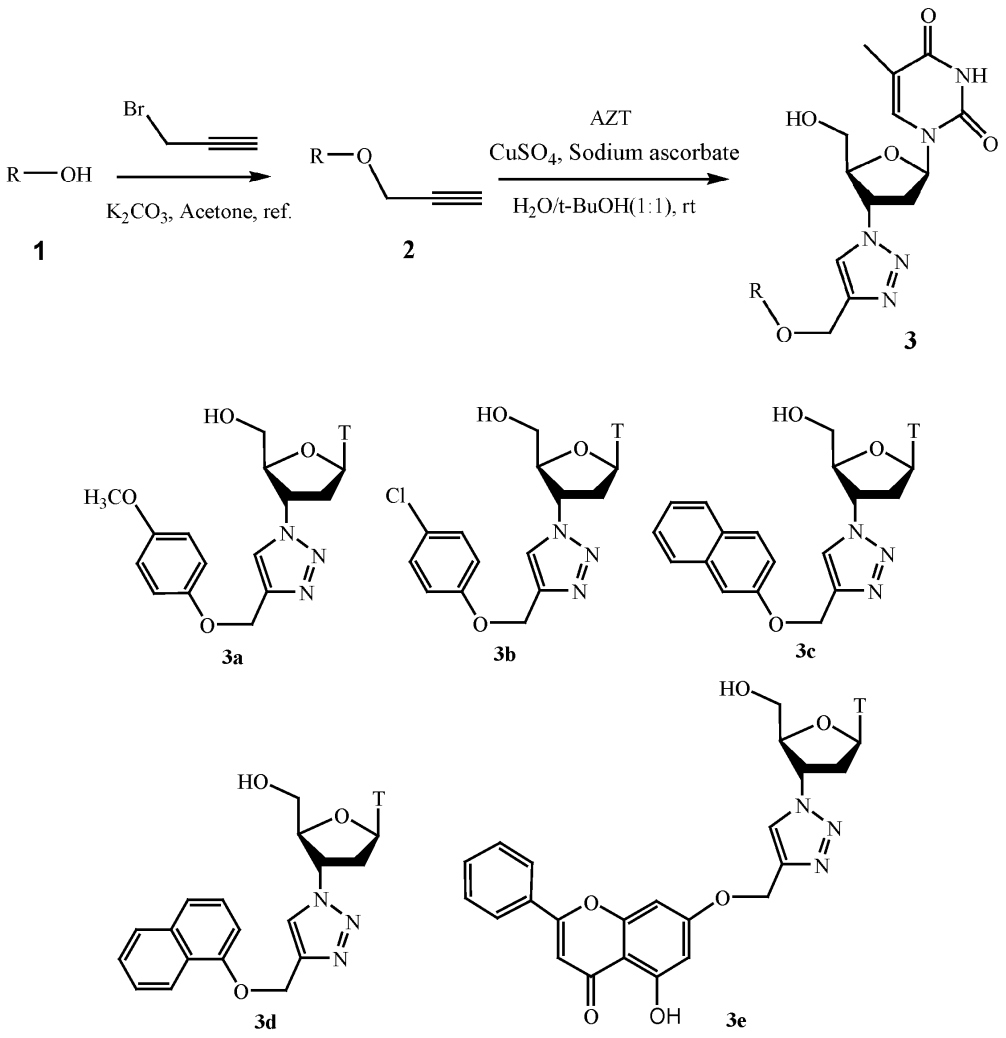
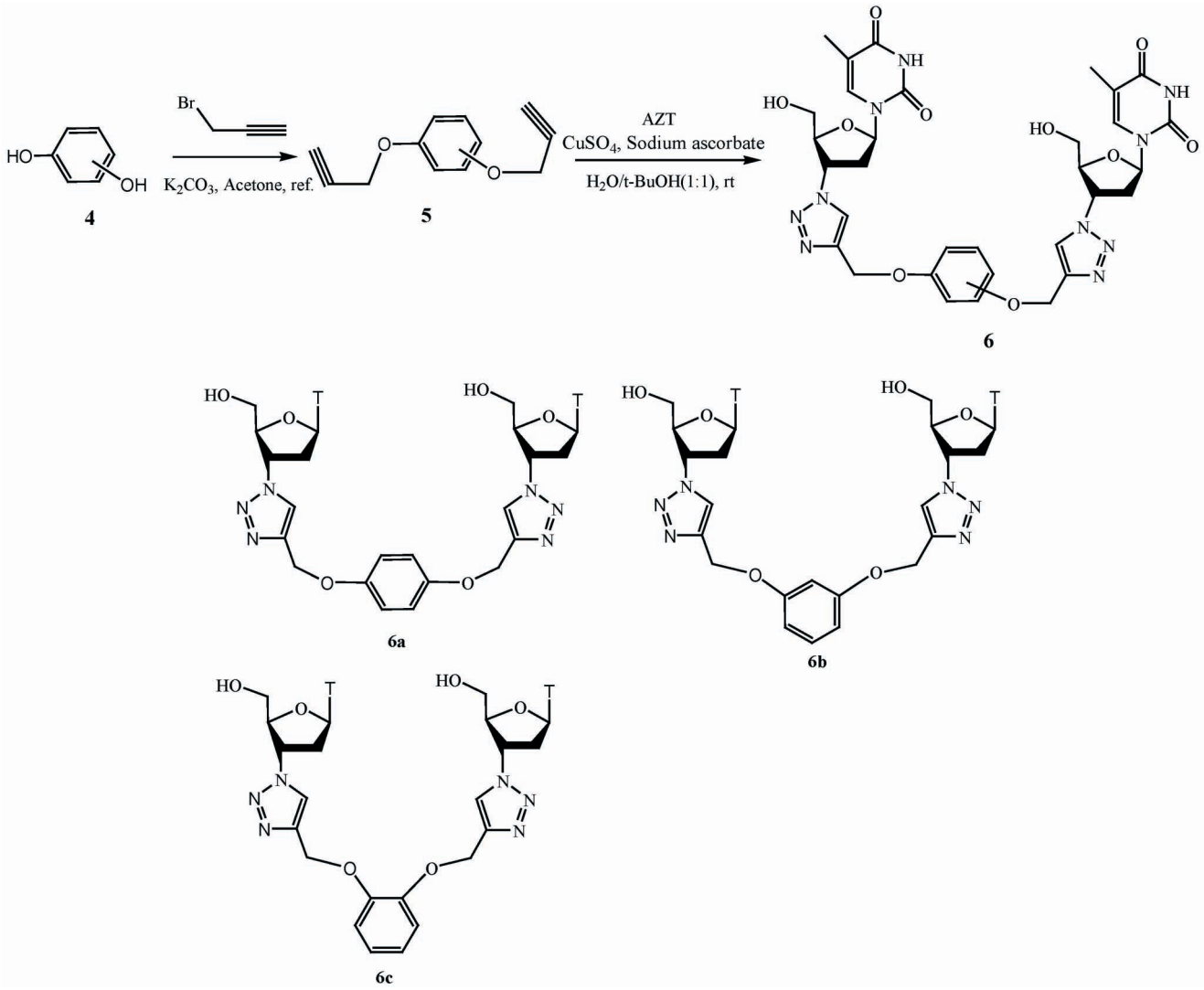
reported by Wigerinck P.'s and Tourirte M.'s groups.[14,15] However, these cycloaddition reactions were typically carried out in refluxing organic solvents (DME, toluene) conditions in which labile molecules may not survive. The cycloadditions performed under the relatively harsh reaction conditions, for example, at relatively high temperature, sometimes resulted in low yields and/or poor regioselectivity.[16] The main purpose of our work is to provide a practical method, through 1,3-dipolar cycloaddition of AZT with alkynes, to regioselectively synthesize a series of novel 2′-deoxythymidine derivatives linked with 1,2,3-triazoles attached by various aromatic moieties, including chrysin groups as shown in Scheme I, and also bis-triazole AZT derivatives as shown in Scheme II. Interestingly enough, it was found that, as described in the following of this paper, even at room temperature, a regioseletive synthesis of novel 1,2,3-triazole derivatives of AZT could successfully been carried out by 1,3-dipolar cycloaddition using $CuSO_4$/sodium ascorbate as the catalyst, *t*-BuOH-H_2O (1:1 v/v) as the solvent in relatively high yields. It is especially worth mentioning that the regioselective products of 1,3-dipolar cycloaddition reaction are insoluble in the reaction solvent (*t*-BuOH-H_2O (1:1 v/v)), and thus they precipitates as they are formed. It is therefore easy to purify the products by simply washing with water. Chrysin, an important naturally occurring flavonoid, possessing multiple biological activities,[17] such as antiviral,[18] antibacterial,[19] antioxidant,[20] anticancer activities,[21] was also successfully incorporate in the related 1,2,3-triazole AZT modification by using the reaction condition mentioned above. Finally a series of novel target products were obtained in relatively high yield under mild reaction conditions as described in

Scheme I Synthesis of 1,2,3-triazole AZT derivatives



Scheme II Synthesis of bis-1,2,3-triazoles AZT derivatives



the following.

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reaction of organic azides and alkynes has recently regained attention, owing to the discovery that the rate of the cycloaddition can be accelerated greatly by Cu(I) catalysis.[11,22] The active Cu(I) ion can be generated directly from Cu(I) salts or in-situ from Cu(II) salts in presence of a reducing agent (often sodium ascorbate or metallic copper). Direct use of Cu(I) salts as catalysts should be avoided in some cases because of their extremely low solubility in aqueous media and their tendency to disproportionate quickly to Cu(0) and Cu(II) under some reaction conditions.[23] Also in most occasions Cu(I) salts must be used in conjunction with a base or ligand in organic or aqueous solvent for achieving higher catalytic efficiency.[22,24] $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as a catalyst system, firstly employed by Sharpless and co-workers for the in situ generation of Cu(I),[11] has been applied to lots of 1,3-dipolar cycloadditions with a relatively high catalytic stability and efficiency.[25] Also $CuSO_4 \cdot 5H_2O$ and sodium ascorbate show very appreciable solubility in the properly chosen cosolvent (*t*-BuOH-H_2O (1:1 v/v)) used in the following 1,3-dipolar cycloaddition. Considering the appreciable stability and solubility of catalysts in the related reaction system, $CuSO_4 \cdot 5H_2O$/sodium ascorbate was therefore chosen as an appropriate catalyst system for the 1,3-dipolar cycloaddition.

The solubility of reactants involved in 1,3-dipolar cycloaddition reaction is another major factor affecting the

reaction efficiency. Different solvents, such as *tert*-butyl alcohol, ethanol, water and the related cosolvents seen by previous reports were employed to carry out the 1,3-dipolar cycloaddition.[11,26] Considering poor solubility of the related aromatic reactants, especially chrysin, in pure water and poor solubility of the Cu(II) salts in organic solvents, *t*-BuOH/H_2O co-solvent at ratio 1:1 (v/v) was chosen as the reaction solvent to enhance the solubility of either the related aromatic reactants or the Cu(II) salts. As described in the following section, the cycloaddition reaction of various aromatic terminal alkyne and AZT was indeed proceeded efficiently at room temperature under the designed reaction condition using $CuSO_4 \cdot 5H_2O$/sodium ascorbate as a catalyst system, and *t*-BuOH/H_2O (1:1, v/v) as a cosolvent.

The title compounds were synthesized as shown in Scheme I and II. Under reflux condition the reaction forming different aryl propargyl ethers took place using different aromatic phenols and propargyl bromine as reactants in acetone. Using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as a catalyst system, and *t*-BuOH/H_2O (1:1, v/v) as a solvent, the reactions between 3′-azido group of AZT and acetylene group of aryl propargyl ethers **2** at room temperature led to a series of mono and bis-1,2,3-triazole AZT derivatives via 1,3-dipolar cycloaddition reaction. The regioselective products of 1,3-dipolar cycloaddition reaction are insoluble in the reaction solvent (*t*-BuOH-H_2O (1:1 v/v)), and thus they precipitates as they are formed. The pure products (**3a-d**) were obtained in relatively high yields after a simple filtration and washing with water. The conversion of aryl propargyl ether into the corresponding mono-1,2,3-triazole AZT derivatives (**3a-d**) was almost quantitative and isolated yields of products were high (≥ 95%). The conversion of chrysin-7-yl propargyl ether (**2e**) into the corresponding 1,2,3-triazole AZT (**3e**) was relatively low and isolated yields of products was 72%, and the conversion of bis-(ethynyloxy) benzene (**5a-c**) into the corresponding bis-1,2,3-triazole AZT (**6a-c**) was comparably higher and isolated yields of products were more than 92%.

A high regioselectivity of the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction was observed. Only 1,4- rather than 1,5-substituted [1,2,3]-trazole was formed based on NMR data analysis of final products. It was reported that the triazole proton in 1,4-substituted trazoles was always shifted considerably downfield (about 8.50 ppm) compared to 1,5-substituted trazoles (about 8.23 ppm).[22] The fact that the triazole proton of products **3a-e** and **6a-c** were found at 8.39-8.55 ppm gives a decisive support for the 1,4-substituted trazole products formed by 1,3-dipolar cycloaddition reaction. NOE effects between the triazole proton and the 4′-proton of glucoyl were also observed, suggesting that the triazole proton and N-substituent are in close proximity as in the 1,4-substituted triazole.

CONCLUSION

An efficient synthesis of novel 1,2,3-triazole and bis-1,2,3-triazoles 3′-azido-2′-deoxythymidine (AZT) derivatives via copper(I)-catalyzed 1,3-dipolar cycloaddition reaction is established. Mono and bis-1,2,3-triazole AZT derivatives are regioselectively obtained in good yields under mild conditions using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as a catalyst system, and *t*-BuOH/H_2O (1:1, v/v) as a solvent.

EXPERIMENTAL

Acetone was dried with K_2CO_3, and then distilled. IR spectra were recorded on a Shimadazuir-408. ^1H, ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer operating at 400.13 and 100.61 MHz, respectively, with ^{13}C spectra being recorded as proton-decoupled. NMR spectra were recorded in DMSO or $CDCl_3$ at room temperature (20 ± 3 °C). ^1H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. *J* values refer to coupling constants, and signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or combinations thereof. TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200-300 mesh). High resolution mass spectra (HR MS) were obtained on a Waters Micromass Q-Tof Micro™ instrument using the ESI technique.

General procedures

Synthesis of mono-1,2,3-triazole AZT derivatives (3a-e)

To a solution of aromatic phenols (**1a-e**) (1.0 mmol) in dry acetone (10 mL) was added anhydrous potassium carbonate (0.276 g, 2 mmol), and the mixture was stirred for 0.5 h, then propargyl bromide (0.118 g, 1.0 mmol) were added. The resulting mixture was stirred and refluxed for an additional 20 h. The mixture was cooled and filtered, and the filtrate was evaporated. The residue was dissolved in dichloromethane (50 mL) and washed with water (2 × 50 mL) and saturated brine (1 × 50 mL). The organic phase was dried over anhydrous sodium sulfate. The crude product was purified with column chromatograph on silica gel and eluted with petroleum ether : ethyl acetate (1:1, v/v), to

give aryl propargyl ethers (**2a-e**).

Compound 2a

Yellow oily liquid, yield: 96.0%; ^{1}H NMR ($CDCl_3$) δ: 6.93 (m, 2H), 6.85 (m, 2H), 4.65 (d, J = 2.4 Hz, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 2.51 (t, J = 2.4 Hz, 1H, ≡CH). ^{13}C NMR ($CDCl_3$) δ: 154.5, 151.6, 116.1, 114.6, 78.9 (CH≡C), 75.4 (CH≡C), 56.5 (OCH_2), 55.6 (OCH_3).

Compound 2b

Colorless liquid, yield: 97.0%; ^{1}H NMR ($CDCl_3$) δ: 7.29 (m, 2H), 6.91 (m, 2H), 4.66 (d, J = 2.4 Hz, 2H, OCH_2), 2.57 (t, J = 2.4 Hz, 1H, ≡CH); ^{13}C NMR ($CDCl_3$) δ: 156.1 (O-C), 129.4, 126.5, 116.3, 78.3 (CH≡C), 76.0 (CH≡C), 56.0 (OCH_2).

Compound 2c

White solid, yield: 94.0%; ^{1}H NMR ($CDCl_3$) δ: 8.25 (m, 1H), 7.75 (m, 1H), 7.42 (m, 3H), 7.31 (m, 1H), 6.85 (m, 1H), 4.80 (d, J = 2.4 Hz, 2H, OCH_2), 2.49 (t, J = 2.4 Hz, 1H, ≡CH); ^{13}C NMR ($CDCl_3$) δ: 153.4 (O-C), 134.6, 127.6, 126.6, 125.7, 125.5, 122.1, 121.3, 105.6, 78.7 (CH≡C), 75.7 (CH≡C), 56.2 (OCH_2).

Compound 2d

White solid, yield: 95.0%; ^{1}H NMR ($CDCl_3$) δ: 7.72-7.76 (m, 3H), 7.43 (m, 1H), 7.36 (m, 1H), 7.16-7.21 (m, 2H), 4.78 (s, 2H, OCH_2), 2.53 (s, 1H, ≡CH); ^{13}C NMR ($CDCl_3$) δ: 155.5 (O-C), 134.3, 129.6, 129.4, 127.7, 126.9, 126.5, 124.1, 118.7, 101.5, 78.5 (CH≡C), 75.0 (CH≡C), 55.9 (OCH_2).

Compound 2e

Yellow solid, yield: 96.0%; ^{1}H NMR (DMSO) δ: 12.81 (s, 1H, OH), 8.06-8.08 (m, 2H), 7.55-7.62 (m, 3H), 7.03 (s, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.44 (d, J = 1.6 Hz, 1H), 4.95 (s, 2H, OCH_2), 3.68 (s, 1H, ≡CH); ^{13}C NMR (DMSO) δ: 182.6 (C=O), 164.0, 163.6, 161.6, 157.6, 132.6, 130.9, 129.6, 126.9, 105.8, 105.7, 99.2, 94.2, 79.5 (CH≡C), 78.8 (CH≡C), 56.7 (OCH_2).

3′-Azido-2′-deoxythymine (0.134 g, 0.5 mmol) and the corresponding aryl propargyl ether (**2a-e**) (0.5 mmol) were dissolved in *t*-BuOH/H_2O (2 mL/2 mL) co-solvent. The reaction mixture was stirred at room temperature for 10 min, and then added $CuSO_4 \cdot 5H_2O$ (0.006 g, 0.025 mmol) and L-ascorbic acid sodium (0.011 g, 0.05 mmol). The reaction mixture was stirred at room temperature until the starting material was consumed as judged by TLC analysis. A white precipitate was generated when the reaction was over. The precipitate was filtered, washed with ice-cold water and dried, and the white solids (**3a-e**) were obtianed.

Compound 3a

Yieled: 96.0%; m.p. 212-213 °C; IR (KBr) ν (cm^{-1}): 3480 (NH), 1709 (C=O), 3076, 2929 (CH_3), 1277 (C-O); HR MS *m/z*: 430.1722 $[M + H]^+$, (calculated for $C_{20}H_{24}N_5O_6$ 430.1727); ^{1}H NMR (DMSO) δ: 11.36 (s, 1H, -NH), 8.40 (s, 1H, =CH), 7.82 (s, 1H), 6.99 (m, 2H), 6.79 (m, 2H), 6.44 (t, J = 6.8 Hz, 1H), 5.39-5.37 (m, 1H), 5.29-5.27 (m, 1H), 5.08 (s, 1H), 4.24-4.21 (m, 1H), 3.68 (s, 3H, OCH_3), 3.73-3.61 (m, 2H), 2.76-2.65 (m, 2H), 1.81 (s, 3H, CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O), 154.1 (C=O), 152.5, 150.9, 143.7, 136.7, 124.5, 116.1, 115.1, 110.1, 84.9, 84.3, 62.1, 61.2, 59.7, 55.8, 37.6, 12.7 (CH_3).

Compound 3b

Yieled: 95.0%; m.p. 212-213 °C; IR (KBr) ν (cm^{-1}): 3491 (NH), 1676 (C=O), 3080, 2935 (CH_3), 1275 (C-O); HR MS *m/z*: 434.1229 $[M + H]^+$, (calculated for $C_{19}H_{21}ClN_5O_5$ 434.1231); ^{1}H NMR (DMSO) δ: 11.36 (s, 1H, -NH), 8.42 (s, 1H, =CH), 7.81 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.43 (t, J = 6.4 Hz, 1H), 5.39 (m, 1H), 5.31 (m, 1H), 5.15 (s, 1H), 4.21 (m, 1H), 3.71 (m, 2H), 2.74 (m, 2H), 1.80 (s, 3H, CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O), 157.3 (C=O), 150.9, 143.1, 136.7, 129.7, 125.0, 124.8, 116.9, 110.1, 84.9, 84.3, 61.8, 61.2, 59.8, 37.6, 12.7 (CH_3).

Compound 3c

Yieled: 96.0%; m.p. 242-243 °C; IR (KBr) ν (cm^{-1}): 3480 (NH), 1685 (C=O), 3082, 2931 (CH_3), 1273 (C-O); HR MS *m/z*: 450.1773 $[M + H]^+$, (calculated for $C_{23}H_{24}N_5O_5$ 450.1777); ^{1}H NMR (DMSO) δ: 11.38 (s, 1H, -NH), 8.50 (s, 1H, =CH), 7.85 (m, 3H), 7.84 (s, 1H), 7.53 (s, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.47 (t, J = 6.4 Hz, 1H), 5.43 (m, 1H), 5.33 (m, 1H), 5.29 (s, 2H), 4.26 (m, 1H), 3.68 (m, 2H), 2.72 (m, 2H), 1.82 (s, 3H, CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O), 156.4 (C=O), 150.9, 143.3, 136.7, 134.6, 129.8, 129.1, 127.9, 127.2, 126.9, 127.8, 119.1, 110.1, 107.6, 84.9, 84.3, 61.6, 61.2, 59.8, 37.6, 12.7 (CH_3).

Compound 3d

Yieled: 95.0%; m.p. 245-246 °C; IR (KBr) ν (cm^{-1}): 3442 (NH), 1697 (C=O), 3082, 2934 (CH_3), 1270 (C-O); HR MS *m/z*: 450.1775 $[M + H]^+$, (calculated for $C_{23}H_{24}N_5O_5$ 450.1777); ^{1}H NMR (DMSO) δ: 11.37 (s, 1H, -NH), 8.55 (s, 1H, =CH), 8.15 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H, 6-H), 7.48 (m, 4H), 7.20 (d, J = 7.2 Hz, 1H), 6.47 (t, J = 6.4 Hz, 1H), 5.42 (m, 1H), 5.36 (s, 2H), 5.30 (m, 1H), 4.26 (m, 1H), 3.67 (m, 2H), 2.72 (m, 2H), 1.81 (s, 3H, CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O),

153.9 (C=O), 150.9, 143.6, 136.7, 134.5, 127.9, 126.9, 126.6, 125.8, 125.3, 124.6, 122.0, 120.8, 110.1, 106.3, 84.9, 84.3, 62.2, 61.2, 59.7, 37.6, 12.7 ($\underline{C}H_3$).

Compound 3e

Yieled: 72.0%; m.p. 223-224 °C; IR (KBr) ν (cm^{-1}): 3418 (NH), 1697 (C=O), 3080, 2930 (CH_3), 1272 (C-O); HR MS *m/z*: 582.1598 $[M + Na]^+$, (calculated for $C_{28}H_{254}N_5O_8Na$ 582.1601); ^1H NMR (DMSO) δ: 12.84 (s, 1H, -OH), 11.36 (s, 1H, -NH), 8.49 (s, 1H, =CH), 8.12 (d, *J* = 7.2 Hz, 2H), 7.82 (s, 1H, 6-H), 7.62 (m, 3H), 7.07 (s, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 6.45 (t, *J* = 6.4 Hz, 1H), 5.38 (m, 1H), 5.30 (s, 2H), 5.29 (t, *J* = 4.2 Hz, 1H), 4.25 (m, 1H), 3.54 (m, 2H), 2.72 (m, 2H), 1.81 (s, 3H, CH_3); ^{13}C NMR (DMSO) δ: 182.6 (C=O), 164.5 (C=O), 164.2 (C=O), 164.0, 161.7, 157.8, 150.9, 142.5, 136.7, 132.7, 131.1, 129.6, 126.9, 125.1, 110.1, 105.9, 105.6, 99.2, 94.1, 84.9, 84.4, 62.3, 61.2, 59.8, 37.6, 12.7 ($\underline{C}H_3$).

Synthesis of bis-1,2,3-triazoles AZT derivatives (6a-c)

Synthesis of bis(ethynyloxy)benzene (**5a-c**) was same as that of **2a-e**.

Compound 5a

Brown solid, yield: 96.0%; ^1H NMR ($CDCl_3$) δ: 6.93 (s, 4H), 4.65 (d, *J* = 2.4 Hz, 4H, OCH_2), 2.51 (t, *J* = 2.4 Hz, 2H, ≡CH); ^{13}C NMR ($CDCl_3$) δ: 152.4 (O-C), 116.0, 78.8 (CH≡$\underline{C}$), 75.4 ($\underline{C}H$≡C), 56.5 (O$\underline{C}H_2$).

Compound 5b

Colorless liquid, yield: 95.0%; ^1H NMR ($CDCl_3$) δ: 7.23 (m, 1H), 6.64 (m, 3H), 4.74 (s, 4H, OCH_2), 2.53 (s, 2H, ≡CH); ^{13}C NMR ($CDCl_3$) δ: 147.6 (O-C), 122.2, 115.0, 102.0, 78.7 (CH≡$\underline{C}$), 75.9 ($\underline{C}H$≡C), 56.8 (O$\underline{C}H_2$).

Compound 5c

Colorless liquid, yield: 96.0%; ^1H NMR ($CDCl_3$) δ: 6.88 (m, 2H), 6.77 (m, 2H), 4.56 (d, *J* = 2.4 Hz, 4H), 2.42 (t, *J* = 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 147.5 (O-C), 121.8, 115.0, 78.4 (CH≡$\underline{C}$), 75.6 ($\underline{C}H$≡C), 56.5 (O$\underline{C}H_2$).

3′-Azido-2′-deoxythymine (0.134 g, 0.5 mmol) and the corresponding bis(ethynyloxy) benzene (**5a-c**) (0.5 mmol) were dissolved in *t*-BuOH/H_2O (4 mL/4 mL) co-solvent. The mixture was stirred for 10 min at room temperature, and added $CuSO_4 \cdot 5H_2O$ (0.012 g, 0.05 mmol) and L-ascorbic acid sodium (0.022 g, 0.1 mmol). The resulting reaction mixture was stirred at room temperature until the material was consumed as monitored by TLC. A precipitate was generated when the reaction was over. After washing with ice-cold water and dried, the products (**6a-c**) were obtained.

Compound 6a

Yieled: 95.0%; m.p. 198-199 °C; IR (KBr) ν (cm^{-1}): 3491 (NH), 1676 (C=O), 3082, 2934 (CH_3), 1275 (C-O); HR MS *m/z*: 743.2510 $[M + Na]^+$, (calculated for $C_{32}H_{36}N_{10}O_{10}Na$ 743.2514); ^1H NMR (DMSO) δ: 11.38 (s, 2H, -NH), 8.42 (s, 2H, =CH), 7.83 (s, 2H, =C$\underline{H}$N), 6.95 (s, 4H), 6.45 (t, *J* = 6.4 Hz, 2H), 5.40 (m, 2H), 5.30 (m, 2H), 5.10 (s, 4H), 4.23 (m, 2H), 3.65 (m, 4H), 2.70 (m, 4H), 1.81 (s, 6H, -CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O), 152.8, 150.9 (C=O), 143.6, 136.7, 124.6, 116.0, 110.1, 84.9, 84.3, 61.9, 61.2, 59.7, 37.6, 12.7 (-$\underline{C}H_3$).

Compound 6b

Yieled: 93.0%; m.p. 194-195 °C; IR (KBr) ν (cm^{-1}): 3480 (NH), 1710 (C=O), 3078, 2940 (CH_3), 1255 (C-O); HR MS *m/z*: 743.2508 $[M + Na]^+$, (calculated for $C_{32}H_{36}N_{10}O_{10}Na$ 743.2514); ^1H NMR (DMSO) δ: 11.38 (s, 2H, -NH), 8.45 (s, 2H, =CH), 7.83 (s, 2H, =C$\underline{H}$N), 7.25 (t, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.68 (m, 2H), 6.45 (t, *J* = 6.4 Hz, 2H), 5.41 (m, 2H), 5.34 (m, 2H), 5.15 (s, 4H), 4.23 (m, 2H), 3.67 (m, 4H), 2.72 (m, 4H), 1.82 (s, 6H, -CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O), 159.7, 150.9 (C=O), 143.3, 136.7, 130.5, 124.7, 110.1, 107.7, 102.0, 84.9, 84.3, 61.5, 61.2, 59.7, 37.6, 12.7 (-$\underline{C}H_3$).

Compound 6c

Yieled: 92.0%; m.p. 197-198 °C; IR (KBr) ν (cm^{-1}): 3437 (NH), 1696 (C=O), 3085, 2931 (CH_3), 1274 (C-O); HR MS *m/z*: 743.2520 $[M + Na]^+$, (calculated for $C_{32}H_{36}N_{10}O_{10}Na$ 743.2514); ^1H NMR (DMSO) δ: 11.36 (s, 2H, -NH), 8.39 (s, 2H, =CH), 7.81 (s, 2H, =C$\underline{H}$N), 7.18 (q, *J* = 5.6 Hz, 2H), 6.93 (q, *J* = 5.6 Hz, 2H), 6.43 (t, *J* = 6.4 Hz, 2H), 5.37 (m, 2H), 5.28 (t, *J* = 5.2 Hz, 2H), 5.14 (s, 4H), 4.21 (m, 2H), 3.64 (m, 4H), 2.68 (m, 4H), 1.79 (s, 6H, -CH_3); ^{13}C NMR (DMSO) δ: 164.2 (C=O), 150.9 (C=O), 148.3, 143.5, 136.7, 124.8, 121.9, 114.9, 110.1, 84.9, 84.3, 62.2, 61.2, 59.7, 37.6, 12.7 (-$\underline{C}H_3$).

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