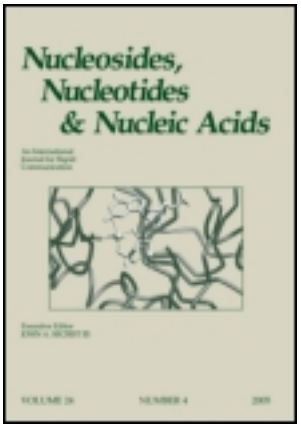

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SYNTHESIS OF ACYCLOVIR AND HBG ANALOGUES HAVING NICOTINONITRILE AND ITS 2-METHYLOXY 1,2,3-TRIAZOLE

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□ *Reaction of pyridin-2(1H)-one **1** with 4-bromobutylacetate (**2**), (2-acetoxyethoxy)methyl bromide (**3**) gave the corresponding nicotinonitrile O-acyclonucleosides, **4** and **5**, respectively. Deacetylation of **4** and **5** gave the corresponding deprotected acyclonucleosides **6** and **7**, respectively. Treatment of pyridin-2(1H)-one **1** with 1,3-dichloropropan-2-ol (**8**), epichlorohydrin (**10**) and allyl bromide (**12**) gave the corresponding nicotinonitrile O-acyclonucleosides **9**, **11**, and **13**, respectively. Furthermore, reaction of pyridin-2(1H)-one **1** with the propargyl bromide (**14**) gave the corresponding 2-O-propargyl derivative **15**, which was reacted via [3+2] cycloaddition with 4-azidobutyl acetate (**16**) and [(2-acetoxyethoxy)methyl]azide (**17**) to give the corresponding 1,2,3-triazole derivatives **18** and **19**, respectively. The structures of the new synthesized compounds were characterized by using IR, ^{1}H, ^{13}C NMR spectra, and microanalysis. Selected members of these compounds were screened for antibacterial activity.*

Keywords Pyridin-2(1*H*)-one; acyclonucleosides; 1,2,3-triazole; [3+2] cycloaddition

INTRODUCTION

3-Cyanopyridin-2-(1*H*)-one and their fused heterocyclic analogues have diverse biological and pharmacological activities, particularly as inhibitors of farnesyl transferase,[1] HIV-integrase strand transfer,[2] insulin-like growth factor-1 receptor (IGF-1R) kinase,[3] anaplastic lymphoma kinase (ALK),[4] and hepatitis B virus (HBV).[5] Pyridin-2-(1*H*)-one have been also reported as antimicrobial,[6–8] antidepressant, cardiotonic,[9] anticancer,[10] and antimalarial.[11] Moreover, amrinone has been established as a positive inotropic and vasodilatatory agent used in the clinic for the treatment of heart failure.[12,13]

3-Cyanopyridine derivatives have been described as intermediates in the synthesis of pyrido[2,3-*d*]pyrimidines as antihistaminic agents[14,15]

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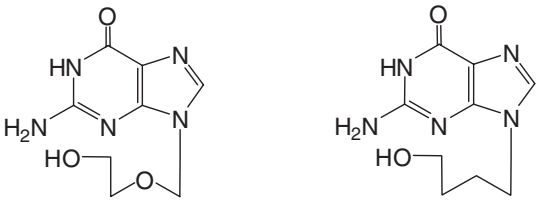


FIGURE 1 Structure of acyclovir and HBG.

and acyclo-3-deazapyrimidine *S*-nucleosides that are active toward HIV.[16] Acyclic nucleosides[17–19] and their chemotherapeutic value have attracted the attention toward the synthesis of various analogues with variant chemical modifications. The above aspects attracted our attention to the synthesis of the acyclic nucleoside of nicotinonitrile derivatives of the well-known antiviral agent acyclovir [18–20] having the (hydroxyethoxy)methyl residue and its analogues. Moreover, these glycone residues have been linked to the pyridine ring via a triazole ring acyclic nucleosides using a click chemistry approach (Figure 1).

RESULTS AND DISCUSSION

Pyridin-2-(1*H*)-one and azinones in general are weak acids that form mesomeric anions that react with an electrophilic reagent on the oxygen, nitrogen, or carbon atom. The anion from pyridin-2(1*H*)-one can be mainly alkylated on nitrogen; Na and K salts predominantly undergo *N*-alkylation (Figure 2).[20]

Reaction of pyridin-2(1*H*)-one **1** with 4-bromobutyl acetate (**2**) and (2-acetoxyethoxy)methyl bromide (**3**)[21] in the presence of potassium carbonate in anhydrous acetone/DMF at room temperature gave the corresponding 2-(acetoxybutyloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (**4**) and 2-[(acetoxyethoxy)methyloxy]-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (**5**), in good yields (Scheme 1), but not the expected *N*-acyclic nucleosides **4a** and **5a**.

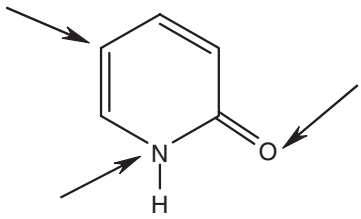
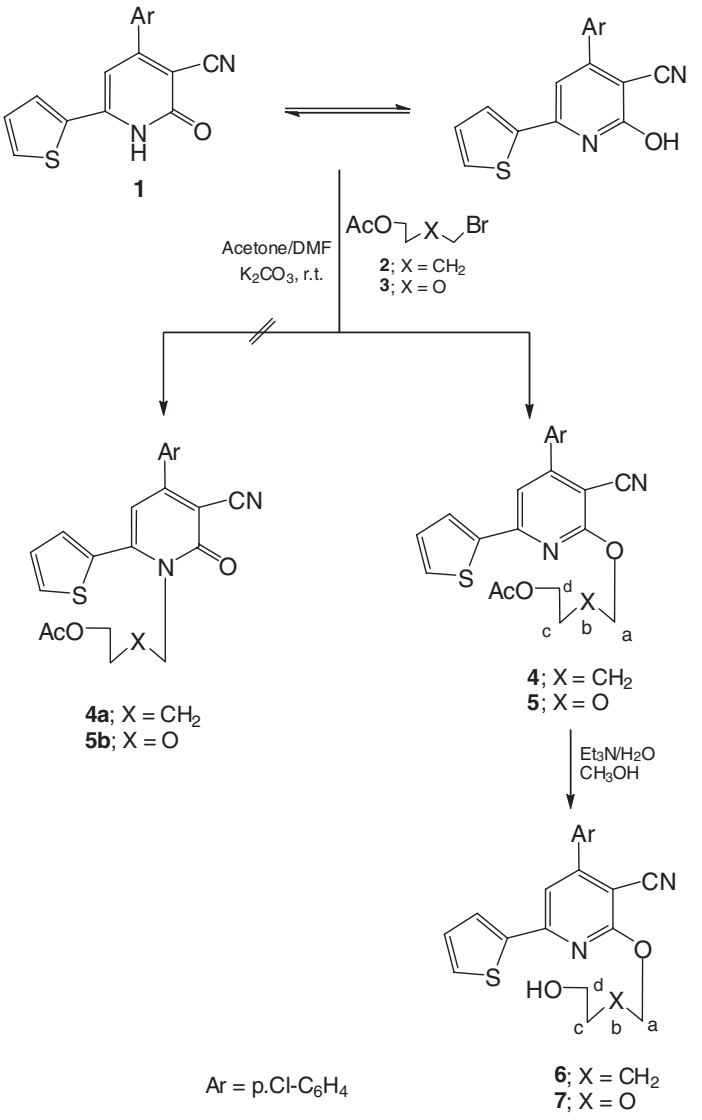
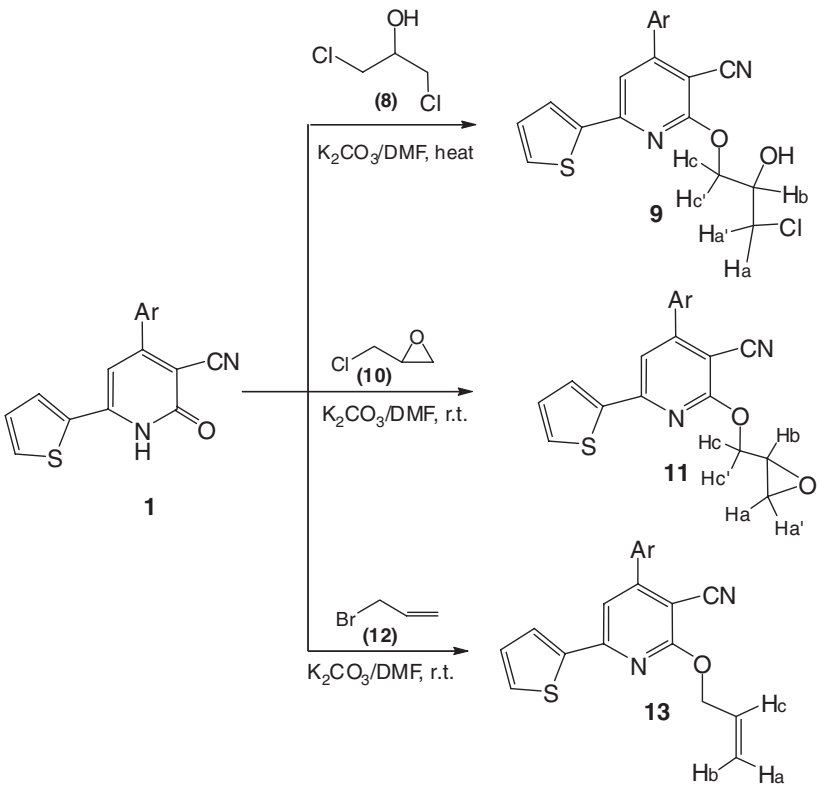


FIGURE 2 Alkylation profile of pyridine-2(1*H*)-one.



SCHEME 1 Acyclovir analogues.

The infrared (IR) spectra of compounds **4** and **5** agreed with absorption bands at 2214–2216 and 1737–1738 cm^{-1} for C≡N and C=O of acetoxy groups. The absence of a band that can be due to an N—C=O group agreed with the structures **4** and **5** and not **4a** and **5a**. ^{1}H NMR spectra of **4** and **5** showed the structure. The ^{13}C NMR spectra showed the characteristic bands for C≡N and C=O of acetoxy groups at δ 115.5 and 170.7 ppm, respectively.



SCHEME 2 Alkylation with functionalized alkyl halides.

Deacetylation of compound **4** and **5** by using triethylamine/methanol and a few drops of water [22–24] gave the corresponding deacetylated derivatives **6** and **7**, respectively (Scheme 1). The IR spectra of **6** and **7** revealed the absence of band at 1737–1738 cm^{-1} for the acetoxy groups and presence of bands at 3410–3426 cm^{-1} for OH groups.

Similarly, alkylation of pyridin-2(1*H*)-one **1** has been investigated using functionalized alkyl halides that are suitable for further chemical modification to provide acyclic nucleoside analogues. Thus, reaction of pyridin-2(1*H*)-one 1 with 1,3-dichloropropan-2-ol (**8**) in the presence of potassium carbonate in dry acetone/DMF for overnight at room temperature, then at reflux for 6 hours, afforded 2-(3-chloro-2-hydroxyprop-1-yloxy)-4-(4-chlorophenyl)-6-thien-2-yl)nicotinonitrile (**9**) as one isomer in moderate yield (48%) (Scheme 2). Its IR spectrum showed bands at 3424 and 2217 cm^{-1} characteristic for OH and C≡N groups. ^{1}H and ^{13}C NMR spectra of **9** showed the characteristic signals corresponding to the presence of one isomer.

Reaction of pyridin-2(1*H*)-one **1** with epichlorohydrin (**10**) and allyl bromide (**12**) in the presence of potassium carbonate in dry acetone/DMF at

room temperature afforded 4-(4-chlorophenyl)-2-(oxiran-2-ylmethyloxy)-6-(thien-2-yl)nicotinonitrile (**11**) and 2-(allyloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (**13**), respectively (Scheme 2). The ^{1}H NMR spectrum of **11** showed signals at δ 2.83, 2.89, and 4.29 ppm as triplet and doublet of doublets corresponding to Ha, Ha′, and Hb, in addition to doublet signals at δ 4.38 and 4.88 ppm for Hc and Hc′ of (OCH_2), respectively. Its ^{13}C NMR spectrum showed signals at δ 44.6 and 49.5 ppm corresponding to CH_2O and CHO of oxiran ring and δ 68.5 ppm for OCH_2 group. The IR spectra of compounds **9**, **11**, and **13** revealed the absence of N—C=O groups; this confirmed that the alkylation occured on the oxygen atom and not on the nitrogen.

The next target is the acyclonucleoside **19** and its C-analogues **18**, which required two synthons, the propargyl derivative as **15** and the azide derivatives **16** and **17**. Thus, reaction of pyridin-2(1*H*)-one **1** with propargyl bromide (**14**) in the presence of anhydrous potassium carbonate gave the corresponding 2-(prop-2-yloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (**15**). The 4-azidobutyl acetate (**16**) and [(2-acetoxyethoxy)methyl]azide (**17**) were prepared from 4-bromobutylacetate (**2**) and (2-acetoxyethoxy)methyl bromide (**3**) by replacement of the halide with azide ion as reported in the literature[25,26] (Scheme 3).

Applying click chemistry for the reaction of **15** with **16** and **17** to achieve the [3+2] cycloaddition reaction in the presence of $CuSO_4.5H_2O$ and sodium ascorbate[27] gave 4-(4-((4-(4-chlorophenyl)-3-cyano-6(thien-2-yl)pyridine-2-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)butyl acetate (**18**) and 2-((4-((4-(4-chlorophenyl)-3-cyano-6(thiophen-2yl)pyridine-2-yloxy)methyl)-1*H*-1,2,3-triazol-yl)methoxy)ethyl acetate (**19**), respectively. The dipolar cycloaddition had taken place regiospecifically because of the steric factor.

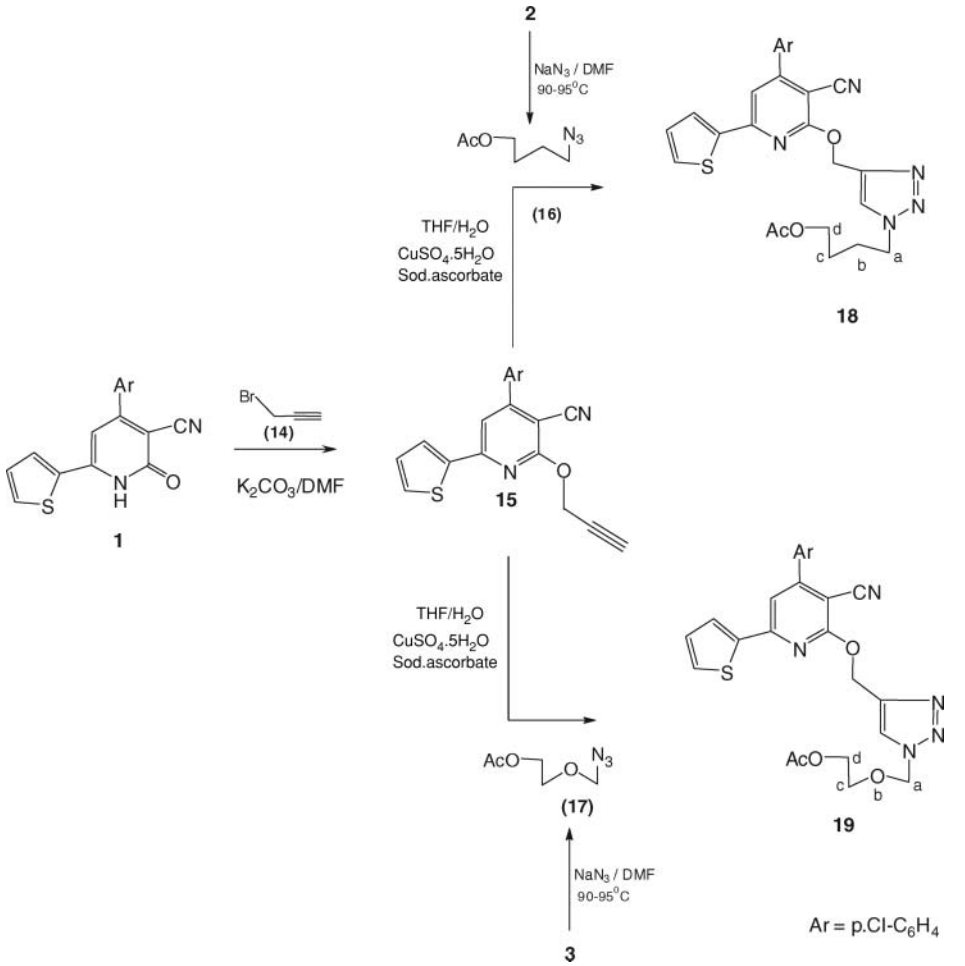
The structures of **18** and **19** were proven on the basis of spectroscopic analysis (IR and ^{1}H, ^{13}C NMR). ^{1}H NMR spectrum of **18** showed multiplets at δ 1.52 and 1.85 ppm for CH_2(c) and CH_2(b), with other signals at 1.95, 4.32, and 4.51 ppm characteristic for CH_3 of acetoxy group, CH_2OCO (d) and NCH_2(a), in addition to a singlet at 5.62 ppm for CH_2O-pyridine, respectively. Its ^{13}C NMR spectrum showed signals at 22.0, 25.5, 26.8, 49.4, 63.1, and 68.9 ppm corresponding to $\underline{C}H_3CO$, $2\underline{C}H_2$, $N\underline{C}H_2$, $\underline{C}HOCO$ and $O\underline{C}H_2$-pyridine, respectively. The spectroscopic analysis data for compound **19** was in agreement with the structure.

Antimicrobial Activity

Acyclic nucleosides **6**, **7**, **9**, **11**, **13**, **18**, and **19** were evaluated for antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* as Gram (+ve) bacteria and *Pseudomonas aeruginosa* and *Escherichia coli* as Gram (−ve) bacteria, using a cup plate agar diffusion method.[28] Ampicillin was used as a reference to evaluate the potency of tested compounds. Nucleosides

TABLE 1 Antimicrobial activity of tested compounds (inhibition zones mm, minimum inhibitory concentration μg/mL)

Compound no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
6	13	7	27	4
7	11	10	28	9
9	0	0	0	1
11	8.5	8	25	3
13	5	4.5	14	2
18	15	8	24	6
19	10	6	23.5	5
Ampicillin	7	6	23	2



SCHEME 3 Synthesis of triazole analogues.

6, **7**, and **18** showed higher antibacterial activity compared to the standard drug (ampicillin). Compounds **11** and **19** showed moderate antibacterial activity compared to the standard drug, whereas the allyloxy nicotinonitrile **13** showed lower antibacterial activity compared to the standard drug (ampicillin). Compound **9** did not show any activity against tested micro-organisms. The results of the biological activities encourage further work on such a ring system (Table 1).

CONCLUSION

The alkylation of 4-(4-chlorophenyl)-2-oxo-6-(thien-2-yl)-1,2-dihydropyridine-3-carbonitrile with 4-bromobutyl acetate, (2-acetoxyethoxy)methyl bromide, 1,3-dichloro-2-propanol, epichlorohydrin, allyl, and propargyl bromide afforded *O*-alkyl products and not the expected *N*-alkylated analogues. The 1,2,3-triazole acyclonucleosides were obtained by the reaction of 2-(prop-2-yloxy)nicotinonitrile with the azide derivatives **2** and **3** via click chemistry. The glycosides **6**, **7**, **11**, **13**, **18**, and **19** showed significant antibacterial activity and futher evaluation against other pathogens is underway.

EXPERIMENTAL

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. TLC was performed on Merck Silica Gel $60F_{254}$ with detection by ultraviolet (UV) light and by the charring with 10% EtOH solution of H_2SO_4. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The operation frequency was 300 MHz for ^1H and 75.5 MHZ for ^{13}C NMR using JOEL-JNM-LA 300 MHz spectrometer. The coupling constants (J) are given in hertz. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Elemental analyses were determined on a Perkin Elmer 240 (microanalysis; Cairo University, Cairo, Egypt).

General Procedure for Alkylation of Pyridin-2(1*H*)-one (1)

A mixture of pyridin-2(1*H*)-one **1** (0.01 mol) and potassium carbonate (0.01 mol) was stirred in dry acetone/DMF (15 mL) for 1 hour; then the alkylating agent (0.011 mol) was added. The reaction mixture was stirred for overnight at room temperature, filtered off, and the solvent was evaporated under reduced pressure. The residue was dried and crystallized from ethanol. In the case of 1,3-dichloropropan-2-ol, the reaction mixture required heating under reflux for 6 hours.

2-(Acetoxybutyloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (4). 83% yield; Pale yellow crystals; m.p. 145–146°C; IR (KBr) 2215 cm^{-1} (C≡N) and 1737 cm^{-1} (C=O, acetoxy); ^1H NMR spectrum (300 MHz; DMSO-d_6) δ

1.63 (m, 2H, $C\underline{H}_2$(c)), 1.71 (m, 2 H, $C\underline{H}_2$(b)), 1.89 (s, 3 H, $C\underline{H}_3CO$), 3.95 (t, 2H, J = 5.76 Hz, $OC\underline{H}_2$(a)), 4.37 (t, 2H, J = 5.89 Hz, $C\underline{H}_2OCO$(d)), 7.09 (t, 1H, J = 3.96, 4.46 Hz, thiophene-H), 7.51 (d, 2H, J = 8.40 Hz, Ar-H), 7.60 (d, 2H, J = 8.40 Hz, Ar-H), 7.62 (s, 1H, pyridine-H-5), 7.68 (d, 1H, J = 4.46 Hz, thiophene-H), 7.93 (d, 1H, J = 3.96 Hz, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 21.1 ($\underline{C}H_3CO$), 25.2, 25.4 ($2\underline{C}H_2$), 63.9 ($O\underline{C}H_2$), 67.3 ($\underline{C}H_2OCO$), 91.9, 112.4, 115.5 (C≡N), 129.1, 129.3, 129.4, 130.8, 131.7, 134.9, 135.5, 142.9, 153.4, 155.3, 164.3 (Ar-C) and 170.7(C=O). Anal. Calcd for $C_{22}H_{19}ClN_2O_3S$ (426.92): C, 61.89; H, 4.49; N, 6.56. Found: C, 61.88; H, 4.47; N, 6.55.

2-[(Acetoxyethoxy)methyloxy]-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (5). 78% yield; Pale yellow crystals; m.p. 105–106°C; IR (KBr) 2214 cm^{-1} (C≡N) and 1738 cm^{-1} (C=O, acetoxy); ^{1}H NMR spectrum (300 MHz; DMSO-d_6) δ 1.92 (s, 3 H, $C\underline{H}_3CO$), 4.32 (t, 2H, J = 5.4 Hz, $OC\underline{H}_2$(c)), 4.58 (t, 2H, J = 5.4 Hz, $C\underline{H}_2OCO$(d)), 6.12 (s, 2H, $OC\underline{H}_2O$(a)), 7.1 (t, 1H, J = 4.03, 4.10 Hz, thiophene-H), 7.52 (d, 2H, J = 8.32 Hz, Ar-H), 7.61 (d, 2H, J = 8.32 Hz, Ar-H), 7.65 (s, 1H, pyridine-H-5), 7.70 (d, 1H, J = 4.10 Hz, thiophene-H), 7.95 (d, J = 4.03 Hz, 1H, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 21.1 ($\underline{C}H_3CO$), 62.3, 65.7 and 69.9 ($2\underline{C}H_2$ and $O\underline{C}H_2O$), 92.1, 112.8, 115.4 (C≡N), 129.3, 129.5, 130.9, 131.9, 132.1, 134.8, 135.5, 142.7, 153.3, 155.5, 164.0 (Ar-C) and 170.7 (C=O). Anal. Calcd for $C_{21}H_{17}ClN_2O_4S$ (428.89): C, 58.81; H, 4.00; N, 6.53. Found: C, 58.80; H, 4.02; N, 6.55.

4-(4-Chlorophenyl)-2-(hydroxybutyloxy)-6-(thien-2-yl)nicotinonitrile (6). Triethylamine (0.5 mL) was added to a solution of **4** (0.01 mol, 4.26 g) in MeOH (20 mL) and a few drops of water. The mixture was stirred overnight at room temperature, then refluxed for 4 hours, evaporated under reduced pressure and the residue was co-evaporated with MeOH until the triethylamine was removed. The residue was crystallized from ethanol to give pale yellow crystals. 86% yield; m.p. 201–203°C, IR (KBr) 2214 cm^{-1} (C≡N) and 3410 cm^{-1} (OH); ^{1}H NMR spectrum (300 MHz; DMSO-d_6) δ 1.61 (m, 2H,$C\underline{H}_2$(c)), 1.85 (m, 2H, $C\underline{H}_2$(b)), 3.49 (q, 2H, J = 6.34 Hz, $C\underline{H}_2OH$(d)), 4.47 (t, 2H, J = 5.09 Hz, $OC\underline{H}_2$(a)), 4.53 (t, 1H, J = 4.49 Hz, OH), 7.24 (t, 1H, J = 3.87, 4.01 Hz, thiophene-H), 7.66 (d, 2H, J = 8.52 Hz, Ar-H), 7.75 (d, 2H, J = 8.52 Hz, Ar-H), 7.80 (s, 1H, pyridine-H-5), 7.83 (d, 1H, J = 4.01 Hz, thiophene-H), 8.09 (d, 1H, J = 3.87 Hz, thiophene-H). ^{13}C NMR (75 MHz DMSO-d_6) δ 25.57, 29.35 ($2\underline{C}H_2$), 60.84 ($\underline{C}H_2OH$), 67.72 ($O\underline{C}H_2$), 112.3, 115.6 (C≡N), 129.1, 129.2, 129.3, 129.5, 130.9, 131.8, 135.0, 135.5, 143.0, 153.4, 155.4 and 164.4 (Ar-C). Anal. Calcd for $C_{20}H_{17}ClN_2O_2S$ (384.88): C, 62.41; H, 4.45; N, 7.28. Found: C, 62.43; H, 4.43; N, 7.25.

2-[(Hydroxyethoxy)methyloxy]-4-(4-chlorophenyl)-6-(thien-2-yl) nicotinonitrile (7). Triethylamine (0.5 mL) was added to a solution of **5** (0.01 mol, 4.28 g) in MeOH (20 mL) and a few drops of water. The mixture was prepared as above to give pale yellow crystals. 88% yield; m.p.

196–198°C. IR (KBr): 3426 cm^{-1} (OH) and 2217 cm^{-1} (C≡N); ^1H NMR spectrum (300 MHz; DMSO-d_6) δ 3.81 (q, 2H, J = 5.29 Hz, CH_2OH(d)), 4.54 (t, 2H, J = 5.01 Hz, OCH_2(c)), 4.93 (t, 1H, J = 5.29 Hz, OH), 6.01 (s, 2H, OCH_2O(a)), 7.23 (t, 1H, J = 3.99, 4.56 Hz, thiophene-H), 7.65 (d, 2H, J = 8.45 Hz, Ar-H), 7.73 (d, 2H, J = 8.45 Hz, Ar-H), 7.77 (s, 1H, pyridine-H-5), 7.85 (d, 1H, J = 4.56 Hz, thiophene-H), 8.07 (d, J = 3.99 Hz, 1H, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 59.46, 69.4, ($2CH_2$), 69.8 (OCH_2O), 112.4, 115.6 (C≡N), 129.2, 129.3, 129.5, 130.6, 130.9, 131.8, 135.0, 135.5, 142.9, 153.3, 155.5 and 164.4 (Ar-C). Anal. Calcd. for $C_{19}H_{15}ClN_2O_3S$ (386.85): C, 58.99; H, 3.91; N, 7.24. Found: C, 59.01; H, 3.92; N, 7.26.

2-(3-Chloro-2-hydroxypropoxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (9). 48% yield; Pale yellow crystals; m.p. 99–100°C; IR (KBr) 3424 cm^{-1} (OH) and 2217 cm^{-1} (C≡N). ^1H NMR spectrum (300 MHz; DMSO-d_6) δ 3.61 (dd, 1H, J = 5.43 Hz, J = 11.13 Hz, H-a'), 3.67 (dd, 1H, J = 5.64 Hz, J = 11.17 Hz, H-a), 3.96 (dd, 1H, J = 5.81 Hz, J = 10.23 Hz, H-c'), 4.05 (dd, 1H, J = 5.15 Hz, J = 10.23 Hz, H-c), 4.40 (m, 1H, H-b), 5.53 (d, 1H, J = 5.23 Hz, OH), 7.11 (t, 1H, J = 4.14, 5.62 Hz, thiophene-H), 7.46 (d, 2H, J = 8.50 Hz, Ar-H), 7.52 (d, 2H, J = 8.50 Hz, Ar-H), 7.61 (s, 1H, pyridine-H-5), 7.70 (d, 1H, J = 5.62 Hz, thiophene-H), 7.96 (d, 1H, J = 4.14 Hz, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 47.01 (CH_2Cl), 68.4 (CHOH), 68.64 (OCH_2), 92.1, 112.7, 115.4 (C≡N), 129.3, 129.5, 130.9, 131.9, 134.9, 135.5, 136.0, 142.8, 153.3, 155.5 and 164.1 (Ar-C). Anal. Calcd for $C_{19}H_{14}Cl_2N_2O_2S$ (405.30): C, 56.31; H, 3.48; N, 6.91. Found: C, 56.30; H, 3.46; N, 6.90.

4-(4-Chlorophenyl)-2-(oxiran-2-ylmethoxy)-6-(thien-2-yl)nicotinonitrile (11). 71% yield; Pale yellow crystals; m.p. 185–187°C; IR (KBr) 2216 cm^{-1} (C≡N); ^1H NMR spectrum (300 MHz; DMSO-d_6) δ 2.83 (t, 1H, J = 1.50, 4.50 Hz, H-a), 2.89 (t, 1H, J = 4.20, 4.50 Hz, H-a'), 4.29 (dd, 1H, J = 6.30 Hz, H-b), 4.83 (d, 1H, J = 2.17 Hz, H-c'), 4.88 (d, 1H, J = 2.27 Hz, H-c), 7.24 (t, 1H, J = 3.95, 4.07 Hz, thiophene-H), 7.66 (d, 2H, J = 8.43 Hz, Ar-H), 7.74 (d, 2H, J = 8.43 Hz, Ar-H), 7.79 (s, 1H, pyridine-H-5), 7.82 (d, 1H, J = 4.07 Hz, thiophene-H), 8.10 (d, 1H, J = 3.95 Hz, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 44.6 (CH_2O, oxiran), 49.5 (CHO, oxiran), 68.5 (OCH_2), 91.8, 113.1, 115.5 (C≡N), 129.2, 129.4, 129.7, 130.8, 131.9, 134.4, 135.4, 142.7, 153.2, 157.7 and 163.8 (Ar-C). Anal. Calcd for $C_{19}H_{13}ClN_2O_2S$ (368.84): C, 61.87; H, 3.55; N, 7.60. Found: C, 61.85; H, 3.54; N, 7.61.

2-(Allyloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (13). 82% yield; Pale yellow crystals; m.p. 201–203°C; IR (KBr) 2216.7 cm^{-1} (C≡N); ^1H NMR spectrum (300 MHz; DMSO-d_6) δ 5.08 (d, 2 H, J = 5.10 Hz, OCH_2), 5.33 (d, 1H, J = 10.2 Hz, H-a), 5.52 (d, 1H, J = 17.4 Hz, H-b), 6.16 (m, 1 H, H-c), 7.24 (t, 1H, J = 4.03, 4.56 Hz, thiophene-H), 7.67 (d, 2H, J = 8.40 Hz, Ar-H), 7.76 (d, 2H, J = 8.40 Hz, Ar-H), 7.80 (s, 1H, pyridine-H-5), 7.83 (d, 1H, J = 4.56 Hz, thiophene-H), 8.11 (d, 1H, J = 4.03 Hz, thiophene-H);

^{13}C NMR (75 MHz DMSO-d_6) δ 68.0 (O$\underline{C}$H$_2$), 112.6 (=$\underline{C}$H$_2$), 115.5 (C≡N), 119.1 ($\underline{C}$H=), 128.3, 128.9, 129.3, 129.5, 130.9, 131.9, 133.1, 134.9, 135.5, 142.8, 153.3, 155.5 and 163.9 (Ar-C). Anal. Calcd for $C_{19}H_{13}ClN_2OS$ (352.84): C, 64.68; H, 3.71; N, 7.94. Found: C, 64.69; H, 3.70; N, 7.93.

2-(Prop-2-ynyloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)nicotinonitrile (15). 87% yield; Pale yellow crystals; m.p. 218–220°C; IR (KBr) 2211 cm^{-1} (C≡N); ^{1}H NMR spectrum (300 MHz; DMSO-d_6) δ 3.64 (t, 1H, J = 1.80 Hz, ≡C$\underline{H}$), 5.21 (dd, 2H, J = 1.80, 10.5 Hz, OC$\underline{H}_2$), 7.23 (t, 1H, J = 3.88, 5.09 Hz, thiophene-H), 7.67 (d, 2H, J = 9.04 Hz, Ar-H), 7.76 (d, 2H, J = 9.04 Hz, Ar-H), 7.78 (s, 1H, pyridine-H-5), 7.81 (d, 1H, J = 5.09 Hz, thiophene-H), 8.09 (d, 1H, J = 3.88 Hz, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 52.2 (O$\underline{C}$H$_2$), 78.3, 78.9 (C≡C), 91.9, 113.2, 115.4 (C≡N), 129.3, 129.5, 130.9, 131.0, 132.2, 134.8, 135.6, 142.6, 153.3, 155.7 and 163.0 (Ar-C). Anal. Calcd for $C_{19}H_{11}ClN_2OS$ (350.82): C, 65.05; H, 3.16; N, 7.99. Found: C, 65.03; H, 3.14; N, 8.00.

General Procedure for Preparation of Triazoles 18 and 19

4-Azidobutyl acetate (**16**) or 2(azidomethoxy)ethyl acetate (**17**) (0.011 mol) and 2-(prop-2-ynyloxy)-4-(4-chlorophenyl)-6-(thien-2-yl)-nicotinonitrile (**15**) (0.01 mol) were dissolved in water/tetrahydrofuran (30:70 (10 mL)). The reaction mixture was stirred at room temperature for 10 minutes, while an aqueous solution of $CuSO_4 \cdot 5H_2O$ (2.0 mL, 5%) and an aqueous solution of (+)-sodium L-ascorbate (2.0 mL, 10%) were added. The reaction mixture was stirred until complete consumption of the starting material indicated by thin layer chromatography (TLC; 3–5 hours). The reaction mixture was evaporated under reduced pressure, extracted with dichloromethane and the organic phase was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to dryness under reduced pressure[27] and the residue was crystallized from ethanol.

4-(4-((4-(4-Chlorophenyl)-3-cyano-6-(thien-2-yl)pyridine-2-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)butyl acetate (18). 54% yield; Pale yellow crystals; m.p. 108–110°C; IR (KBr) 2216 cm^{-1} (C≡N) and 1731 cm^{-1} (C=O, acetoxy); ^{1}H NMR spectrum (300 MHz; DMSO-d_6) δ 1.52 (m, 2 H, C$\underline{H}_2$(c)), 1.85 (m, 2 H, C$\underline{H}_2$(b)), 1.95 (s, 3 H, C$\underline{H}_3$CO), 4.32 (t, 2H, J = 5.51 Hz, C$\underline{H}_2$OCO (d)), 4.51 (t, 2H, J = 5.74 Hz, NC$\underline{H}_2$ (a)), 5.62 (s, 2H, OC$\underline{H}_2$), 7.24 (t, 1H, J = 3.12, 3.96 Hz, thiophene-$\underline{H}$), 7.66 (d, 2H, J = 8.35 Hz, Ar-H), 7.71 (d, 2H, J = 8.35 Hz, Ar-H), 7.80 (s, 1H, pyridine-H-5), 7.82 (s, 1H, triazole-H), 8.11 (d, 1H, J = 3.96 Hz, thiophene-H), 8.23 (d, 1H, J = 3.12 Hz, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 22.0 ($\underline{C}$H$_3$CO), 25.5, 26.8 (2$\underline{C}$H$_2$), 49.4 (N$\underline{C}$H$_2$), 63.1 ($\underline{C}$H$_2$OCO), 68.9 (O$\underline{C}$H$_2$-pyridine), 92.1, 113.0, 115.5 (C≡$\underline{N}$), 128.3, 128.9, 129.3, 129.6, 130.9, 131.8, 133.9, 135.2, 141.7, 142.5, 152.8, 155.1, 162.0 (Ar-C) and 170.0 (C=O). Anal. Calcd for

$C_{25}H_{22}ClN_5O_3S$ (507.99): C, 59.11; H, 4.37; N, 13.79. Found: C, 59.13; H, 4.36; N, 13.78.

2-((4-((4-(4-Chlorophenyl)-3-cyano-6-(thien-2yl)pyridine-2-yloxy)methyl)-1*H*-1,2,3-triazol-yl)methoxy)ethyl acetate (19). 61% yield; Pale yellow crystals; m.p. 95–97°C. IR (KBr) 2212 cm^{-1} (C≡N) and 1737 cm^{-1} (C=O, acetoxy); ^1H NMR spectrum (300 MHz; DMSO-d_6) δ 1.89 (s, 3 H, CH_3CO), 3.86 (t, 2H, J = 5.28 Hz, OCH_2(c)), 4.37 (t, 2H, J = 5.28 Hz, CH_2OCO(d)), 5.10 (s, 2H, OCH_2), 5.65 (s, 2H, NCH_2O(a)), 7.25 (t, 1H, J = 3.39, 4.17 Hz, thiophene-H), 7.60 (d, 2H, J = 8.35 Hz, Ar-H), 7.72 (d, 2H, J = 8.35 Hz, Ar-H), 7.78 (s, 1H, pyridine-H-5), 7.97 (s, 1H, triazole-H), 7.81 (d, 1H, J = 4.17 Hz, thiophene-H), 8.12 (d, 1H, J = 3.39 Hz, thiophene-H); ^{13}C NMR (75 MHz DMSO-d_6) δ 21.08 (CH_3CO), 60.27 (OCH_2). 62.72 (CH_2OCO), 65.44 (NCH_2O), 74.5 (OCH_2), 92.3, 112.8, 115.5 (C≡N), 125.8, 129.3, 129.5, 130.9, 132.0, 134.8, 135.5, 142.2, 142.4, 142.8, 153.3, 155.6, 163.7 (Ar-C) and 170.4 (C=O). Anal. Calcd for $C_{24}H_{20}ClN_5O_4S$ (509.96): C, 56.52; H, 3.95; N, 13.73. Found: C, 56.54; H, 3.96; N, 13.72.

Antimicrobial Activity

The antimicrobial activities of some newly synthesized compounds were screened for their antibacterial activity against six species of bacteria and one fungi, namely, *Staphylococcus aureus* and *Bacillus subtilis* as Gram +ve and *Pseudomonas aeruginosa* and *Escherichia coli* as Gram −ve using a cup plate agar diffusion method.[28] The tested compounds were dissolved in dimethyl sulfoxide to obtain a solution of 1 μg/mL concentration. The inhibition zones were measured in (mm) at the end of an incubation period of 48 hours at 37°C. Dimethyl sulfoxide showed no inhibition zones. Ampicillin was used as reference.

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