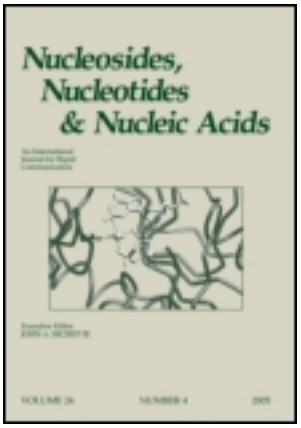

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Ahmed H. Moustafa [a], Hassan A. El-Sayed [a], Abd El-Fattah Z. Haikal [a] & Rasha A. Abd El-Hady [a]

[a] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME 2-PYRIDONE NUCLEOSIDES CONTAINING A SULFONAMIDE MOIETY

Ahmed H. Moustafa, Hassan A. El-Sayed, Abd El-Fattah Z. Haikal, and Rasha A. Abd El-Hady
Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

□ *Glycosylation of 2-pyridonesulfonamide* ***1a,b*** *with glycosyl/galactosyl bromide gave the corresponding glycosides* ***2a,b, 3a,b, 6a,b,*** *and* ***7a,b****, respectively. Deacetylation of the resulting glycosides gave the corresponding glycosides* ***4a,b, 5a,b, 8a,b,*** *and* ***9a,b****, respectively, in good yields. Furthermore, reaction of 2-pyridonesulfonamide* ***1b*** *with lactosyl bromide gave a mixture the corresponding N, O-lactosides* ***10*** *and* ***11,*** *which were deacetylated to give the corresponding glycosides* ***12*** *and* ***13****, 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 antimicrobial activity.*

Keywords 2-Pyridonesulfonamide; glycosylation; lactosylation; antimicrobial activity

INTRODUCTION

The 2-pyridone structure has attracted considerable attention due to its widespread occurrence in biologically important molecules (e.g., coenzyme of vitamin B_6 family and in numerous alkaloids)[1–5] and in a number of biologically active molecules.[1,2,6–11] For instance, pyridine-containing compounds constitute an important class of anti-fibrosis drugs.[12–14] Furthermore, the pyridone nucleus is associated with several biological activities such as antimicrobial,[15] antiviral,[16] anticancer,[17] $\beta-$lactamase inhibitors and anti−inflammatory,[18] and antimalarial agents. [19] On the other hand, compounds containing sulfonamide moieties have shown a wide range of biological activities,[20,21] such as antibacterial,[22,23] antimicrobial,[8,24,25] antitumor,[26] antiviral against HIV,[27] COX-2 selective inhibition,[28,29] anticonvulsant, hypoglycemic, antihypertensive, histamine-H_2-receptor antagonistic, and herbicidal activities.[30–32] Compounds combining the structural features of pyridone and sulfonamide group into pyridonesulfonamide (PS)

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Address correspondence to Hassan A. El-Sayed, Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt. E-mail: hasanneg@gmail.com

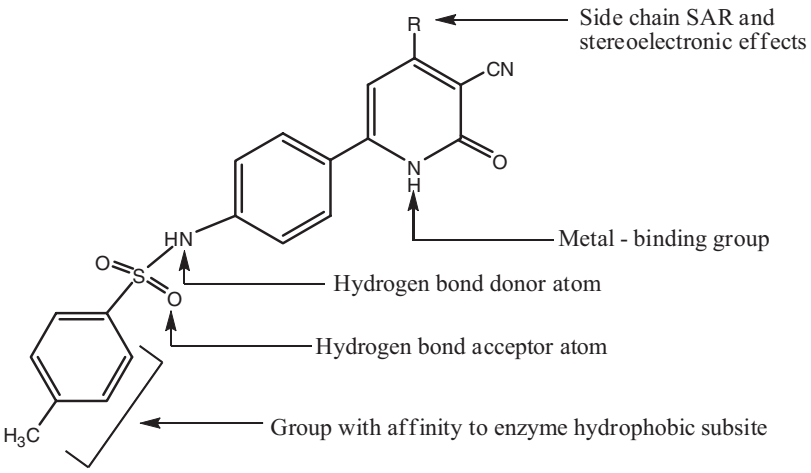


FIGURE 1 Design of PS derivatives and structure–activity relationships.

have shown affinity toward metalloproteinases (Figure 1).[22] As a continuation of our program for the search of biologically active pyridine-based small molecules, herein, we wish to report on the synthesis and the biological evaluations of glycosyalted pyridonesulfonamides **2–13**.

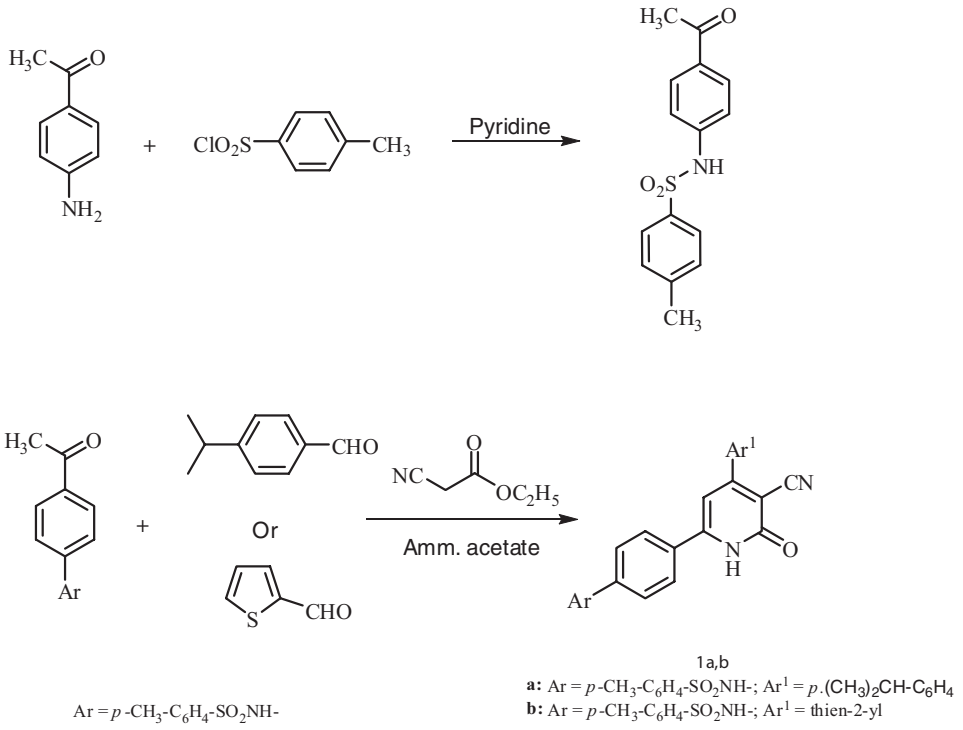
RESULTS AND DISCUSSION

In order to gain more insights into the structure–activity relationship of pyridonesulfonamides, we have manipulated the electronic effect on the 4-aryl moiety of the pyridone ring. The electronic effects are altered by the varying electron-donating and electron-withdrawing substituents at the 4 and 6 positions of the pyridone ring.

The 2-pyridonesulfonamide derivatives **1a,b** were synthesized according to literature procedures[30,33,34] (Scheme 1). The IR spectra of **1a** and **1b** displayed bands at 3225, 3231, 2217, 2218 and 1657, 1662 cm^{-1}, indicating the presence of NH, C≡N, and C=O groups, respectively. Additionally, the ^{1}H NMR and ^{13}C NMR are in agreement with the structures (see the Experimental section).

The glycosylation of **1a,b** with 2,3,4,6-tetra-*O*-acetyl-β-D-gluco or/galacto pyranosyl bromide in anhydrous DMF/K_2CO_3 afforded a mixture of the *O*-glycosyl derivatives (**2a,b; 6a,b**) and the *N*-glycosyl derivatives (**3a,b; 7a,b**), which were separated by silica gel chromatography, respectively (Scheme 2).

The structures of the *O*- and *N*-glycosides derivatives were elucidated from their analytical data, ^{1}H and ^{13}C NMR and IR. The IR spectra of **3a,b** and **7a,b** showed the presence of bands at 1642, 1660, 1699, and 1685 cm^{-1},

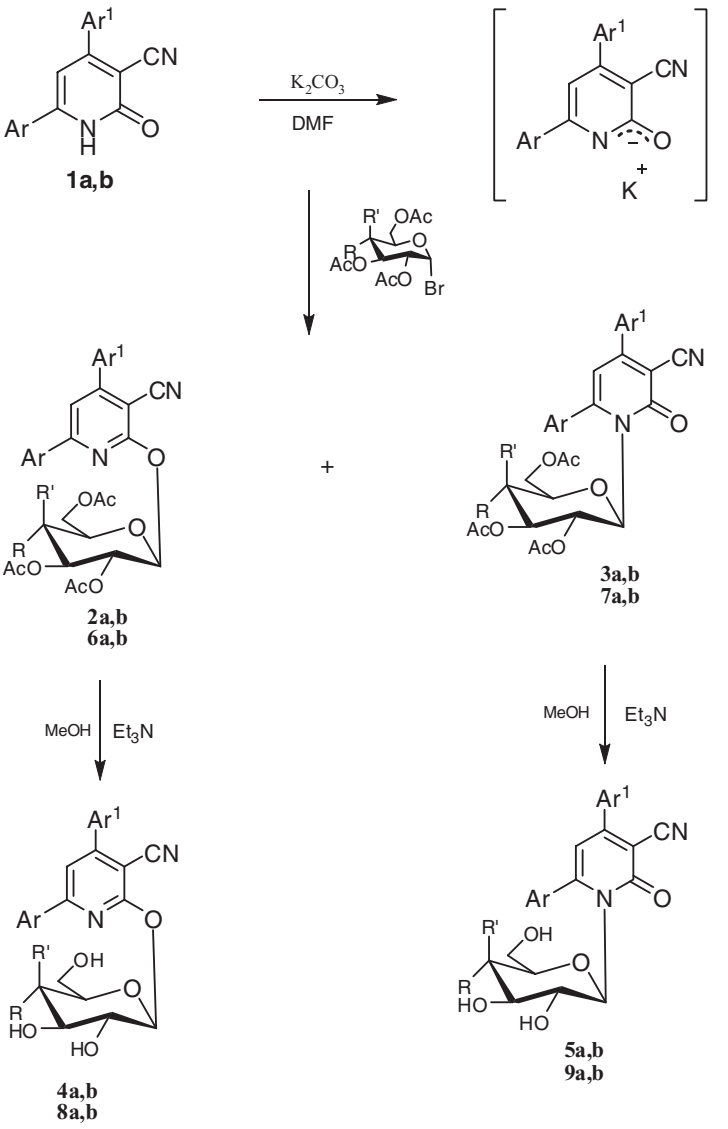


SCHEME 1 Synthesis of 2-pyridonesulfonamide derivatives.

characterized the presence of amidic carbonyl groups, and assigned the formation of *N*-glycosides, respectively, which disappeared with **2a,b** and **6a,b**. Thus, the β-configuration of compounds **2a,b, 3a,b, 6a,b,** and **7a,b** was supported by their ^{1}H and ^{13}C NMR spectra, which revealed the anomeric protons as doublets at $\delta = 6.21, 6.49, 6.20, 6.49, 6.57, 6.48, 6.35$, and 6.42 ppm with coupling constants of $J = 8.10$–8.40 Hz, respectively. The anomeric carbons were seen at $\delta = 93.79, 93.83, 91.25, 91.23, 93.90$, and 89.91 ppm, respectively, which distinguished the formation of *O*- and *N*-glycosides.

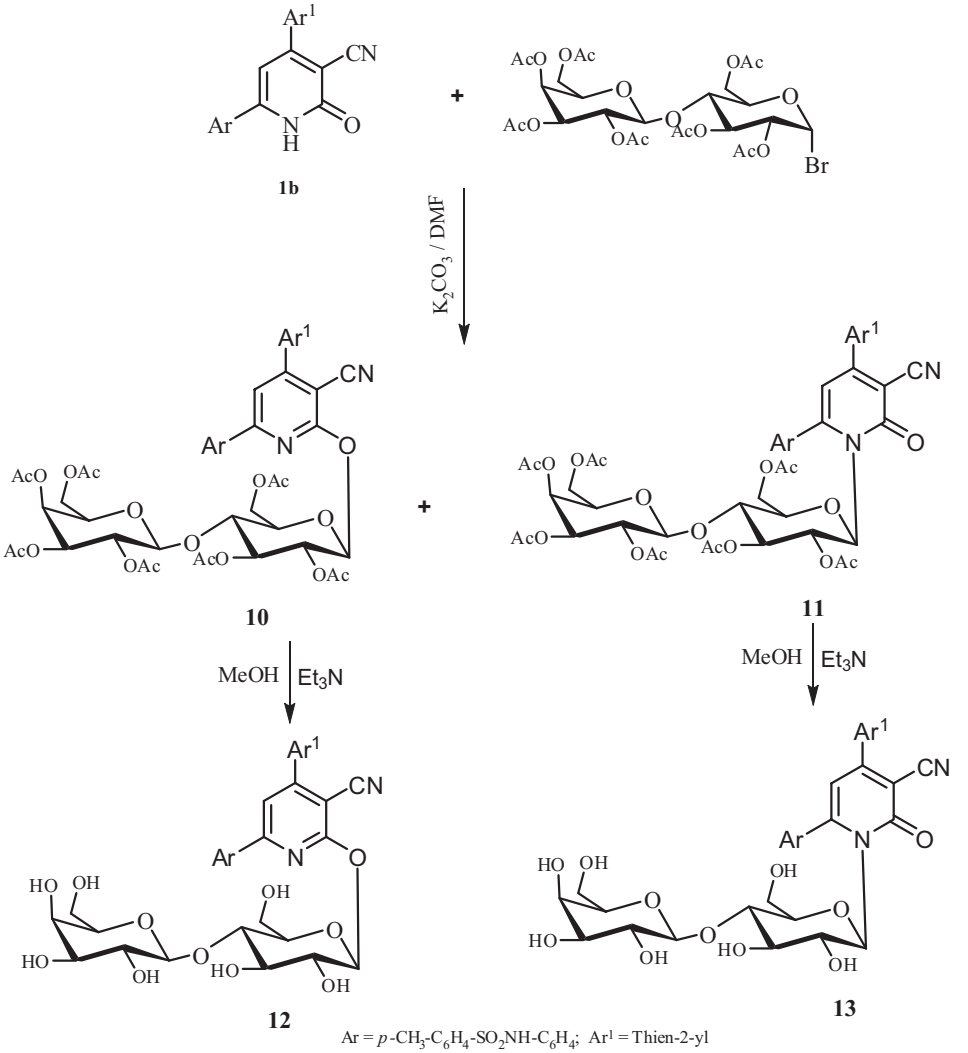
The deacetylation of *O*- and *N*-glycoside derivatives **2a,b, 3a,b, 6a,b**, and **7a,b** in the presence of TEA/MeOH and few drops of water[35,36] led to the formation of the free glycosides **4a,b, 5a,b, 8a,b**, and **9a,b**, respectively, in high yield (Scheme 2). The IR spectra of the resulting compounds exhibited broadbands at 3379–3432 cm^{-1} attributed to the hydroxyl groups. The ^{1}H NMR spectra and elemental analysis of the deacetylated compounds also confirmed the structures of the compounds.

Additionally, the reaction of *N*-(4-(5-cyano-6-oxo-4-(4-thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzensulfonamide (**1b**) with 2,3–6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-gluco-pyranosyl bromide gave the corresponding *O*- and *N*-lactoside derivatives **10** and **11**, respectively.



Comp. No.	Ar	Ar^1	R	R′
1a	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	*p*.$(CH_3)_2CH$-C_6H_4		
1b	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	Thien-2-yl		
2a, 3a	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	*p*.$(CH_3)_2CH$-C_6H_4	OAc	H
2b, 3b	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	Thien-2-yl	OAc	H
6a, 7a	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	*p*.$(CH_3)_2CH$-C_6H_4	H	OAc
6b, 7b	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	Thien-2-yl	H	OAc
4a, 5a	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	*p*.$(CH_3)_2CH$-C_6H_4	OH	H
4b, 5b	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	Thien-2-yl	OH	H
8a, 9a	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	*p*.$(CH_3)_2CH$-C_6H_4	H	OH
8b, 9b	*p*.CH_3-C_6H_4-SO_2-NH-C_6H_4	Thien-2-yl	H	OH

SCHEME 2 Glycosylation of 2-pyridonesulfonamide derivatives.



SCHEME 3 Lactosylation of 2-pyridonesulfonamide derivatives.

Deacetylation of lactosides derivatives **10** and **11** under the previous conditions gave the corresponding deprotected lactosides **12** and **13**, respectively (Scheme 3). The IR spectrum of **10** displayed bands at 2219 and 1747 cm^{-1} for the C≡N and acetoxy carbonyl groups, respectively, with the absence of the amide carbonyl group, which indicates the formation of the *O*-lactoside. In compound **11**, the presence of a band at 1642 cm^{-1} assigned the formation of *N*-lactoside, which was separated by silica gel chromatography. The ^1H NMR spectrum of compound **10** exhibited signals at $\delta = 1.90$–2.11 ppm for seven acetoxy methyl groups and a doublet at $\delta = 6.65$ ppm that was characteristic for the anomeric proton with $J = 8.72$ Hz,

thus confirming the diaxial orientation (β-configuration) of compound **10**. Its ^{13}C NMR spectrum showed the anomeric carbon at $\delta = 89.0$ ppm. The IR spectra of the deprotected lactosides **12** and **13** revealed the absence of acetoxy carbonyl groups and the presence of OH groups as broadbands at 3385 and 3391 cm^{-1}, respectively. Also, the structure of compounds confirmed by its ^1H NMR results, as well as elemental analysis (see the Experimental section).

CONCLUSION

In summary, we have described the synthesis of some *O*- and *N*-glycosides derivatives by alkylation of 2-pyridonesulfonamide with glucosyl or/galactosyl and lactosyl bromide. Some of the synthesized compounds were screened for antimicrobial activity, which showed that compounds **4b, 5a, 7b, 8a, 9a**, and **12** have significant antibacterial activity and compounds **2a, 3b, 6a**, and **10** have higher activity, while all the tested compounds have a significant antifungal activity compared with the standard drugs.

EXPERIMENTAL

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. Thin layer chromatography (TLC) was performed on Merck Silica Gel $60F_{254}$ with detection by ultraviolet light (UV) and by the charring with 10% EtOH solution of H_2SO_4. The IR spectra (KBr discs) were recorded on a Pye Unicam Sp-3–300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer (Cairo University, Cairo, Egypt). 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. The antimicrobial activities were carried in the Microbiology Department, Faculty of Pharmacy, Zagazig University. Elemental analyses were determined on a Perkin Elmer 240 (Microanalysis Center, Konstanz University, Germany).

N-(4-Acetylphenyl)-4-Methylbenzensulfonamide

A mixture of *p*-aminoacetophenone (10 mmol) and toluenesulfonyl chloride (10 mmol) in pyridine (10 mL) was heated under reflux for 2 hours. After cooling, the reaction mixture was poured into ice water, the formed product filtered off, washed with water, and recrystallized from ethanol. Yield: 93%, mp: 218–220°C. IR (KBr): 3219 cm^{-1} (NH), and 1666 cm^{-1} (C=O, acetyl). ^1H NMR (DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 3.33 (s, 3H, CH_3CO), 7.18 (d, 2H, $J = 8.40$ Hz, Ar—H), 7.35 (d, 2H, $J = 7.50$ Hz, Ar—H), 7.70 (d, 2H, $J = 8.40$ Hz, Ar—H), 7.80 (d, 2H, $J = 7.50$ Hz, Ar—H),

10.76 (s, 1H, NH). Anal. calcd for $C_{15}H_{15}NO_3S$ (289.35): C, 62.26; H, 5.23; N, 4.84. Found: C, 62.23; H, 5.24; N, 4.85.

General Procedure for Synthesis of Heterocyclic Bases (1a,b)

A mixture of *N*-(4-acetylphenyl)-4-methylbenzensulfonamide (10 m mol), ethyl cyanoacetate (10 mmol), appropriate aldehyde (10 mmol), and ammonium acetate (80 mmol) in ethanol (20 mL) was heated under reflux for 5 hours, according to the literature,[33] the formed product was filtered off and recrystallized from acetic acid.

General Procedure for Synthesis of Nucleosides

A solution of 2,3,4,6-tetra-β-D-gluco, galacto, and lactopyranosyl bromide (10 mmol) in dry DMF (10 mL) was added to a solution of compound **1a,b** (10 mmol) in dry DMF (10 mL) in the presence of anhydrous K_2CO_3 (11 mmol), the reaction mixture was stirred at room temperature and followed by TLC. The solvent was removed under reduced pressure, the residue was washed with distilled water to remove the inorganic residue, and then the formed solid product was separated by silica gel chromatography (200–400 mesh) using CH_2Cl_2/MeOH (9.9:0.1) as eluent.

General Procedure for Deacetylation

A mixture of nucleosides (10 mmol) in methanol (20 mL), triethylamine (1 mL) and few drops of water was stirred overnight at room temperature,[35,36] and then the solvent was removed under reduced pressure. The residue was crystallized from methanol.

***N*-(4-(5-Cyano-4-(4-isopropylphenyl)-6-oxo-1,6-dihydropyridin-2-yl)phe-ny)-4-methylbenzensulfonamide (1a).** Yield: 60%, as yellow crystals, mp: 320–321°C. IR (KBr): 3225 cm^{-1} (NH), 2217 cm^{-1} (C≡N), and 1657 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 1.25 (d, 6H, J = 6.9 Hz, $(CH_3)_2CH$), 2.33 (s, 3H, CH_3), 2.96 (m, 1H, $CH(CH_3)_2$), 6.78 (s, 1H, pyridone-H-5), 7.22 (d, 2H, J = 8.70 Hz, Ar—H), 7.35 (d, 2H, J = 8.40 Hz, Ar—H), 7.41 (d, 2H, J = 8.40 Hz, Ar—H), 7.62 (d, 2H, J = 8.10 Hz, Ar—H), 7.73 (d, 2H, J = 8.10 Hz, Ar—H), 7.79 (d, 2H, J = 8.70 Hz, Ar—H), 10.65 (s, 1H, NH), 12.91 (s, 1H, NH). Anal. calcd for $C_{28}H_{25}N_3O_3S$ (483.58): C, 69.54; H, 5.21; N, 8.69. Found: C, 69.56; H, 5.22; N, 8.68.

***N*-(4-(5-Cyano-6-oxo-4-(4-thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzensulfonamide (1b).** Yield: 63%, as yellow crystals, mp: 315–317°C. IR (KBr): 3231 cm^{-1} (NH), 2218 cm^{-1} (C≡N), and 1662 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3H, CH_3), 6.71 (s, 1H, pyridone-H-5), 7.07–7.65 (m, 10H, Ar—H), 7.85 (t, 1H, J = 4.50, 4.23 Hz, thiophene-H), 10.93 (s, 1H, NH), 12.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 21.4 (CH_3), 104.2, 115.5 (C≡N), 118.9, 127.2, 128.1, 129.0, 129.4, 130.3,

131.1, 132.2, 132.7, 135.6, 137.0, 137.2, 141.1, 144.1, 151.1, and 162.6 (Ar-C and C=O). Anal. calcd for $C_{23}H_{17}N_3O_3S_2$ (447.53): C, 61.73; H, 3.83; N, 9.39. Found: C, 61.71; H, 3.82; N, 9.40.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (2a).** Yield: 60%, as colorless crystals, mp: 107–109°C. IR (KBr): 3256 cm^{-1} (NH), 2223 cm^{-1} (C≡N), and 1755 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.10 (d, 6H, J = 6.9 Hz ($(C\underline{H}_3)_2CH$)), 1.85, 1.96, 1.99, and 2.03 (4s, 12H, 4 $C\underline{H}_3CO$), 2.36 (s, 3H, $C\underline{H}_3$), 2.84 (m, 1H, $C\underline{H}(CH_3)_2$), 4.15 (dd, 1H, $J_{5',6'}$ = 4.45, $J_{6',6''}$ = 11.72 Hz, H-6′), 4.25 (dd, 1H, $J_{5',6'}$ = 4.96, $J_{6',6''}$ = 11.72 Hz, H-6″), 4.91 (m, 1H, H-5′), 5.07 (t, 1H, J = 9.23 Hz, H-4′), 5.27 (t, 1H, $J_{1',2'}$ = 8.15, $J_{2',3'}$ = 9.58 Hz, H-2′), 5.49 (dd, 1H, $J_{2',3'}$ = 9.58, $J_{3',4'}$ = 9.23 Hz, H-3′), 6.21 (d, 1H, $J_{1',2'}$ = 8.15 Hz, H-1′), 6.71 (s, 1H, pyridone-H-5), 7.12 (d, 2H, J = 8.43 Hz, Ar—H), 7.22 (d, 2H, J = 8.32 Hz, Ar—H), 7.53 (d, 2H, J = 8.32 Hz, Ar—H), 7.71 (d, 2H, J = 8.17 Hz, Ar—H), 7.87 (d, 2H, J = 8.17 Hz, Ar—H), 8.13 (d, 2H, J = 8.42 Hz, Ar—H), 10.56 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 15.8 ($(\underline{C}H_3)_2CH$), 20.08, 20.11, 20.15, and 20.20 (4 $\underline{C}H_3CO$), 20.32 (CH_3), 30.4 ($\underline{C}H(CH_3)_2$), 63.25 (C-6′), 65.7 (C-4′), 66.73 (C-3′), 68.7 (C-2′), 70.48 (C-5′), 93.79 (C-1′), 115.0 (C≡N), 119.3, 127.3, 128.2, 128.6, 129.1, 129.3, 130.2, 131.4, 133.6, 136.9, 137.0, 139.5, 141.0, 152.1, 158.0, 158.6, 162.1, (Ar-C and C=N), 168.0, 169.3, 170.0, and 171.2 (4 C=O). Anal. calcd for $C_{42}H_{43}N_3O_{12}S$ (813.87): C, 61.98; H, 5.33; N, 5.16. Found: C, 62.01; H, 5.32; N, 5.19.

***N*-(4-(5-Cyano-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (2b).** Yield: 63%, as colorless crystals, mp: 101–103°C. IR (KBr): 3274 cm^{-1} (NH), 2226 cm^{-1} (C≡N), and 1735 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.96, 1.98, 2.01, and 2.05 (4s, 12H, 4 $C\underline{H}_3CO$), 2.20 (s, 3H, $C\underline{H}_3$), 3.98 (dd, 1H, $J_{5',6'}$ = 4.78, $J_{6',6''}$ = 11.53 Hz, H-6′), 4.31 (dd, 1H, $J_{5',6'}$ = 5.06, $J_{6',6''}$ = 11.53 Hz, H-6″), 5.0 (m, 1H, H-5′), 5.28 (t, 1H, J = 9.42 Hz, H-4′), 5.47 (t, 1H, $J_{1',2'}$ = 8.23, $J_{2',3'}$ = 9.12 Hz, H-2′), 5.83 (dd, 1H, $J_{2',3'}$ = 9.12, $J_{3',4'}$ = 9.41 Hz, H-3′), 6.49 (d, 1H, $J_{1',2'}$ = 8.23 Hz, H-1′), 6.89 (s, 1H, pyridone-H-5), 7.15–7.83 (m, 10H, Ar—H), 8.11 (dd, 1H, J = 4.24, 3.85 Hz, thiophene-H), 10.57 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 20.34, 20.72, 21.01, and 21.40 (4 $\underline{C}H_3CO$), 21.64 (CH_3), 69.66 (C-6′), 70.47 (C-4′), 71.83 (C-3′), 72.04 (C-2′), 72.46 (C-5′), 93.83 (C-1′), 113.4, 115.0 (C≡N), 119.3, 127.1, 128.2, 128.7, 129.0, 129.3, 130.3, 131.0, 133.6, 137.0, 139.5, 141.0, 144.0, 148.7, 156.8, 162.6 (Ar-C and C=N), 169.3, 169.8, 170.0, and 170.3, (4 C=O). Anal. calcd for $C_{37}H_{35}N_3O_{12}S_2$ (777.82): C, 57.13; H, 4.54; N, 5.40. Found: C, 57.11; H, 4.57; N, 5.38.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-oxo-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (3a).** Yield: 15%, as colorless crystals, mp: 116–118°C. IR (KBr): 3255 cm^{-1} (NH), 2223 cm^{-1} (C≡N), 1743 cm^{-1} (C=O, acetoxy), and

1642 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): $\delta = 1.10$ (d, $J = 6.9$ Hz, 6H, $(CH_3)_2CH$), 1.85, 1.95, 1.99, and 2.02 (4s, 12H, 4 CH_3CO), 2.19 (s, 3H, CH_3), 2.84 (m, 1H, $CH(CH_3)_2$), 4.14 (dd, 1H, $J_{5',6'} = 4.45$, $J_{6',6''} = 11.71$ Hz, H-6′), 4.25 (dd, 1H, $J_{5',6'} = 4.96$, $J_{6',6''} = 11.71$ Hz, H-6″), 4.91 (m, 1H, H-5′), 5.07 (t, 1H, $J = 9.22$ Hz, H-4′), 5.27 (t, 1H, $J_{1',2'} = 8.10$, $J_{2',3'} = 9.58$ Hz, H-2′), 5.49 (dd, 1H, $J_{2',3'} = 9.58$, $J_{3',4'} = 9.22$ Hz, H-3′), 6.20 (d, 1H, $J_{1',2'} = 8.10$ Hz, H-1′), 6.71 (s, 1H, pyridone-H-5), 7.12 (d, 2H, $J = 8.42$ Hz, Ar—H), 7.21 (d, 2H, $J = 8.32$ Hz, Ar—H), 7.53 (d, 2H, $J = 8.32$ Hz, Ar—H), 7.72 (d, 2H, $J = 8.16$ Hz, Ar—H), 7.87 (d, 2H, $J = 8.16$ Hz, Ar—H), 8.13 (d, 2H, $J = 8.42$ Hz, Ar—H), 10.56 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 15.78$ ($(CH_3)_2CH$), 20.07, 20.11, 20.14, and 20.18 (4 CH_3CO), 20.32 (CH_3), 30.4 ($CH(CH_3)_2$), 63.35 (C-6′), 65.7 (C-4′), 66.73 (C-3′), 68.75 (C-2′), 70.48 (C-5′), 91.25 (C-1′), 115.0 (C≡N), 119.3, 127.3, 128.2, 128.6, 129.1, 129.3, 130.2, 131.4, 133.6, 136.9, 137.0, 139.5, 141.0, 152.1, 158.1, 158.6 (Ar-C), 168.6, 169.0, 169.5, 170.0, and 171.2 (5 C=O). Anal. calcd for $C_{42}H_{43}N_3O_{12}S$ (813.87): C, 61.98; H, 5.33; N, 5.16. Found: C, 62.0; H, 5.35; N, 5.15.

***N*-(4-(5-Cyano-6-oxo-4-(thien-2-yl)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (3b).** Yield: 13%, as colorless crystals, mp: 113–115°C. IR (KBr): 3270 cm^{-1} (NH), 2224 cm^{-1} (C≡N), 1731 cm^{-1} (C=O, acetoxy), and 1660 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): $\delta = 1.98$, 1.99, 2.00, and 2.03 (4s, 12H, 4 CH_3CO), 2.20 (s, 3H, CH_3), 3.98 (dd, 1H, $J_{5',6'} = 4.77$, $J_{6',6''} = 11.53$ Hz, H-6′), 4.31 (dd, 1H, $J_{5',6'} = 5.06$, $J_{6',6''} = 11.53$ Hz, H-6″), 5.0 (m, 1H, H-5′), 5.28 (t, 1H, $J = 9.42$ Hz, H-4′), 5.47 (t, 1H, $J_{1',2'} = 8.23$, $J_{2',3'} = 9.12$ Hz, H-2′), 5.83 (dd, 1H, $J_{2',3'} = 9.12$, $J_{3',4'} = 9.41$ Hz, H-3′), 6.49 (d, 1H, $J_{1',2'} = 8.20$ Hz, H-1′), 6.89 (s, 1H, pyridone-H-5), 7.15–7.83 (m, 10H, Ar—H), 8.11 (dd, 1H, $J = 4.24$, 3.83 Hz, thiophene-H), 10.57 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 20.34$, 20.72, 21.01, and 21.40 (4 CH_3CO), 21.65 (CH_3), 69.66 (C-6′), 70.47 (C-4′), 71.83 (C-3′), 72.04 (C-2′), 72.46 (C-5′), 91.23 (C-1′), 113.4, 115.0 (C≡N), 119.3, 127.1, 128.2, 128.7, 129.0, 129.3, 130.3, 131.0, 133.6, 137.0, 139.5, 141.0, 144.0, 148.7, 156.8, (Ar-C), 168.1, 169.3, 169.8, 170.0, and 170.3 (5 C=O). Anal. calcd for $C_{37}H_{35}N_3O_{12}S_2$ (777.82): C, 57.13; H, 4.54; N, 5.40. Found: C, 57.10; H, 4.52; N, 5.39.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-(β-D-glucopyranosyloxy)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (4a).** Yield: 88%, as colorless crystals from methanol, mp: 122–125°C. IR (KBr): 3385 cm^{-1} (broad, 4OH), 3243 cm^{-1} (NH), and 2220 cm^{-1} (C≡N). ^1H NMR (DMSO-d_6/D_2O): $\delta = 1.11$ (d, $J = 6.9$ Hz 6H, $(CH_3)_2CH$), 2.19 (s, 3H, CH_3), 2.84 (m, 1H, $CH(CH_3)_2$), 3.63–3.49 (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′ and H-2′), 4.50 (t, 1H, $J = 4.02$ Hz, OH-6′, D_2O exchangeable), 4.68 (d, 1H, $J = 4.21$ Hz, OH-4′, D_2O exchangeable), 5.12 (d, 1H, $J = 5.12$ Hz, OH-3′, D_2O exchangeable), 5.29 (d, 1H, $J = 5.36$ Hz, OH-2′, D_2O exchangeable), 6.18 (d, 1H, $J_{1',2'} = 8.18$ Hz, H-1′), 7.02 (s, 1H, pyridone-H-5), 7.12 (d, 2H, $J =$

8.42 Hz, Ar—H), 7.21 (d, 2H, $J = 8.32$ Hz, Ar—H), 7.53 (d, 2H, $J = 8.32$ Hz, Ar—H), 7.72 (d, 2H, $J = 8.16$ Hz, Ar—H), 7.87 (d, 2H, $J = 8.16$ Hz, Ar—H), 8.13 (d, 2H, $J = 8.42$ Hz, Ar—H). Anal. calcd for $C_{34}H_{35}N_3O_8S$ (645.72): C, 63.24; H, 5.46; N, 6.51. Found: C, 63.22; H, 5.47; N, 6.49.

***N*-(4-(5-Cyano-6-(β-D-glucopyranosyloxy)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (4b).** Yield: 87%, as colorless crystals from methanol, mp: 120–123°C. IR (KBr): 3379 cm^{-1} (broad, 4OH), 3259 cm^{-1} (NH), and 2221 cm^{-1} (C≡N). ^1H NMR (DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 3.65–3.48 (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′ and H-2′), 4.60 (t, 1H, $J = 3.46$ Hz, OH-6′, D_2O exchangeable), 5.09 (d, 1H, J = 4.31 Hz, OH-4′, D_2O exchangeable), 5.16 (d, 1H, $J = 4.28$ Hz, OH-3′, D_2O exchangeable), 5.39 (d, 1H, $J = 4.85$ Hz, OH-2′, D_2O exchangeable), 6.08 (d, 1H, $J_{1',2'} = 8.16$ Hz, H-1′), 7.01 (s, 1H, pyridone-H-5), 7.21–7.97 (m, 10H, Ar—H), 8.10 (dd, 1H, J = 5.06, 4.43 Hz, thiophene-H), 10.25 (s, 1H, NH, D_2O exchangeable). Anal. calcd for $C_{29}H_{27}N_3O_8S_2$ (609.67): C, 57.13; H, 4.46; N, 6.89. Found: C, 57.15; H, 4.45; N, 6.92.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-oxo-1-(β-D-glucopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (5a).** Yield: 89%, as colorless crystals from methanol, mp: 130–132°C. IR (KBr): 3384 cm^{-1} (broad, 4OH), 3243 cm^{-1} (NH), 2222 cm^{-1} (C≡N), and 1644 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): $\delta = 1.12$ (d, 6H, $J = 6.9$ Hz (CH_3)$_2$CH), 2.20 (s, 3H, CH_3), 2.87 (m, 1H, $CH(CH_3)_2$), 3.35–3.40 (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′ and H-2′), 4.46 (t, 1H, $J = 4.01$ Hz, OH-6′, D_2O exchangeable), 4.70 (d, 1H, $J = 4.22$ Hz, OH-4′, D_2O exchangeable), 5.02 (d, 1H, $J = 5.12$ Hz, OH-3′, D_2O exchangeable), 5.11 (d, 1H, $J = 5.34$ Hz, OH-2′, D_2O exchangeable), 6.12 (d, 1H, $J_{1',2'} = 8.12$ Hz, H-1′), 6.88 (s, 1H, pyridone-H-5), 7.28 (d, 2H, $J = 7.8$ Hz, Ar—H), 7.33 (d, 2H, $J = 8.4$ Hz, Ar—H), 7.41 (d, 2H, $J = 8.4$ Hz, Ar—H), 7.69 (d, 2H, $J = 8.10$ Hz, Ar—H), 7.84 (d, 2H, $J = 8.10$ Hz, Ar—H), 8.24 (d, 2H, $J = 7.8$ Hz, Ar—H), 10.75 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): $\delta = 15.7$ ((CH_3)$_2$CH), 21.43 (CH_3), 33.80 ($CH(CH_3)_2$), 61.1 (C-6′), 68.0 (C-2′), 70.1 (C-3′), 77.0 (C-4′), 78.3 (C-5′), 93.19 (C-1′), 115.4 (C≡N), 119.4, 127.1, 127.3, 128.6, 129.0, 130.0, 133.1, 133.9, 1351, 137.4, 141.0, 142.1, 145.3, 145.8, 155.1, 155.4, and 169.3 (Ar-C and C=O amide). Anal. calcd for $C_{34}H_{35}N_3O_8S$ (645.72): C, 63.24; H, 5.46; N, 6.51. Found: C, 63.23; H, 5.44; N, 6.54.

***N*-(4-(5-Cyano-6-oxo-4-(thien-2-yl)-1-(β-D-glucopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (5b).** Yield: 85%, as colorless crystals from methanol, mp: 127–129°C. IR (KBr): 3427 cm^{-1} (broad, 4OH), 3260 cm^{-1} (NH) and 2218 cm^{-1} (C≡N), and 1655 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): $\delta = 2.31$ (s, 3H, CH_3), 3.64–3.50 (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′ and H-2′), 4.60 (t, 1H, $J = 3.46$ Hz, OH-6′, D_2O exchangeable), 5.09 (d, 1H, $J = 4.31$ Hz, OH-4′, D_2O exchangeable), 5.16 (d, 1H, $J = 4.28$ Hz, OH-3′, D_2O exchangeable), 5.39 (d, 1H, $J = 4.85$ Hz,

OH-2′, D_2O exchangeable), 6.18 (d, 1H, $J_{1',2'}$ = 8.20 Hz, H-1′), 7.01 (s, 1H, pyridone-H-5), 7.20–7.98 (m, 10H, Ar—H), 8.10 (dd, 1H, J = 5.06, 4.43 Hz, thiophene-H), 10.23 (s, 1H, NH, D_2O exchangeable). Anal. calcd for $C_{29}H_{27}N_3O_8S_2$ (609.67): C, 57.13; H, 4.46; N, 6.89. Found: C, 57.16; H, 4.43; N, 6.90.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyloxy)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (6a).** Yield: 59%, as colorless crystals, mp: 113–115°C. IR (KBr): 3261 cm^{-1} (NH), 2226 cm^{-1} (C≡N), and 1755 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.21 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$), 1.99, 2.00, 2.02, and 2.03 (4s, 12H, 4 CH_3CO), 2.31 (s, 3H, CH_3), 2.96 (m, 1H, $CH(CH_3)_2$), 4.03 (dd, 1H, $J_{5',6'}$ = 6.12, $J_{6',6''}$ = 11.56 Hz, H-6′), 4.15 (dd, 1H, $J_{5',6''}$ = 6.29, $J_{6',6''}$ = 11.56 Hz, H-6″), 4.68 (m, 1H, H-5′), 5.37 (t, 1H, $J_{3',2'}$ = 10.50, $J_{3',4'}$ = 2.84 Hz, H-3′), 5.43 (t, 1H, $J_{2',1'}$ = 8.40, $J_{2',3'}$ = 10.50 Hz, H-2′), 5.52 (t, 1H, $J_{4',3'}$ = 2.85, $J_{4',5'}$ = 3.30 Hz, H-4′), 6.57 (d, 1H, $J_{1',2'}$ = 8.40 Hz, H-1′), 6.87 (s, 1H, pyridone-H-5), 7.26 (d, 2H, J = 7.8 Hz, Ar—H), 7.32 (d, 2H, J = 8.4 Hz, Ar—H), 7.42 (d, 2H, J = 8.4 Hz, Ar—H), 7.68 (d, 2H, J = 8.10 Hz, Ar—H), 7.85 (d, 2H, J = 8.10 Hz, Ar—H), 8.24 (d, 2H, J = 7.8 Hz, Ar—H), 10.72 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 15.8 ($(CH_3)_2CH$), 20.15, 20.36, 20.93, and 21.0 (4 CH_3CO), 23.64 (CH_3), 33.36 ($CH(CH_3)_2$), 61.8 (C-6′), 67.6 (C-4′), 70.2 (C-2′), 71.2 (C-3′), 71.8 (C-5′), 93.9 (C-1′), 114.9 (C≡N), 118.8, 126.6, 126.8, 128.6, 128.7, 129.7, 1311, 133.1, 136.5, 137.0 140.5, 142.2, 143.5, 150.7, 156.1, 156.6, 161.7 (Ar-C and C=N), 168.7, 169.5, 169.7, and 170.0 (4 C=O). Anal. calcd for $C_{42}H_{43}N_3O_{12}S$ (813.87): C, 61.98; H, 5.33; N, 5.16. Found: C, 61.95; H, 5.31; N, 5.18.

***N*-(4-(5-Cyano-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyloxy)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (6b).** Yield: 62%, as colorless crystals, mp: 109–111°C. IR (KBr): 3267 cm^{-1} (NH), 2218 cm^{-1} (C≡N), and 1738 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.98, 2.01, 2.03, and 2.05 (4s, 12H, 4 CH_3CO), 2.32 (s, 3H, CH_3), 4.02 (dd, 1H, $J_{5',6'}$ = 6.12, $J_{6',6''}$ = 11.57 Hz, H-6′), 4.13 (dd, 1H, $J_{5',6'}$ = 6.29, $J_{6',6''}$ = 11.57 Hz, H-6″), 4.68 (m, 1H, H-5′), 5.36 (t, 1H, $J_{3',2'}$ = 10.50, $J_{3',4'}$ = 2.84 Hz, H-3′), 5.43 (t, 1H, $J_{2',1'}$ = 8.40, $J_{2',3'}$ = 10.50 Hz, H-2′), 5.53 (t, 1H, $J_{4',3'}$ = 2.85, $J_{4',5'}$ = 3.30 Hz, H-4′), 6.48 (d, 1H, $J_{1',2'}$ = 8.40 Hz, H-1′), 6.88 (s, 1H, pyridone-H-5), 7.30–7.90 (m, 10H, Ar—H), 8.24 (dd, 1H, J = 4.24, 3.85 Hz, thiophene-H), 10.65 (s, 1H, NH). Anal. calcd for $C_{37}H_{35}N_3O_{12}S_2$ (777.82): C, 57.13; H, 4.54; N, 5.40. Found: C, 57.11; H, 4.53; N, 5.43.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-oxo-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (7a).** Yield: 16%, as colorless crystals, mp: 119–121°C. IR (KBr): 3260 cm^{-1} (NH), 2226 cm^{-1} (C≡N), 1755 cm^{-1} (C=O, acetoxy), and 1699 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): δ = 1.21 (d, J = 6.9 Hz,

6H, ((C$\underline{H}_3$)$_2$CH), 1.99, 2.0, 2.02, and 2.03 (4s, 12H, 4 C$\underline{H}_3$CO), 2.31 (s, 3H, C$\underline{H}_3$), 2.96 (m, 1H, C$\underline{H}$(CH$_3$)$_2$), 4.03 (dd, 1H, $J_{5',6'} = 6.12$, $J_{6',6''} = 11.56$ Hz, H-6′), 4.15 (dd, 1H, $J_{5',6''} = 6.30$, $J_{6',6''} = 11.56$ Hz, H-6″), 4.68 (m, 1H, H-5′), 5.37 (t, 1H, $J_{3',2'} = 10.48$, $J_{3',4'} = 2.85$ Hz, H-3′), 5.43 (t, 1H, $J_{2',1'} = 8.23$, $J_{2',3'} = 10.48$ Hz, H-2′), 5.52 (t, 1H, $J_{4',3'} = 2.85$, $J_{4',5'} = 3.30$ Hz, H-4′), 6.35 (d, 1H, $J_{1',2'} = 8.23$ Hz, H-1′), 6.87 (s, 1H, pyridone-H-5), 7.26 (d, 2H, $J =$ 7.8 Hz, Ar—H), 7.32 (d, 2H, $J = 8.4$ Hz, Ar—H), 7.42 (d, 2H, $J = 8.4$ Hz, Ar—H), 7.68 (d, 2H, $J = 8.10$ Hz, Ar—H), 7.85 (d, 2H, $J = 8.10$ Hz, Ar—H), 8.24 (d, 2H, $J = 7.8$ Hz, Ar—H), 10.72 (s, 1H, NH). ^{13}C NMR (DMSO-d$_6$): $\delta = 15.8$ ((C$\underline{H}_3$)$_2$CH), 20.15, 20.36, 20.93, and 21.0 (4 C$\underline{H}_3$CO), 23.64 (CH$_3$), 33.36 (C$\underline{H}$(CH$_3$)$_2$), 61.8 (C-6′), 67.6 (C-4′), 70.2 (C-2′), 71.2 (C-3′), 71.8 (C-5′), 89.91 (C-1′), 114.8 (C≡N), 118.8, 126.6, 126.8, 128.6, 128.7, 129.7, 131.1, 133.1, 136.5, 137.0 140.5, 142.2, 143.5, 150.7, 156.1, and 156.6 (Ar-C), 168.2, 169.0, 169.5, 169.7, and 170.0 (5 C=O). Anal. calcd for $C_{42}H_{43}N_3O_{12}S$ (813.87): C, 61.98; H, 5.33; N, 5.16. Found: C, 61.97; H, 5.30; N, 5.15.

***N*-(4-(5-Cyano-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (7b).** Yield: 12%, as colorless crystals, mp: 118–120°C. IR (KBr): 3262 cm^{-1} (NH), 2218 cm^{-1} (C≡N), and 1748 cm^{-1} (C=O, acetoxy) and 1685 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d$_6$): $\delta = 1.98$, 2.02, 2.03, and 2.04 (4s, 12H, 4 C$\underline{H}_3$CO), 2.31 (s, 3H, C$\underline{H}_3$), 4.03 (dd, 1H, $J_{5',6'} = 6.12$, $J_{6',6''} = 11.56$ Hz, H-6′), 4.14 (dd, 1H, $J_{5',6'} = 6.30$, $J_{6',6''} = 11.56$ Hz, H-6″), 4.67 (m, 1H, H-5′), 5.38 (t, 1H, $J_{3',2'} = 10.49$, $J_{3',4'} = 2.85$ Hz, H-3′), 5.44 (t, 1H, $J_{2',1'} = 8.38$, $J_{2',3'} = 10.49$ Hz, H-2′), 5.51 (t, 1H, $J_{4',3'} = 2.85$, $J_{4',5'} = 3.30$ Hz, H-4′), 6.42 (d, 1H, $J_{1',2'} = 8.38$ Hz, H-1′), 6.89 (s, 1H, pyridone-H-5), 7.23–7.89 (m, 10H, Ar—H), 8.25 (dd, 1H, $J =$, 3.85, 3.39 Hz, thiophene-H), 10.68 (s, 1H, NH). Anal. calcd for $C_{37}H_{35}N_3O_{12}S_2$ (777.82): C, 57.13; H, 4.54; N, 5.40. Found: C, 57.10; H, 4.55; N, 5.42.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-(β-D-galactopyranosyloxy)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (8a).** Yield: 86%, as colorless crystals from methanol, mp: 124–126°C. IR (KBr): 3419 cm^{-1} (broad, 4OH), 3240 cm^{-1} (NH), and 2224 cm^{-1} (C≡N). ^{1}H NMR (DMSO-d$_6$): $\delta = 1.24$ (d, $J = 6.9$ Hz, 6H, ((C$\underline{H}_3$)$_2$CH), 2.32 (s, 3H, C$\underline{H}_3$), 2.98 (m, 1H, C$\underline{H}$(CH$_3$)$_2$), 3.67 (m, 3H, H-3′, H-6′, and H-6″), 3.73 (m, 3H, H-2′, H-4′, and H-5′), 4.61 (m, 2H, OH-4′, OH-6′, D$_2$O exchangeable), 4.90 (d, 1H, $J = 5.21$ Hz, OH-3′, D$_2$O exchangeable), 5.28 (d, 1H, $J = 4.48$ Hz, OH-2′, D$_2$O exchangeable), 6.06 (d, 1H, $J_{1',2'} = 8.32$ Hz, H-1′), 6.92 (s, 1H, pyridone-H-5), 7.19 (d, 2H, $J = 7.89$ Hz, Ar—H), 7.27 (d, 2H, $J =$ 8.34 Hz, Ar—H), 7.34 (d, 2H, $J = 8.34$ Hz, Ar—H), 7.60 (d, 2H, $J = 8.12$ Hz, Ar—H), 7.65 (d, 2H, $J = 8.12$ Hz, Ar—H), 8.11 (d, 2H, $J = 7.89$ Hz, Ar—H), 10.64 (s, 1H, NH, D$_2$O exchangeable). Anal. calcd for $C_{34}H_{35}N_3O_8S$ (645.72): C, 63.24; H, 5.46; N, 6.51. Found: C, 63.22; H, 5.45; N, 6.48.

***N*-(4-(5-Cyano-6-(β-D-galactopyranosyloxy)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (8b).** Yield: 87%, as colorless crystals from methanol, mp: 125–127°C. IR (KBr): 3420 cm^{-1} (broad, 4OH), 3245 cm^{-1} (NH), and 2219 cm^{-1} (C≡N). ^1H NMR (DMSO-d_6/D_2O): δ = 2.31 (s, 3H, $C\underline{H}_3$) 3.65 (m, 3H, H-3′, H-6′, and H-6″), 3.80 (m, 3H, H-2′, H-4′, and H-5′), 6.27 (d, 1H, $J_{1',2'}$ = 8.23 Hz, H-1′), 6.85 (s, 1H, pyridone-H-5), 7.26–7.91 (m, 10H, Ar—H), 8.24 (dd, 1H, J = 5.08, 3.83 Hz, thiophene-H). Anal. calcd for $C_{29}H_{27}N_3O_8S_2$ (609.67): C, 57.13; H, 4.46; N, 6.89. Found: C, 57.12; H, 4.45; N, 6.87.

***N*-(4-(5-Cyano-4-(isopropylphenyl)-6-oxo-1-(β-D-galactopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (9a).** Yield: 88%, as colorless crystals from methanol, mp: 132–134 °C. IR (KBr): 3391 cm^{-1} (broad, 4OH), 3240 cm^{-1} (NH), and 2225 cm^{-1} (C≡N), 1646 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6/D_2O): δ = 1.23 (d, J = 6.9 Hz, 6H, $((C\underline{H}_3)_2CH)$), 2.32 (s, 3H, $C\underline{H}_3$), 2.98 (m, 1H, $C\underline{H}(CH_3)_2$), 3.68 (m, 3H, H-3′, H-6′, and H-6″), 3.79 (m, 3H, H-2′, H-4′, and H-5′), 6.03 (d, 1H, $J_{1',2'}$ = 8.20 Hz, H-1′), 6.90 (s, 1H, pyridone-H-5), 7.18 (d, 2H, J = 7.89 Hz, Ar—H), 7.27 (d, 2H, J = 8.34 Hz, Ar—H), 7.32 (d, 2H, J = 8.34 Hz, Ar—H), 7.61 (d, 2H, J = 8.12 Hz, Ar—H), 7.66 (d, 2H, J = 8.12 Hz, Ar—H), 8.12 (d, 2H, J = 7.89 Hz, Ar—H). Anal. calcd for $C_{34}H_{35}N_3O_8S$ (645.72): C, 63.24; H, 5.46; N, 6.51. Found: C, 63.22; H, 5.47; N, 6.53.

***N*-(4-(5-Cyano-6-oxo-4-(thien-2-yl)-1-(β-D-galactopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (9b).** Yield: 89%, as colorless crystals from methanol, mp: 130–132°C. IR (KBr): 3432 cm^{-1} (broad, 4OH), 3240 cm^{-1} (NH), and 2221 cm^{-1} (C≡N), 1665 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6/D_2O): δ = 2.32 (s, 3H, $C\underline{H}_3$) 3.67 (m, 3H, H-3′, H-6′, and H-6″), 3.81 (m, 3H, H-2′, H-4′, and H-5′), 6.28 (d, 1H, $J_{1',2'}$ = 8.20 Hz, H-1′), 6.82 (s, 1H, pyridone-H-5), 7.23–7.89 (m, 10H, Ar—H), 8.23 (dd, 1H, J = 5.08, 3.83 Hz,thiophene-H). Anal. calcd for $C_{29}H_{27}N_3O_8S_2$ (609.67): C, 57.13; H, 4.46; N, 6.89. Found: C, 57.10; H, 4.44; N, 6.92.

***N*-(4-(5-Cyano-6-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl-(*1→4*)-(2′,3′,6′-tri-*O*-acetyl-β-D-glucopyranosyloxy)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (10).** Yield: 52%, as colorless crystals, mp: 124–126°C. IR (KBr): 3249 cm^{-1} (NH), 2219 cm^{-1} (C≡N), and 1747 cm^{-1} (C=O, acetoxy). ^1H NMR (DMSO-d_6): δ = 1.90, 1.91, 1.96, 2.00, 2.02, 2.04, and 2.11 (7s, 21H, 7 $C\underline{H}_3CO$), 2.32 (s, 3H, $C\underline{H}_3$), 3.98–4.06 (m, 3H, H-2′b, H-6′a, H-6′b), 4.89 (dd, 1H, $J_{6''a,6'a}$ = 11.87, $J_{6''a,5'a}$ = 5.52 Hz, H-6″a), 4.90 (m, 1H, H-5′b), 4.92 (dd, 1H, $J_{6''b,5'b}$ = 6.46 Hz, H-6″b), 4.93 (m, 1H, H-5′a), 5.24 (d, 1H, $J_{1'b,2'b}$ = 7.65 Hz, H-1′b), 5.25 (dd, 1H, $J_{4'b,3'b}$ = 3.23, $J_{4'b,5'b}$ = 3.98 Hz, H-4′b), 5.26 (dd, 1H, $J_{2'a,1'a}$ = 8.72, $J_{2'a,3'a}$ = 8.40 Hz, H-2′a), 5.33 (dd, 1H, $J_{4'a,3'a}$ = 9.13, $J_{4'a,5'a}$ = 9.90 Hz, H-4′a), 5.40 (dd, 1H, $J_{3'b,4'b}$ = 3.23, $J_{3'b,2'b}$ = 8.87 Hz, H-3′b), 5.62 (dd, 1H, $J_{3'a,2'a}$ = 8.40, $J_{3'a,4'a}$ = 9.13 Hz, H-3′a), 6.65 (d, 1H, $J_{1'a,2'a}$ = 8.72 Hz, H-1′a), 6.95 (s, 1H,

pyridone-H-5), 7.23–7.90 (m, 10H, Ar—H), 8.23 (dd, 1H, J = 5.08, 3.93 Hz, thiophene-H), 10.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 20.1, 20.41, 20.45, 20.49, 20.57, 20.95, and 21.01 (7 $\underline{C}H_3CO$), 30.29 ($\underline{C}H_3$), 60.8 (C-6′b), 62.1 (C-6′a), 66.2 (C-4′b), 68.2 (C-2′b), 68.5 (C-2′a), 69.6 (C-5′b), 70.1 (C-3′b), 70.3 (C-3′a), 70.8 (C-4′a), 72.2 (C-5′a), 89.4 (C-1′b), 94.1 (C-1′a). 112.8, 114.7 (C≡N), 118.7, 126.7, 128.6, 128.9, 129.8, 130.5, 130.7, 131.1, 133.0, 136.3, 136.5, 140.5, 143.5, 148.2, 156.3, and 162.2 (Ar-C and C=N), 169.1, 169.3, 169.6, 170.0, 170.4, 172.3, and 172.7 (7 C=O). Anal. calcd for $C_{49}H_{51}N_3O_{20}S_2$ (1066.07): C, 55.21; H, 4.82; N, 3.94. Found: C, 55.18; H, 4.85; N, 3.92.

***N*-(4-(5-Cyano-6-oxo-4-(thien-2-yl)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galacto pyranosyl-(*1→4*)-(2′,3′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)-1,6-dihydropyri din-2-yl)phenyl)-4-methylbenzenesulfonamide (11).** Yield: 11%, as colorless crystals, mp: 133–135°C. IR (KBr): 3249 cm^{-1} (NH), 2223 cm^{-1} (C≡N), 1743 cm^{-1} (C=O, acetoxy), and 1642 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 1.90, 1.91, 1.96, 2.00, 2.02, 2.04, and 2.11 (7s, 21H, 7 CH_3CO), 2.32 (s, 3H, CH_3), 3.98–4.06 (m, 3H, H-2′b, H-6′a, H-6′b), 4.89 (dd, 1H, $J_{6''a,6'a}$ = 11.87, $J_{6''a,5'a}$ = 5.52 Hz, H-6″a), 4.90 (m, 1H, H-5′b), 4.92 (dd, 1H, $J_{6''b,5'b}$ = 6.46 Hz, H-6″b), 4.93 (m, 1H, H-5′a), 5.24 (d, 1H, $J_{1'b,2'b}$ = 7.65 Hz, H-1′b), 5.25 (dd, 1H, $J_{4'b,3'b}$ = 3.23, $J_{4'b,5'b}$ = 3.98 Hz, H-4′b), 5.26 (dd, 1H, $J_{2'a,1'a}$ = 8.72, $J_{2'a,3'a}$ = 8.40 Hz, H-2′a), 5.33 (dd, 1H, $J_{4'a,3'a}$ = 9.13, $J_{4'a,5'a}$ = 9.90 Hz, H-4′a), 5.40 (dd, 1H, $J_{3'b,4'b}$ = 3.23, $J_{3'b,2'b}$ = 8.87 Hz, H-3′b), 5.62 (dd, 1H, $J_{3'a,2'a}$ = 8.40, $J_{3'a,4'a}$ = 9.13 Hz, H-3′a), 6.65 (d, 1H, $J_{1'a,2'a}$ = 8.72 Hz, H-1′a), 6.95 (s, 1H, pyridone-H-5), 7.23–7.90 (m, 10H, Ar—H), 8.23 (dd, 1H, J = 5.08, 3.93 Hz, thiophene-H), 10.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 20.1, 20.41, 20.45, 20.49, 20.57, 20.95, and 21.01 (7 $\underline{C}H_3CO$), 30.29 ($\underline{C}H_3$), 60.8 (C-6′b), 62.1 (C-6′a), 66.2 (C-4′b), 68.2 (C-2′b), 68.5 (C-2′a), 69.6 (C-5′b), 70.1 (C-3′b), 70.3 (C-3′a), 70.8 (C-4′a), 72.2 (C-5′a), 80.9 (C-1′a), 89.0 (C-1′b). 112.8, 114.7 (C≡N), 118.7, 126.7, 128.6, 128.9, 129.8, 130.5, 130.7, 131.1, 133.0, 136.3, 136.5, 140.5, 143.5, 148.2, and 156.3 (Ar-C and C=N), 167.8, 169.1, 169.3, 169.6, 170.0, 170.4, 172.3, and 172.7 (8 C=O). Anal. calcd for $C_{49}H_{51}N_3O_{20}S_2$ (1066.07): C, 55.21; H, 4.82; N, 3.94. Found: C, 55.19; H, 4.83; N, 3.92.

***N*-(4-(5-Cyano-6-(β-D-galactopyranosyl-*(1→4)*-(β-D-glucopyranosyloxy)-4-(thien-2-yl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (12).** Yield: 88%, as colorless crystals from methanol, mp: 143–145°C. IR (KBr): 3385 cm^{-1} (7 OH), 3242 cm^{-1} (NH), and 2220 cm^{-1} (C≡N). ^{1}H NMR (DMSO-d_6/D_2O): δ = 2.12 (s, 3H, CH_3), 3.50–3.65 (4 m, 12H, H-2′b, H-3′b, H-4′b, H-5′b, H-6′b, H-6″b, H-2′a, H-3′a, H-4′a, H-5′a, H-6′a, and H-6″a), 5.67 (d, 1H, $J_{1'b,2'b}$ = 7.85 Hz, H-1′b), 5.97 (d, 1H, $J_{1'a,2'a}$ = 8.86 Hz, H-1′a), 6.98 (s, 1H, pyridone-H-5), 7.10–7.84 (m, 10H, Ar—H), 8.11 (dd, 1H, J = 5.23, 4.21 Hz, thiophene-H). Anal. calcd for $C_{35}H_{37}N_3O_{13}S_2$ (771.81): C, 54.47; H, 4.83; N, 5.44. Found: C, 54.48; H, 4.84; N, 5.45.

***N*-(4-(5-Cyano-6-oxo-4-(thien-2-yl)-1-(β-D-galactopyranosyl-(1→4)-(β-D-glucopyranosyl)-1,6-dihydropyridin-2-yl)phenyl)-4-methylbenzenesulfonamide (13).** Yield: 86%, as colorless crystals from methanol, mp: 152–154°C. IR (KBr): 3391 cm^{-1} (7 OH), 3238 cm^{-1} (NH), 2225 cm^{-1} (C≡N), and 1646 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6/D_2O): δ = 2.12 (s, 3H, CH_3), 3.50–3.65 (4 m, 12H, H-2′b, H-3′b, H-4′b, H-5′b, H-6′b, H-6″b, H-2′a, H-3′a, H-4′a, H-5′a, H-6′a, and H-6″a), 5.67 (d, 1H, $J_{1'b,2'b}$ = 7.85 Hz, H-1′b), 5.88 (d, 1H, $J_{1'a,2'a}$ = 8.83 Hz, H-1′a), 6.98 (s, 1H, pyridone-H-5), 7.10–7.84 (m, 10H, Ar—H), 8.11 (dd, 1H, J = 5.23, 4.21 Hz, thiophene-H). Anal. calcd for $C_{35}H_{37}N_3O_{13}S_2$ (771.81): C, 54.47; H, 4.83; N, 5.44. Found: C, 54.49; H, 4.85; N, 5.43.

Biological Activity

The antimicrobial activity of the synthetic compounds were evaluated against fungi, namely (*Aspergillus niger* and *Candida albicans*) and antibacterial, namely (*Staphylococcus aureus* and *Staphylococcus epidermidis*) (Gram +ve) and (*Escherichia Coli, Klebsiella Pneumoniae* and *Pseudomonas aeruginosa*) (Gram –ve) as stock cultures in the Microbiology Department, Faculty of Pharmacy, Zagazig Univesity using the well diffusion method.[37] After seeding of the cooled-solid medium by the microbial suspension and pouring in sterile plates, the cultures were incubated overnight for pre-germination, and then 300 μg of each tested compound was pipette to the wells of the plate cultures. Blanks of dissolving solvent were made. The cultures were incubated for 7 days at 30°C for fungal growth and for 2 days at 37°C for bacterial growth. The antimicrobial activity was expressed by the diameter of

TABLE 1 Antibacterial activities of some new synthesized compounds

	Inhibition zone (mm)				
	Gram (+ve)		Gram (−ve)		
Comp. No.	*S. aureus* ***ATCC6538***	*S. epidermidis* ***ATCC12228***	*E. coli* ***ATCC10536***	*K. pneumoniae* ***ATCC27736***	*P. aeruginosa* ***ATCC9022***
2a	18	18	17	17	16
3b	19	20	18	18	16
4b	21	20	16	20	17
5a	22	22	18	21	17
6a	19	18	17	17	17
7b	21	20	17	20	17
8a	22	22	19	19	17
9a	21	22	18	16	17
10	19	19	18	19	16
12	20	19	18	16	18
Amoxycillin (300 μg/mL)	20	19	16	15	15

TABLE 2 Antifungal activities of some new synthesized compounds

Inhibition zone (mm)		
	Fungi	
Comp. No.	*C. albicans* ***ATCC10231***	*A. niger* ***ATCC 16404***
2a	20	18
3b	18	18
4b	20	21
5a	18	21
6a	20	21
7b	21	19
8a	19	20
9a	20	20
10	17	19
12	18	20
Amphotericin B (300 μg/mL)	16	14

inhibitory zone comparing to amoxycillin and amphotericin B as standard antibacterial and antifungal agents, respectively.

Antimicrobial Activity

It clearly observed from the obtained data in Table 1, the tested compounds **4b, 5a**, **7b, 8a, 9a**, and **12** showed significant antibacterial activity against Gram (+ve) (*S. aureus* and *S. epidermidis*) and significant antibacterial activity against (*E. coli, K. Pneumoniae*, and *P. aeruginosa*) as Gram (−ve) using the well diffusion method[38] compared with amoxycillin as standard. Compounds **2a, 3b, 6a**, and **10** were showed higher activity against Gram (+ve) and Gram (−ve) compared with Amoxycillin. For antifungal activity, in Table 2, it was observed that all the tested compounds have a significant antifungal activity against (*A. niger*) and (*C. albicans*) than the standard drug Amphotericin B.

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