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ORIGINAL ARTICLE

Synthesis, anticancer and antibacterial evaluation of novel (isopropylidene) uridine-[1,2,3]triazole hybrids

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Abstract A series of novel (isopropylidene) uridine-[1,2,3]triazole hybrids (**3a**–**3n**) were efficiently synthesized via the copper-catalyzed azide–alkyne cycloaddition (CuAAC) from N-propargyl 2′,3′-O-(isopropylidene) uridine with different aryl azides. All the synthesized compounds were screened for their *in vitro* anticancer and antibacterial activities. The anticancer activity results revealed that compounds **3d** and **3f** have registered equipotent activity against MCF-7 and **3n** has shown excellent activity against HeLa in comparison with the standard drug Cisplatin. Remaining compounds have shown moderate to good anticancer activity against MCF-7 and HeLa cell lines. The antibacterial activity screening results revealed that, compounds **3b** and **3n** have shown excellent inhibition against *Escherichia coli* and *Bacillus subtilis*, **3d** against *Proteus vulgaris*, **3k** against *Staphylococcus aureus* and **3l** against *S. aureus* and *B. subtilis* have shown equipotent activity in comparison with the standard drug Streptomycin.

1. Introduction

Nucleoside and their derivatives have emerged as molecules with potentially useful therapeutic properties that have gained considerable attention from both synthetic and medicinal chemists due to their versatile biological activities in various therapeutic areas. Zidovudine (3′-azido-3′-deoxythymidine) was the first U.S. government-approved drug for the treatment of HIV, marketed under the brand name Retrovir (Fig 1). Uridine derivatives are currently used as anti influenza drugs [1]. Over the past few years, several derivatives of the nucleosides are known to possess antimicrobial [2], anticancer [3], anti-inflammatory [4] and antiviral activities [5–8].

On the other hand, 1,2,3-triazole derivatives are known to exhibit significant biological activities such as antimicrobial [9,10], anticancer [11], antioxidant [12] anti-HIV [13],

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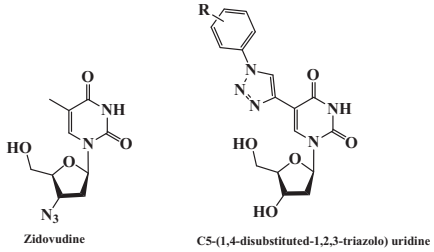

Figure 1 Some of the uridine core containing biologically active agents.

anti-inflammatory [14], antiprotozoal [15], anticonvulsant [16], antihistamine [17] and anti-tubercular properties [18]. Such compounds have also been reported as β3-selective adrenergic receptor agonists [19], kinase inhibitors [20] and other enzyme inhibitors [21].

In continuation of our research toward the synthesis of biologically potent heterocyclic compounds [22,23], herein, we report the synthesis of Nucleoside (uridine) based 1,2, 3-triazole derivatives by using the Cu (I) Catalyzed Azide Alkyne Cyclization (CuAAC) reaction and their *in vitro* anticancer and anti bacterial activities.

2. Experimental section

2.1. General

Copper (I) iodide and propargyl bromide were purchased from Sigma–Aldrich and Cs_2CO_3 was purchased from S.D. Fine Chemicals Limited. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm). Elemental analysis was performed on PerkinElmer 2400 Series II CHNS/O elemental analyzer. Melting points were determined using a Cintex apparatus and were uncorrected. FTIR spectra were recorded using a Bruker spectrometer and are reported in the frequency of absorption (cm^{-1}). NMR (^1H & ^{13}C) spectra were recorded on 300 and 75 MHz instruments and $CDCl_3$ was used as solvent. ^1H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm). Coupling constant (*J*) values are presented in Hertz and spin multiples are given as s (singlet), d (doublet), t (triplet), dd (doublets of doublet) and m (multiplet). Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV.

2.2. Synthesis

2.2.1. Synthesis of 2′,3′-O-(1-Methylethylidene)-3-(2-propyn-1-yl)uridine (2)

To a stirred solution of 2′,3′-O-(1-Methylethylidene)uridine (5 g, 17.60 mmol) in acetonitrile (100 mL) were added propargyl bromide (2.44 mL, 22.00 mmol) and cesium carbonate (5.72 g, 17.60 mmol) and stirred at room temperature for 30 min. Then, the reaction mixture was filtered and concentrated under reduced pressure to afford crude compound. The crude was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and the resulted residue was purified by column chromatography (SiO_2, 2% MeOH–$CHCl_3$) to afford (4.48 g, 79 ± 1%) 2′,3′-O-(1-Methy lethylidene)-3-(2-propyn-1-yl)uridine (2).

2.2.2. General procedure for synthesis of 1,4-disubstituted 1,2,3-triazole derivatives (3a-3n)

To a solution of aryl amine ($ArNH_2$, 1 mmol, 1.2 eq) in conc. HCl (5 ml) was added an aqueous solution of $NaNO_2$ (3 eq) and stirred for 30 min at 0–5 °C. Then, an aqueous solution of NaN_3 (1.5 eq) was added slowly at 0–5 °C and stirred for another 30 min. After completion of the reaction by TLC analysis, the crude mixture containing the azido derivative was added to a mixture of compound-2 (1 eq) and CuI (5 mol%) in THF and the reaction mixture was stirred at room temperature for 6–12 h. The solvent was removed and the resulted residue was dissolved in CH_2Cl_2, washed with water (3 × 20 mL), dried over Na_2SO_4 and evaporated to afford the crude compounds. The crude compounds were purified by column chromatography using silica gel (100–200 mesh) and 2% MeOH–$CHCl_3$ system as an eluent to afford 1,2,3-triazole derivatives (**3a**–**3n**) in good yields.

2.3. Spectral data

2.3.1. 2′,3′-O-(1-Methylethylidene)-3-(2-propyn-1-yl)uridine (2)

White solid. Yield: 65%. mp = 93 °C. IR (KBr) υ_{max}/cm^{-1}: 3471 (NH, amide), 3281 (C—H, alkyne), 3097 (CH, aromatic), 2989, 2939 (CH, Sp^3CH), 2126 (C≡C, alkyne), 1711 (C—CO—C), 1666 (N—CO—N), 1544 (C=C, aromatic), 1273, 1157, 1109 (C—O—C, ether) and 1083 (C—OH, 1° alcohol). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.39 (s, 3H, —CH_3), 1.58 (s, 3H, —CH_3), 2.45 (s, 1H, CH≡C), 2.89 (br s, 1H, OH), 3.81 (dd, *J* = 12.0, 3.2 Hz, 1H, H-5′), 3.94 (dd, *J* = 12.0, 2.5 Hz, 1 H, H-5″), 4.33 (m, 1 H, H-4′), 4.71 (s, 2H, CH_2N), 4.94 (dd, *J* = 3.3, 6.2 Hz, 1H, H-3′), 5.05 (dd, *J* = 2.8, 6.5 Hz, 1 H, H-2′), 5.63 (d, *J* = 2.8 Hz, 1 H, H-1′), 5.83 (d, *J* = 8.0 Hz, 1 H, H-5), 7.38 (d, *J* = 7.9 Hz, 1 H, H-6). MS (ESI) *m/z*: 323 [M + H].

2.3.2. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo[3,4-d][1,3]dioxol-4-yl]-3-{[1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3a)

White solid. Yield: 87%. mp = 128 °C, reaction time 8 h. IR (KBr) υ_{max}/cm^{-1}: 3440 (OH, alcohol), 3092 (CH, aromatic), 2989 (CH, Sp^3CH), 1700 (C—CO—N), 1675 (N—CO—N), 1582 (C=C, aromatic), 1515 (N—N, triazole), 1211 (C—O—C, 3° ether), 1157, 1107 (C—O—C, ether), 1080 (C—OH, 1° alcohol), 850, 810, 771 (C—H aromatic bending), ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.36 (s, 3H, —CH_3), 1.57 (s, 3H, —CH_3), 2.84 (br s, 1H, OH), 3.71 (s, 3H, OCH_3), 3.80 (dd, *J* = 12.0, 3.4 Hz, 1H, H-5′), 3.93 (dd, *J* = 12.0, 2.6 Hz, 1H, H-5″), 4.30–4.33 (m, 1H, H-4′), 4.95 (dd, *J* = 3.3, 6.2 Hz, 1H, H-3′), 5.01 (dd, *J* = 2.8, 6.5 Hz, 1H, H-2′), 5.35 (m, 2H, CH_2N), 5.61 (d, *J* = 2.8 Hz, 1H, H-1′), 5.85 (d, *J* = 8.0 Hz, 1H, H-5), 7.02 (d, *J* = 9 Hz, 2H, Ar-H), 7.37 (d, *J* = 7.9 Hz, 1H, H-6), 7.62 (d, *J* = 9 Hz, 2H, Ar-H), 8.01 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.1 (CH_3), 27.1 (CH_3), 33.5 (CH_2N), 55.6 (O—CH_3), 62.5 (C-5′), 80.2 (C-3′), 83.5 (C-2′), 86.8 (C-4′), 96.6 (C-1′), 102.1 (C-5),

113.1 (N—*C*H═C, triazole), 115.3 (Ar—C-3, C-5), 119.3 (*C*$(CH_3)_2$), 122.4 (Ar—C-2, C-6), 129.1 (Ar—C-1), 139.2 (Ar C), 140.9 (N—CH═*C*, triazole), 141.5 (C-6), 150.6 (C-2), 160.6 (Ar—C-4), 163.7 (C-4). MS (ESI) *m/z*: 472 $[M+H]^+$ (calc 471.17), Elemental analysis (%) found: C 55.58, H 5.44, N 14.89; calcd for $C_{22}H_{25}N_5O_7$: C 55.52, H 5.46, N 14.95.

2.3.3. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(naphthalene-1-yl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3b)

White solid. Yield: 70%. mp = 116 °C. reaction time 9 h. IR (KBr) υ_{max}/cm^{-1}: 3430 (OH, alcohol), 3083 (CH, aromatic), 2987 (CH, Sp^3CH), 1717 (C—CO—N), 1661 (N—CO—N), 1575 (C═C, aromatic), 1521 (N═N, triazole), 1216, 1121 (C—O—C, ether), 1074 (C—OH, 1° alcohol), 880, 812, 771 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3),1.58 (s, 3H, —CH_3), 2.85 (br s, 1H, OH), 3.82 (dd, *J* = 12.0, 3.4 Hz, 1H, H-5′), 3.94 (dd, *J* = 12.0, 2.6 Hz, 1H, H-5″), 4.30–4.33 (m, 1H, H-4′), 4.99 (dd, *J* = 3.2, 6.5 Hz, 1H, H-3′), 5.08 (dd, *J* = 2.7, 6.4 Hz, 1H, H-2′), 5.39 (m, 2H, CH_2N), 5.62 (d, *J* = 2.6 Hz, 1H, H-1′), 5.82 (d, *J* = 8.0 Hz, 1H, H-5), 7.42 (d, *J* = 7.9 Hz, 1H, Ar), 7.50–7.60 (m, 4H, Ar), 7.62 (d, *J* = 8.0 Hz, 1H, H-6), 7.95 (d, *J* = 7.7 Hz, 1H, Ar), 8.00 (s, 1H, triazole), 8.02 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.2 (CH_3), 27.2 (CH_3), 35.8 (CH_2N), 62.6 (C-5′), 80.5 (C-3′), 84.0 (C-2′), 87.9 (C-4′), 95.1 (C-1′), 102.0 (C-5), 116.0 (N—*C*H═C, triazole), 120.1 (*C*$(CH_3)_2$), 125.1 (Ar—C-1), 126.3 (Ar—C-3,C-7, C-8), 126.7 (Ar—C-9), 128.4 (Ar—C-4,C-6), 131.6 (Ar—C-2), 133.7 (Ar—C-5), 138.2 (Ar—C-10) 140.6 (N—CH═*C*, triazole), 142.4 (C-6), 149.7 (C-2), 160.2 (Ar—C-4) 163.5 (C-4). MS (ESI) *m/z*: 514 [M + Na] (calc 491.18). Elemental analysis (%) found: C 60.79, H 5.13, N 14.28; calcd for $C_{25}H_{25}N_5O_6$: C 60.90, H 5.15, N 14.32.

2.3.4. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(2-chloro-5-nitrophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3c)

Pale yellow solid. Yield: 82%. mp = 142 °C. reaction time 9 h. IR (KBr) υ_{max}/cm^{-1}: 3429 (OH, alcohol), 3092 (CH, aromatic), 2989, 2932 (CH, Sp^3CH), 1710 (C—CO—N), 1665 (N—CO—N), 1586 (C═C, aromatic), 1534 (N═N, triazole), 1350 (N—O aromatic NO_2), 1218 (C—O—C, 3° ether), 1157, 1107 (C—O—C, ether), 1077 (C—OH, 1° alcohol), 880, 812, 772 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm):1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 3.20 (br s, 1H, OH), 3.83 (d, *J* = 10.8 Hz, 1H, H-5′), 3.93 (d, *J* = 11.1 Hz, 1H, H-5″), 4.32 (m, 1H, H-4′), 4.94 (dd, *J* = 3.3, 6.4 Hz, 1H, H-3′), 5.06 (dd, *J* = 2.7, 6.5 Hz, 1H, H-2′), 5.35 (m, 2H, CH_2N), 5.70 (d, *J* = 2.8 Hz, 1H, H-1′), 5.79 (d, *J* = 8.1 Hz, 1H, H-5), 7.52 (s, 1H, Ar), 7.80 (d, *J* = 7.9 Hz, 1H, H-6), 8.20 (s, 1H, triazole), 8.25–8.55 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.2 (CH_3), 27.2 (CH_3), 35.6 (CH_2N), 62.6 (C-5′), 80.3 (C-3′), 83.8 (C-2′), 87.0 (C-4′), 96.8 (C-1′), 102.0 (C-5), 114.2 (N—*C*H═C, triazole), 120.0 (*C*$(CH_3)_2$), 120.3 (Ar—C-6), 123.5 (Ar—C-4), 125.9 (Ar—C-3), 133.1 (Ar—C-1), 135.1 (Ar—C-5), 140.2 (Ar—C-2), 140.7 (N—CH═*C*, triazole), 142.6 (C-6), 150.7 (C-2), 162.0 (C-4). MS (ESI) *m/z*: 521 $[M+H]^+$ (calc 520.11). Elemental analysis (%) found: C 48.36, H 4.06, N 16.23; calcd for $C_{21}H_{21}ClN_6O_8$: C 48.33, H 4.12, N 16.26.

2.3.5. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-({1-[5-fluoro-2-(hyroxymethyl) phenyl]-1H-1,2,3-triazole-4-yl}methyl)-1,2,3,4-tetrahydro pyrimidine-2,4-dione (3d)

White solid. Yield: 71%. mp = 162 °C. reaction time 10 h. IR (KBr) υ_{max}/cm^{-1}: 3440 (OH, alcohol), 3089 (CH, aromatic), 2983, 2937 (CH, Sp^3CH), 1718 (C—CO—C), 1661 (N—CO—N), 1586 (C═C, aromatic), 1525 (N═N, triazole), 1216 (C—O—C, 3° ether), 1147, 1101 (C—O—C, ether), 1072 (C—OH, 1° alcohol), 881, 814, 770, (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.36 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 3.21 (br s, 1H, OH), 3.40–3.55 (br m, 1H, OH) 3.80 (dd, *J* = 12.0, 2.7 Hz, 1H, H-5′), 3.92 (dd, *J* = 11.9, 1.6 Hz, 1H, H-5″), 4.31 (d, *J* = 2.4 Hz, 1H, H-4′), 4.45 (s, 2H, CH_2OH), 4.99 (dd, *J* = 2.8, 5.9 Hz, 1H, H-3′), 5.08 (dd, *J* = 2.4, 6.1 Hz, 1H, H-2′), 5.25 (m, 2H, CH_2N), 5.64 (d, *J* = 2.2 Hz, 1H, H-1′), 5.80 (d, *J* = 7.9 Hz, 1H, H-5), 7.15–7.24 (m, 2H, Ar), 7.45 (d, *J* = 8.0 Hz, 1H, H-6), 7.55–7.62 (m, 1H, Ar) 8.06 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.0 (CH_3), 27.1 (CH_3), 35.6 (CH_2N), 58.6 (Ar—*C*H_2OH), 62.5 (C-5′), 80.9 (C-3′), 84.3 (C-2′), 87.1 (C-4′), 96.6 (C-1′), 102.3 (C-5), 115.7 (Ar—C-4,C-6), 118.0 (N—*C*H═C, triazole), 121.0 (*C*$(CH_3)_2$), 126.9 (Ar—C-1), 128.7 (Ar—C-3), 136.3 (Ar—C-2), 141.2 (N—CH═*C*, triazole), 142.6 (C-6), 150.5 (C-2), 159.3 (Ar—C-5), 162.8 (C-4). MS (ESI) *m/z*: 490 [M + H] (calc 489.16). Elemental analysis (%) found: C 53.85, H 4.96, N 14.31; calcd for $C_{22}H_{24}FN_5O_7$: C 53.81, H 4.98, N 14.34.

2.3.6. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(3-nitrophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3e)

Pale yellow solid. Yield; 85%. mp = 151 °C. reaction time 10 h. IR (KBr) υ_{max}/cm^{-1}: 3430 (OH, alcohol), 3097 (CH, aromatic), 2986, 2938 (CH, Sp^3CH), 1717 (C—CO—C), 1661 (N—CO—N), 1583 (C═C, aromatic), 1521 (N═N, triazole), 1347 (N—O aromatic NO_2), 1222 (C—O—C, 3° ether), 1148, 1100 (C—O—C, ether), 1080 (C—OH, 1° alcohol), 885, 812, 770 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 2.91 (br s, 1H, OH), 3.85 (d, *J* = 10.3 Hz, 1H, H-5′), 3.95 (d, *J* = 10.8 Hz, 1H, H-5″), 4.30–4.32 (m, 1H, H-4′), 5.00 (dd, *J* = 3.1, 6.7 Hz, 1H, H-3′), 5.09 (dd, *J* = 2.8, 6.4 Hz, 1H, H-2′), 5.30 (m, 2H, CH_2N), 5.65 (d, *J* = 2.8 Hz, 1H, H-1′), 5.82 (d, *J* = 7.8 Hz, 1H, H-5), 7.45 (d, *J* = 7.9 Hz, 1H, H-6), 7.70–7.80 (m, 1H, Ar), 8.15–8.30 (m, 3H, Ar), 8.60 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.1 (CH_3), 26.3 (CH_3), 38.3 (CH_2N), 62.5 (C-5′), 80.2 (C-3′), 82.7 (C-2′), 89.0 (C-4′), 99.6 (C-1′), 102.3 (C-5), 111.2 (Ar—C-2), 118.1 (N—*C*H═C, triazole), 121.3 (*C*$(CH_3)_2$), 123.1 (Ar—C-2), 125.2 (Ar—C-4), 129.5 (Ar—C-1,C-5), 136.3 (Ar—C-6,C-3), 140.9 (N—CH═*C*, triazole), 142.5 (C-6), 149.6 (C-2), 164.8 (C-4). MS (ESI) *m/z*: 487 [M + H] (calc 486.15). Elemental analysis (%) found: C 55.75, H 4.56, N 17.29; calcd for $C_{21}H_{22}N_6O_8$: C 55.72, H 4.53, N 17.34.

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2.3.7. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(4-chlorophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3f)

Pale yellow solid. Yield: 88%. mp = 156 °C. reaction time 8 h. IR (KBr) υ_{max}/cm^{-1}: 3437 (OH, alcohol), 3096 (CH, aromatic), 2972 (CH, Sp^3CH), 1740 (C—CO—C), 1658 (N—CO—N), 1501 (N=N, triazole), 1212 (C—O—C, 3° ether), 1157 (C—O—C, ether), 1088 (C—OH, 1° alcohol), 832, 809, 783 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 2.95 (br s, 1H, OH), 3.82 (d, *J* = 11.1 Hz, 1H, H-5′), 3.95 (d, *J* = 10.9 Hz, 1H, H-5″), 4.31 (d, *J* = 2.4 Hz, 1H, H-4′), 4.98 (dd, *J* = 3.0, 5.9 Hz, 1H, H-3′), 5.02 (dd, *J* = 2.9, 6.0 Hz, 1H, H-2′), 5.30 (m, 2H, CH_2N), 5.62 (d, *J* = 2.1 Hz, 1H, H-1′), 5.79 (d, *J* = 7.9 Hz, 1H, H-5), 7.44 (d, *J* = 7.9 Hz, 1H, H-6), 7.49 (d, *J* = 8.7 Hz, 2H, Ar), 7.68 (d, *J* = 8.7 Hz, 2H, Ar), 8.05 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.0 (CH_3), 26.0 (CH_3), 41.5 (CH_2N), 63.0 (C-5′), 80.6 (C-3′), 83.8 (C-2′), 87.4 (C-4′), 98.3 (C-1′), 102.4 (C-5), 118.1 (N—*C*H=C, triazole), 120.2 (*C*(CH_3)$_2$), 123.2 (Ar—C-2,C-6), 128.7 (Ar—C-3,C-5), 134.3 (Ar—C-4), 134.9 (Ar—C-1), 141.2 (N—CH=*C*, triazole), 141.9 (C-6), 150.3 (C-2), 163.4 (C-4). MS (ESI) *m*/*z*: 498 [M + Na] (calc 475.12). Elemental analysis (%) found: C 54.70, H 4.72, N 14.78; calcd for $C_{21}H_{22}ClN_5O_6$: C 54.68, H 4.71, N 14.80.

2.3.8. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(4-methylphenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3g)

White solid. Yield: 85%. mp = 123 °C. reaction time 10 h. IR (KBr) υ_{max}/cm^{-1}: 3429 (OH, alcohol), 3092 (CH, aromatic), 2989, 2932 (CH, Sp^3CH), 1710 (C—CO—C), 1665 (N—CO—N), 1586 (C=C, aromatic), 1534 (N=N, triazole), 1218, 1157 (C—O—C, ether), 1077 (C—OH, 1° alcohol), 771, 875, 809 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.33 (s, 3H, —CH_3), 1.58 (s, 3H, —CH_3), 2.30 (s, 3H, CH_3), 3.21 (br s, 1H, OH), 3.81 (d, *J* = 10.1 Hz, 1H, H-5′), 3.92 (d, *J* = 10.3 Hz, 1H, H-5″), 4.25–4.35 (m, 1H, H-4′), 4.97 (dd, *J* = 3.0, 6.2 Hz, 1H, H-3′), 5.05 (dd, *J* = 3.2, 6.4 Hz, 1H, H-2′), 5.28 (m, 2H, CH_2N), 5.71 (d, *J* = 1.8 Hz, 1H, H-1′), 5.81 (d, *J* = 8.1 Hz, 1H, H-5), 7.48 (d, *J* = 8.1 Hz, 2H, Ar), 7.61 (d, *J* = 8.1 Hz, 2H, Ar), 7.80 (d, *J* = 7.8 Hz, 1H, H-6) 8.12 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 22.8 (Ar—CH_3), 25.1 (CH_3), 26.6 (CH_3), 38.2 (CH_2N), 61.4 (C-5′), 81.3 (C-3′), 83.9 (C-2′), 89.3 (C-4′), 99.6 (C-1′), 103.4 (C-5), 119.3 (N—*C*H=C, triazole), 123.4 (*C*(CH_3)$_2$), 129.3 (Ar—C-3, C-5), 132.1 (Ar—C-1), 135.3 (Ar—C-2, C-6), 136.8 (Ar—C-4), 143.1 (N—CH=*C*, triazole), 145.2 (C-6), 151.8 (C-2), 163.7 (C-4). MS (ESI) *m*/*z*: 456 [M + H] (calc 455.18). Elemental analysis (%) found: C 58.11, H 5.53, N 15.39; calcd for $C_{22}H_{25}N_5O_6$: C 58.14, H 5.56, N 15.41.

2.3.9. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(4-nitrophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3h)

Pale yellow solid. Yield: 86%. mp = 168 °C. reaction time 12 h. IR (KBr) υ_{max}/cm^{-1}: 3427 (OH, alcohol), 3089 (CH, aromatic), 2989, 2932 (CH, Sp^3CH), 1722 (C—CO—C), 1660 (N—CO—N), 1599 (C=C, aromatic), 1526 (N=N, triazole), 1219, 1157 (C—O—C, ether), 1082 (C—OH, 1° alcohol), 855, 808, 772 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 2.93 (br s, 1H, OH), 3.84 (d, *J* = 10.4 Hz, 1H, H-5′), 3.94 (d, *J* = 11.2 Hz, 1H, H-5″), 4.31 (d, *J* = 2.7 Hz, 1H, H-4′), 4.95 (dd, *J* = 3.1, 6.7 Hz, 1H, H-3′), 5.04 (dd, *J* = 2.8, 6.4 Hz, 1H, H-2′), 5.35 (m, 2H, CH_2N), 5.64 (d, *J* = 2.8 Hz, 1H, H-1′), 5.81 (d, *J* = 8.1 Hz, 1H, H-5), 7.48 (d, *J* = 8.1 Hz, 1H, H-6), 7.61 (d, *J* = 8.2 Hz, 2H, Ar), 8.33 (d, *J* = 8.2 Hz, 2H, Ar), 8.20 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.2 (CH_3), 27.2 (CH_3), 35.6 (CH_2N), 62.6 (C-5′), 80.3 (C-3′), 83.9 (C-2′), 86.9 (C-4′), 96.4 (C-1′), 101.9 (C-5), 114.3 (N—*C*H=C, triazole), 120.5 (*C*(CH_3)$_2$), 121.8 (Ar—C-2,C-6)-, 125.4 (Ar—C-3,C-5), 140.9 (N—CH=*C*, triazole), 142.1 (Ar—C-1) 144.2 (C-6), 147.1 (Ar—C-4), 150.7, (C-2), 162.0 (C-4); MS (ESI) *m*/*z*: 487 [M + H] (calc 486.15). Elemental analysis (%) found: C 55.75, H 4.58, N 17.32; calcd for $C_{21}H_{22}N_6O_8$: C 55.73, H 4.59, N 17.34.

2.3.10. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(2-methylphenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3i)

White solid. Yield: 80% .mp = 113 °C. reaction time 11 h. IR (KBr) υ_{max}/cm^{-1}: 3429 (OH, alcohol), 3092 (CH, aromatic), 2989, 2932 (CH, Sp^3CH), 1710 (C—CO—C), 1665 (N—CO—N), 1586 (C=C, aromatic), 1534 (N=N, triazole), 1212 (C—O—C, 3° ether), 1155, 1107 (C—O—C, ether), 1081 (C—OH, 1° alcohol), 881, 812, 789 (C—H aromatic bending). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.32 (s, 3H, —CH_3), 1.55 (s, 3H, —CH_3), 2.34 (s, 3H, CH_3), 2.91 (br s, 1H, OH), 3.71 (d, *J* = 10.2 Hz, 1H, H-5′), 3.91 (d, *J* = 10.0 Hz, 1H, H-5″), 4.29–4.35 (m, 1H, H-4′), 4.95 (dd, *J* = 2.7, 5.9 Hz, 1H, H-3′), 5.05 (dd, *J* = 3.0, 6.1 Hz, 1H, H-2′), 5.28 (m, 2H, CH_2N), 5.65 (d, *J* = 2.3 Hz, 1H, H-1′), 5.82 (d, *J* = 8.1 Hz, 1H, H-5), 7.49 (d, *J* = 7.8 Hz, 1H, H-6), 7.49–7.56 (m, 4H, Ar), 8.10 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 22.1 (Ar—CH_3), 25.3 (CH_3), 27.2 (CH_3), 38.1 (CH_2N), 63.1 (C-5′), 81.2 (C-3′), 83.3 (C-2′), 88.5 (C-4′), 96.6 (C-1′), 102.3 (C-5), 114.2 (N—*C*H=C, triazole), 120.6 (*C*(CH_3)$_2$), 122.1 (Ar—C-6), 125.3 (Ar—C-5), 127.3 (Ar-C-1), 131.2 (Ar—C-3,C-4), 138.8 (Ar—C-2), 139.1 (N—CH=—*C*, triazole), 142.2 (C-6), 149.8 (C-2), 162.3 (C-4); MS (ESI) *m*/*z*: 456 [M + H] (calc 455.18). Elemental analysis (%) found: C 58.11, H 5.45, N 15.39; calcd for $C_{22}H_{25}N_5O_6$: C 58.13, H 5.48, N 15.42.

2.3.11. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-[(1-phenyl-1H-1,2,3-triazole-4-yl) methyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (3j)

White solid. Yield: 85%. mp = 119 °C. reaction time 6 h. IR (KBr) υ_{max}/cm^{-1}: 3462 (OH, alcohol), 3092 (CH, aromatic), 2989, 2932 (CH, Sp^3CH), 1710 (C—CO—C), 1665 (N—CO—N), 1586 (C=C, aromatic), 1534 (N=N, triazole), 1218, 1157 (C—O—C, ether), 1081 (C—OH, 1° alcohol), 875, 810, 783 (C—H aromatic bending). ^1H—NMR (300 MHz, $CDCl_3$, δ in ppm): 1.37 (s, 3H, —CH_3), 1.58 (s, 3H, —CH_3), 2.98 (br s, 1H, OH), 3.82 (d, *J* = 10.2 Hz, 1H, H-5′), 3.95 (d, *J* = 10.0 Hz, 1H, H-5″), 4.31 (m, 1H, H-4′), 4.96 (dd, *J* = 3.2, 6.4 Hz, 1H, H-3′), 5.02 (dd, *J* = 3.1, 6.1 Hz, 1H,

H-2′), 5.25 (m, 2H, CH_2N), 5.60 (d, J = 2.8 Hz, 1H, H-1′), 5.81 (d, J = 8.0 Hz, 1H, H-5), 7.45 (d, J = 8.0 Hz, 1H, H-6), 7.50 (m, 2H, Ar), 7.67 (m, 3H, Ar), 8.05 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.1 (CH_3), 27.3 (CH_3), 36.4 (CH_2N), 62.8 (C-5′), 81.0 (C-3′), 84.3 (C-2′), 88.4 (C-4′), 98.5 (C-1′), 102.2 (C-5), 118.2 (N—*C*H═C, triazole), 121.3 (*C*(CH_3)$_2$), 122.4 (Ar—C-2, C-6), 128.1 (Ar—C-3, C-5), 129.3 (Ar—C-4), 136.5 (Ar—C-1), 140.1 (N—CH═*C*, triazole), 143.2 (C-6), 149.3 (C-2), 164.2 (C-4). MS (ESI) m/z: 442 [M + H] (calc 441.16). Elemental analysis (%) found: C 57.19, H 5.15, N 15.88; calcd for $C_{21}H_{23}N_5O_6$: C 57.21, H 5.12, N 15.91.

2.3.12. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(3-chlorophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3k)

Pale yellow solid. Yield: 76%. mp = 141 °C. reaction time 10 h. IR (KBr) υ_{max}/cm^{-1}: 3466 (OH, alcohol), 3052 (CH, aromatic), 2972 (CH, Sp^{3}CH), 1740 (C—CO—C), 1656 (N—CO—N), 1594 (C═C, aromatic), 1534 (N═N, triazole), 1212, 1157 (C—O—C, ether), 1077 (C—OH, 1° alcohol), 855, 806, 786 (C—H aromatic bending). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 2.90 (br s, 1H, OH), 3.82 (dd, J = 12.0, 3.3 Hz, 1H, H-5′), 3.94 (dd, J = 12.0, 2.4 Hz, 1H, H-5″), 4.30–4.32 (m, 1H, H-4′), 4.97 (dd, J = 3.3, 6.4 Hz, 1H, H-3′), 5.07 (dd, J = 2.7, 6.2 Hz, 1H, H-2′), 5.30 (m, 2H, CH_2N), 5.62 (d, J = 2.5 Hz, 1H, H-1′), 5.82 (d, J = 8.0 Hz, 1H, H-5), 7.37–7.46 (m, 3H, Ar), 7.62 (d, J = 8.3 Hz, 1H, H-6), 7.75–7.78 (m, 1H, Ar), 8.06 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.8 (CH_3), 27.6 (CH_3), 36.2 (CH_2N), 63.4 (C-5′), 80.5 (C-3′), 85.2 (C-2′), 88.4 (C-4′), 97.5 (C-1′), 102.4 (C-5), 112.2 (N—*C*H═C, triazole), 120.3 (*C*(CH_3)$_2$), 125.1 (Ar—C-2), 127.6 (Ar—C-6), 128.3 (Ar—C-4), 132.1 (Ar—C-5), 134.7 (Ar—C-3), 138.2 (Ar—C-1), 140.0 (N—CH═*C*, triazole), 141.8 (C-6), 149.6 (C-2), 163.2 (C-4). MS (ESI) m/z: 498 [M + Na] (calc 475.12). Elemental analysis (%) found: C 53.00, H 4.66, N 14.72; calcd for $C_{21}H_{22}ClN_5O_6$: C 53.08, H 4.72, N 14.80.

2.3.13. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(3,5-dichlorophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3l)

White solid. Yield. 79%. mp = 138 °C. reaction time 12 h. IR (KBr) υ_{max}/cm^{-1}: 3499 (OH, alcohol), 3086 (CH, aromatic), 3000 (CH, Sp^{3}CH), 1740 (C—CO—C), 1663 (N—CO—N), 1587 (N═N, triazole), 1214, 1104 (C—O—C, ether), 1084 (C—OH, 1° alcohol), 852, 814, 766 (C—H aromatic bending). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.36 (s, 3H, —CH_3), 1.58 (s, 3H, —CH_3), 2.65 (br s, 1H, OH), 3.82 (dd, J = 12.0, 3.2 Hz, 1H, H-5′), 3.95 (dd, J = 12.0, 2.4 Hz, 1H, H-5″), 4.31 (d, J = 2.7 Hz, 1H, H-4′), 5.00 (dd, J = 3.3, 6.2 Hz, 1H, H-3′), 5.05 (dd, J = 2.7, 6.4 Hz, 1H, H-2′), 5.30 (m, 2H, CH_2N), 5.60 (d, J = 2.7 Hz, 1H, H-1′), 5.82 (d, J = 8.0 Hz, 1H, H-5), 7.38 (d, J = 7.9 Hz, 1H, H-6), 7.42 (s, 1H, Ar), 7.67–7.70 (m, 2H, Ar), 8.05 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.3 (CH_3), 27.2 (CH_3), 35.9 (CH_2N), 64.0 (C-5′), 81.5 (C-3′), 85.0 (C-2′), 88.4 (C-4′), 96.5 (C-1′), 101.5 (C-5), 117.3 (N—*C*H═C, triazole), 121.1 (*C*(CH_3)$_2$), 123.6 (Ar—C-2,C-6), 129.9 (Ar—C-4), 131.5 (Ar—C-1), 136.3 (Ar—C-3,C-5), 140.0 (N—CH═*C*, triazole), 141.8 (C-6), 150.6 (C-2), 162.4 (C-4). MS (ESI) m/z: 510 [M + H] (calc 509.08); Elemental analysis (%) found: C 49.42, H 4.19, N 13.78; calcd for $C_{21}H_{21}Cl_2N_5O_6$: C 49.31, H 4.20, N 13.80.

2.3.14. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(4-bromophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydropyrimidine-2,4-dione (3m)

Pale brown solid. Yield. 84%. mp = 172 °C. reaction time 10 h. IR (KBr) υ_{max}/cm^{-1}: 3465 (OH, alcohol), 3083 (CH, aromatic), 2997, 2971 (CH, Sp^{3}CH), 1740 (C—CO—C), 1660 (N—CO—N), 1571 (N═N, triazole), 1212, 1157 (C—O—C, ether), 1076 (C—OH, 1° alcohol), 856, 808, 752 (C—H aromatic bending).^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 2.89 (br s, 1H, OH), 3.82 (d, J = 10.3 Hz, 1H, H-5′), 3.95 (d, J = 10.9 Hz, 1H, H-5″), 4.30–4.33 (m, 1H, H-4′), 4.98 (dd, J = 3.1, 6.0 Hz, 1H, H-3′), 5.09 (dd, J = 2.8, 6.2 Hz, 1H, H-2′), 5.28 (s, 2H, CH_2N), 5.63 (d, J = 2.7 Hz, 1H, H-1′), 5.82 (d, J = 8.0 Hz, 1H, H-5), 7.43 (d, J = 7.9 Hz, 1H, H-6), 7.51 (d, J = 8.7 Hz, 2H, Ar), 7.63 (d, J = 8.7 Hz, 2H, Ar), 8.05 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.1 (CH_3), 27.2 (CH_3), 36.5 (CH_2N), 62.3 (C-5′), 81.5 (C-3′), 83.8 (C-2′), 88.4 (C-4′), 97.6 (C-1′), 102.5 (C-5), 118.3 (N—*C*H═C, triazole), 119.5 (*C*(CH_3)$_2$), 123.4 (Ar—C-4), 129.2 (Ar—C-2,C-6), 132.4 (Ar—C-3,C-5), 135.3 (Ar—C-1), 140.1 (N—CH═*C*, triazole), 142.0 (C-6), 150.1 (C-2), 164.1 (C-4). MS (ESI) m/z: 520 [M + H] (calc 519.07); Elemental analysis (%) found: C 48.37, H 4.36, N 13.46; calcd for $C_{21}H_{22}BrN_5O_6$: C 48.36, H 4.35, N 13.50.

2.3.15. 1-[6-(hydroxymethyl)-2,2-dimethyl-tetrahydro-2H-furo [3,4-d][1,3]dioxol-4-yl]-3-{[1-(2,6-dibromo-4-fluorophenyl)-1H-1,2,3-triazole-4-yl]methyl}-1,2,3,4-tetrahydro pyrimidine-2,4-dione (3n)

Brown solid. Yield: 86%. mp = 161 °C. reaction time 8 h; IR (KBr) υ_{max}/cm^{-1} 3429 (OH, alcohol), 3092 (CH, aromatic), 2989, 2932 (CH, Sp^{3}CH), 1710 (C—CO—C), 1665 (N—CO—N), 1586 (C═C, aromatic), 1534 (N═N, triazole), 1218 (C—O—C, 3° ether), 1157, 1107 (C—O—C, ether), 1077 (C—OH, 1° alcohol), 879, 809, 785 (C—H aromatic bending). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 1.35 (s, 3H, —CH_3), 1.59 (s, 3H, —CH_3), 2.79 (br s, 1H, OH), 3.85 (d, J = 11.2 Hz, 1H, H-5′), 3.94 (d, J = 10.8 Hz, 1H, H-5″), 4.32 (d, J = 1.8 Hz, 1H, H-4′), 4.99 (dd, J = 3.1, 6.0 Hz, 1H, H-3′), 5.06 (dd, J = 2.8, 6.2 Hz, 1H, H-2′), 5.34 (s, 2H, CH_2N), 5.61 (d, J = 2.7 Hz, 1H, H-1′), 5.83 (d, J = 8.0 Hz, 1H, H-5), 7.38 (d, J = 8.0 Hz, 1H, H-6), 7.43 (s, 2H, Ar), 8.06 (s, 1H, triazole). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 25.3 (CH_3), 26.1 (CH_3), 35.8 (CH_2N), 61.6 (C-5′), 81.8 (C-3′), 85.0 (C-2′), 88.2 (C-4′), 97.4 (C-1′), 102.5 (C-5), 114.1 (N—*C*H═C, triazole), 119.4 (*C*(CH_3)$_2$), 121.3 (Ar—C-3,C-5), 124.1 (Ar—C-2,C-6), 132.4 (Ar—C-1), 140.0 (N—CH═*C*, triazole), 141.2 (C-6), 150.3 (C-2), 163.2 (C-4) 167.1 (Ar—C-4). MS (ESI) m/z: 616 [M + H] (calc 614.97); Elemental analysis (%) found: C 40.76, H 3.27, N 11.45; calcd for $C_{21}H_{20}Br_2FN_5O_6$: C 40.74, H 3.30, N 11.46.

2.4. Assay of in vitro anticancer activity

The synthesized compounds were evaluated for their *in vitro anticancer* activity against two different human cancer cell lines, *i.e.* breast cancer cell line (MCF-7) and cervical carcinoma cell line (HeLa). Cell viability in the presence of the test samples were measured by the MTT-microcultured tetrazolium assay [27]. This assay is a quantitative colorimetric method for the determination of cell viability. The assessed parameter is the metabolic activity of viable cells. Metabolically active cells reduce the pale yellow tetrazolium salt (MTT) to a dark blue water-insoluble formazan, which can be directly quantified after solubilization with DMSO. The absorbance of formazan directly correlates with the number of viable cells. MCF-7 and HeLa cells were plated into a 96-well plate at a density of $1x10^4$ cells/well. Cells were grown overnight in the full medium and then switched to the low serum media. DMSO was used as control. After 48 h of treatment with different concentrations of test compounds, the cells were incubated with MTT (2.5 mg/mL) in the CO_2 chamber for 2 h. The medium was then removed and 100 μL of DMSO was added into each well to dissolve formazan crystals. After thoroughly mixing, the plates were read at 570 nm for optical density which is directly correlated with cell quantity. The results were represented as percentage of viability. All the experiments were carried out in triplicate. The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability.

2.5. Assay of in vitro antibacterial activity

The minimum inhibitory concentrations (MIC) of synthesized compounds (**3a**–**3n**) were tested against Gram-positive organisms such as *Staphylococcus aureus* (**MTCC 96**) and *Bacillus subtilis* (**MTCC 441**) and gram negative bacteria *Escherichia coli* (**MTCC 443**) and *Proteus vulgaris* (**MTCC 1771**) by the broth dilution method recommended by the National Committee for Clinical Laboratory (NCCL) standards [28]. Serial dilutions of the test compounds were performed at concentrations ranging from 150 to 0.58 μg mL^{-1} in a 200 mL culture medium final volume. Afterward each well was seeded with a 50 μL microbial suspension of 0.5 MacFarland density. In each test a microbial culture control and a sterility control (negative) were performed. The plates were incubated for 24 h at 37 °C. The lowest concentration which inhibited the visible microbial growth was considered the MIC.

3. Results and discussion

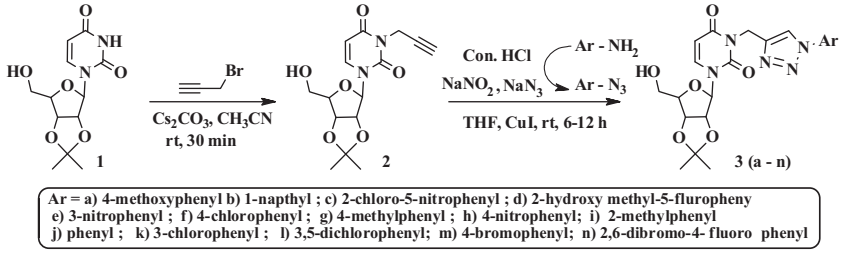
3.1. Chemistry

The synthetic route for the preparation of uridine derived 1,2,3-triazoles is depicted in Scheme 1. 2′,3′-O-(isopropylidene) uridine was subjected to propargylation using propargyl bromide in the presence of Cs_2CO_3 to yield (79 ± 1%) of the compound-**2** [24]. Aryl azides were synthesized from diazonium salts of aryl amines and NaN_3 [25]. Compounds (**3a**–**3n**) were synthesized by the treatment of 2′, 3′-O-(isopropyli dene)-3-(2-propyn-1-yl) uridine (**2**) with aryl azides in the presence of catalytic amount of CuI in THF at room temperature [26]. 2′,3′-O-(isopropylidene) uridine was used instead of Uridine to simplify the reaction. Uridine on direct alkylation yielded only 20–25% N-propargyl product.

All the crude compounds were purified by column chromatography using silica gel (60–120 mesh) and 2% MeOH in $CHCl_3$ as eluent. The elemental analysis results were within ± 0.2% of the calculated values indicate the purity of compounds. The structures of newly synthesized compounds were confirmed by IR, ^1H NMR, ^{13}C NMR and Mass spectral data. Frequency of absorption in the region of 1515–1587 cm^{-1} (N═N) in IR spectra, signal at 8.00–8.60 ppm (H-5 of triazole) in ^1H NMR spectra and two signals at 112.2–119.3 ppm (N─***C***H═C,C-4) and 139.1–143.1 ppm (N─CH═***C***, C-5) in ^{13}C NMR spectra confirmed the formation of the triazole ring. Similarly, the molecular ion peak from the mass spectra and elemental analyses data are further evidence for the formation of the products.

3.2. In vitro anticancer activity

The examination of anticancer activity results (Table 1) revealed that, compound derived from 2-hydroxy methyl-5-fluoro phenyl on the triazole ring, *i.e.*, **3d** has exhibited excellent activity against MCF-7 (IC_{50}: **11.34** μM) and good activity against HeLa (IC_{50}: **16.48** μM) when comparing with the standard drug Cisplatin. Compound derived from 4-chloro phenyl on the triazole ring, *i.e.*, **3f** has exhibited excellent activity against MCF-7 (IC_{50}: **11.73** μM). Compound **3n**, bearing 2, 6-dibromo-4-fluoro group on the triazole ring against Hela (IC_{50}:**7.93** μM), **3b** and **3c** against MCF-7 (IC_{50}:**14.20** and **18.58** μM) have shown good activity. The remaining compounds have exhibited moderate activity against both cancer cell lines ranging from 20.21 to > 200 μM.



Scheme 1 Synthetic route of 1, 4-disubstituted 1,2,3-triazole derivatives (**3a**–**3n**).

Table 1 Inhibition values (IC_{50}) of 1,2,3-triazole derivatives (**3a**–**3n**) on human tumor cell lines MCF-7 and HeLa.

Entry	Product	MCF-7 (IC_{50})	HeLa (IC_{50})
1	**3a**	52.33	55.99
2	**3b**	14.20	20.21
3	**3c**	18.58	54.95
4	**3d**	11.34	16.48
5	**3e**	> 200	> 200
6	**3f**	11.73	51.88
7	**3g**	> 200	> 200
8	**3h**	45.01	> 200
9	**3i**	53.41	69.09
10	**3j**	> 200	> 200
11	**3k**	49.17	24.85
12	**3l**	25.68	34.13
13	**3m**	> 200	50.66
14	**3n**	35.30	7.93
15	**Cisplatin**	11.44	7.28

3.3. In vitro antibacterial activity

The minimum inhibitory concentrations (MIC) of synthesized compounds (**3a**–**3n**) were tested against Gram-positive and Gram negative bacteria. The antibacterial activity screening results (Table 2) revealed that, compounds possessing the napthyl group and 2, 6-dibromo-4-chloro phenyl group on the triazole ring (**3b** and **3n**) have shown excellent activity against *E. coli* and *B. Subtilis* when comparing with the standard drug Streptomycin. Compound **3d** against *P. vulgaris*, **3k** against *S. aureus*, and compound **3l** against *S. aureus* and *B. subtilis* have shown promising antibacterial activity.

Structure–activity relationship of the compounds (**3a**–**3n**) revealed that, the 1st position of the triazole ring bearing napthyl (**3b**), 2-hydroxymethyl 5-fluoro phenyl (**3d**), 3-chloro phenyl (**3k**), 3,5-dichloro phenyl (**3l**) and 2,6-dibromo-4-fluoro phenyl (**3n**) were found to be potent antibacterial agents and the compounds bearing 4-methoxy phenyl (**3a**) and 2-chloro-5-nitro phenyl (**3c**) were found to be moderate antibacterial agents than the remaining compounds.

Table 2 The MIC of 1, 2, 3-triazole derivatives (**3a**–**3n**) on different bacterial strains.

MIC (μg/ml)				
Compound	*E. coli*	*S. aureus*	*P. vulgaris*	*B. Subtilis*
3a	75	37.5	9.37	> 150
3b	2.343	> 150	> 150	4.687
3c	> 150	9.37	> 150	18.75
3d	> 150	> 150	4.687	> 150
3e	> 150	> 150	> 150	> 150
3f	37.5	75	> 150	> 150
3g	> 150	> 150	> 150	> 150
3h	> 150	> 150	> 150	> 150
3i	37.5	75	> 150	> 150
3j	> 150	> 150	75	37.5
3k	> 150	2.343	> 150	> 150
3l	> 150	4.687	> 150	2.343
3m	> 150	> 150	> 150	> 150
3n	1.171	> 150	> 150	2.343
Streptomycin	6.25	6.25	3.125	6.25

4. Conclusion

In summary, we have designed and synthesized a series of novel 1, 2, 3-triazole clubbed uridine hybrids and evaluated for their anticancer and antibacterial activities. Among the series, compounds **3d** and **3f** have shown potent activity against breast cancer cell line-MCF-7 and compound **3n** has shown excellent activity against cervical carcinoma cell line (HeLa) than the standard drug Cisplatin. The active compounds can be considered as future drug candidates for cancer therapy, and by effecting a simple modification in the structure a new potent analog can be generated that has desired anticancer activity with good efficacy. Similarly, compounds **3b** and **3n** have shown marked antibacterial activity against *E. coli* & *B. subtilis*, **3d** against *S. aureus*, **3k** against *S. aureus* & *B. subtilis* and **3l** against *P. vulgaris* have shown very good antibacterial activity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jscs.2015.12.001.

References

[1] R. Saladino, C. Crestini, A.T. Palamara, M.C. Danti, F. Manetti, F. Corelli, E. Garaci, M. Botta, Synthesis, biological evaluation and pharmacophore generation of uracil, 4(3H)-pyrimidinone and uridine derivatives as potent and selective inhibitors of parainfluenza 1 (Sendai) virus, J. Med. Chem. 44 (2001) 4554–4562.
[2] S. Cao, L.Q. Sun, M. Wang, Antimicrobial activity and mechanism of action of Nu-3, a protonated modified nucleotide, Ann. Clin. Microbiol. Antimicrob. 10 (2011) 1.
[3] D. Murata, Y. Endo, T. Obata, K. Sakamoto, Y. Syouji, M. Kadohira, A. Matsuda, T. Sasaki, A crucial role of uridine/cytidine kinase 2 in antitumor activity of 3′-ethynyl nucleosides, Drug Metab. Dispos. 32 (2004) (2004) 1178–1182.
[4] P. Xiao, H. Huang, J. Chen, X. Li, In vitro antioxidant and anti-inflammatory activities of Radix Isatidis extract and bioaccessibility of six bioactive compounds after simulated gastro-intestinal digestion, J. Ethnopharmacol. 57 (2014) 55–61.
[5] C.H. Schettler, Virus hepatitis of geese 3. Properties of the causal agent, Avian Pathol. 2 (1973) 179–193.
[6] R.Z. Sterzycki, I. Ghazzouli, V. Brankovan, J.C. Martin, M.M. Mansuri, Synthesis and anti-HIV activity of several 2′-fluoro-containing pyrimidine nucleosides, J. Med. Chem. 33 (1990) 2150–2157.
[7] D.B. Smith, G. Kalayanov, C. Sund, A. Winqvist, P. Pinho, T. Maltseva, V. Morisson, V. Leveque, S. Rajyaguru, S.L. Pogam, I. Najera, K. Benkestock, X.X. Zhou, H. Maag, N. Cammack, J.

A. Martin, S. Swallow, N.G. Johansson, K. Klumpp, M. Smith, The design, synthesis, and antiviral activity of 4′-azidocytidine analogues against hepatitis C virus replication: the discovery of 4′-azidoarabinocytidine, J. Med. Chem. 52 (2009) 219–223.

[8] E. Krol, I. Wandzik, W. Szeja, G. Grynkiewicz, B. Szewczyk, In vitro antiviral activity of some uridine derivatives of 2-deoxy sugars against classical swine fever virus, Antiviral Res. 86 (2010) 54–162.

[9] B.S. Holla, M. Mahalinga, M.S. Karthikeyan, B. Poojary, P.M. Akberali, N.S. Kumari, Synthesis, characterization and antimicrobial activity of some substituted 1,2,3-triazoles, Eur. J. Med. Chem. 40 (2005) 1173–1178.

[10] R.P. Jadhav, H.N. Raundal, A.A. Patil, V.D. Bobade, Synthesis and biological evaluation of a series of 1,4-disubstituted 1,2,3-triazole derivatives as possible antimicrobial agents, J. Saudi Chem. Soc. (2015), http://dx.doi.org/10.1016/j.jscs.2015.03.003.

[11] C.J. Carroux, G.M. Rankin, J. Moeker, L.F. Bornaghi, K. Atneni, J. Morizzi, S.A. Charman, D. Vullo, C.T. Supuran, S.A. Poulsen, A prodrug approach toward cancer-related carbonic anhydrase inhibition, J. Med. Chem. 56 (2013) 9623–9634.

[12] M.F. Mady, G.E.A. Awad, K.B. Jørgensen, Ultrasound-assisted synthesis of novel 1,2,3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents, Eur. J. Med. Chem. 84 (2014) 433–443.

[13] R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.F. Perno, A. Karlsson, J. Balzarini, M.J. Camarasa, 1,2,3-Triazole-[2,5-bis-O-(tert-butyldimethylsilyl)-beta-D-ribofuranosyl]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole 2″,2″-dioxide) (TSAO) analogs: synthesis and anti-HIV-1 activity, J. Med. Chem. 37 (1994) 4185–4194.

[14] P.S. Rao, C. Kurumurthy, B. Veeraswamy, G.S. Kumar, Y. Poornachandra, C.G. Kumar, V.S. Babu, S. Kotamraju, B. Narsaiah, Synthesis of novel 1,2,3-triazole substituted-N-alkyl/aryl nitrone derivatives, their anti-inflammatory and anticancer activity, Eur. J. Med. Chem. 80 (2014) 184–191.

[15] S.A. Bakunov, S.M. Bakunova, T. Wenzler, M. Ghebru, K.A. Werbovetz, R. Brun, R.R. Tidwell, Synthesis and antiprotozoal activity of cationic 1,4-diphenyl-1*H*-1,2,3-triazoles, J. Med. Chem. 53 (2010) 254–272.

[16] J.L. Kelley, C.S. Koble, R.G. Davis, E.W. McLean, F.E. Soroko, B.R. Cooper, 1-(Fluorobenzyl)-4-amino-1H-1,2,3-triazolo[4,5-c]pyridines: synthesis and anticonvulsant activity, J. Med. Chem. 38 (1995) 4131–4134.

[17] D.R. Buckle, C.J.M. Rockell, H. Smith, B.A. Spicer, Studies on 1,2,3-triazoles(Piperazinylalkoxy)-[1]benzopyrano[2,3-d]-1,2,3-triazol-9(1H)-ones with combined H1-antihistamine and mast cell stabilizing properties, J. Med. Chem. 29 (1986) 2262–2267.

[18] S.R. Patpi, L. Pulipati, P. Yogeeswari, D. Sriram, N. Jain, B. Sridhar, R. Murthy, D.T. Anjana, Design, synthesis, and structure-activity correlations of novel dibenzo[b, d]furan, dibenzo[b, d]thiophene, and n-methylcarbazole clubbed 1,2,3-triazoles as potent inhibitors of *Mycobacterium tuberculosis*, J. Med. Chem. 55 (2012) 3911–3922.

[19] L.L. Brockunier, E.R. Parmee, H.O. Ok, M.R. Candelore, M.A. Cascieri, L.F. Colwell, L. Deng, W.P. Feeney, M.J. Forrest, G.J. Hom, D.E. MacIntyre, L. Tota, M.J. Wyvratt, M.H. Fisher, A. E. Weber, Human β_3-adrenergic receptor agonists containing1,2,3-triazole substituted benzene sulphonamides, Bioorg. Med. Chem. Lett. 10 (2000) 2111–2114.

[20] P.H. Olesen, A.R. Sørensen, B. Urso, P. Kurtzhals, A.N. Bowler, U. Ehrbar, B.F. Hansen, Synthesis and in vitro characterization of 1-(4-aminofurazan-3-yl)-5-dialkylaminomethyl-1*H*-[1-3]triazole-4-carboxylic acid derivatives. A new class of selective GSK-3 inhibitors, J. Med. Chem. 46 (2003) 3333–3341.

[21] V.P. Mocharla, B. Colasson, L.V. Lee, S. Roeper, B.K. Sharpless, C.H. Wong, H.C. Kolb, In situ click chemistry: enzyme-generated inhibitors of carbonic anhydrase II, Angew. Chem. Int. Ed. 44 (2005) 116–120.

[22] S. Narsimha, T.R. Kumar, N.S. Kumar, S. Yakub, N.V. Reddy, Synthesis and antibacterial activity of (1-aryl-1,2,3-triazol-4-yl) methyl esters of morpholine-3-carboxylic acid, Med. Chem. Res. 23 (2014) 5321–5327.

[23] K. Battula, S. Narsimha, V.R. Nagavelli, P. Bollepelli, M.S. Rao, Synthesis and antimicrobial evaluation of some novel thiomorpholine derived 1,4-disubstituted 1,2,3-triazoles, J. Serb. Chem. Soc. (2015), http://dx.doi.org/10.2298/JSC150818088B.

[24] A.M. Bello, E. Poduch, M. Fujihashi, M. Amani, Y. Li, I. Crandall, R. Hui, P.I. Lee, K.C. Kain, E.F. Pai, L.P. Kotra, A. Potent, Covalent inhibitor of orotidine 5′-monophosphate decarboxylase with antimalarial activity, J. Med. Chem. 50 (2007) 915–921.

[25] J.C. Kauer, R.A. Carboni, Aromatic azapentalenes. III. 1,3a,6,6a-Tetraazapentalenes, J. Am. Chem. Soc. 89 (1967) 2633–2637.

[26] V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, A stepwise huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes, Angew. Chem. Int. Ed. 41 (2002) 2596–2599.

[27] F. Denizot, R. Lang, Rapid colorimetric assay for cell growth and survival: modifications to the tetrazolium dye procedure giving improved sensitivity and reliability, J. Immunol. Methods 89 (1986) 271–277.

[28] NCCL (National Committee for Clinical Laboratory), Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, which Grows Aerobically, fifth ed., Approved Standard M7–A5, Nat. Comm. Clin. Lab. stand, Villanova, PA, 2000.