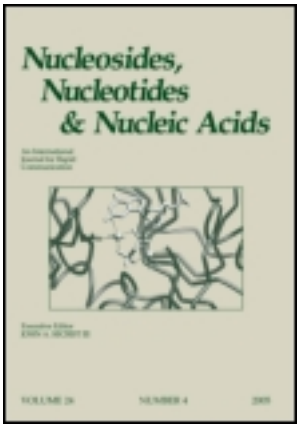


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

Microwave-Assisted Synthesis of 2(1H)-Pyridones and Their Glucosides as Cell Proliferation Inhibitors

Shaikha S. Al-Neyadi [a] , Ahmed H. Hassan [b] & Ibrahim M. Abdou [a]

[a] Department of Chemistry, Faculty of Science , United Arab Emirates University , Al-Ain , United Arab Emirates

[b] Department of Biochemistry, Faculty of Medicine & Health Science , United Arab Emirates University , Al-Ain , United Arab Emirates

Published online: 24 Feb 2011.

To cite this article: Shaikha S. Al-Neyadi , Ahmed H. Hassan & Ibrahim M. Abdou (2011) Microwave-Assisted Synthesis of 2(1H)-Pyridones and Their Glucosides as Cell Proliferation Inhibitors, Nucleosides, Nucleotides and Nucleic Acids, 30:2, 120-134, DOI: 10.1080/15257770.2010.551646

To link to this article: http://dx.doi.org/10.1080/15257770.2010.551646

Nucleosides, Nucleotides and Nucleic Acids, 30:120–134, 2011

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770.2010.551646

MICROWAVE-ASSISTED SYNTHESIS OF 2(1*H*)-PYRIDONES AND THEIR GLUCOSIDES AS CELL PROLIFERATION INHIBITORS

Shaikha S. Al-Neyadi,[1] Ahmed H. Hassan,[2] and Ibrahim M. Abdou[1]
[1]*Department of Chemistry, Faculty of Science, United Arab Emirates University, Al-Ain, United Arab Emirates*
[2]*Department of Biochemistry, Faculty of Medicine & Health Science, United Arab Emirates University, Al-Ain, United Arab Emirates*

□ *A new series of substituted 2(1*H*)-pyridones (**4a–i**) and their glucosides (**5,6a–e**) were prepared as potential agents against leukemia (HL-60) cells. Glucosides (**5,6a–e**) were synthesized using three independent methods. Microwave protocol as an ecologically new method was used to synthesize the target compounds. Structures of the new products were confirmed using one- and two-dimensional NMR spectroscopy. In vitro exposure of pyridones substituted at position 4 with a 2-thienyl or 2-(trifluoromethyl)phenyl were found to exhibit high antiproliferation activities; in particular, 3-cyano-4-(thien-2′-yl)-6-(4″-chlorophenyl)-2(1*H*)-pyridone (**4c**) and its glucoside analogue (**6c**) had the highest activity.*

Keywords Microwave synthesis; pyridone glucosides; spectroscopy; antiproliferation activities

INTRODUCTION

Development of potent and effective anticancer drugs is one of the more pressing goals of current medicinal chemistry.[1,2] Various nucleosides have been reported to have important biological properties.[3] In particular, 4-amino-3-fluoro-1-(β-D-ribofuranosyl)-2(1*H*)-pyridone (**1**) inhibits the growth of HL-60 lymphoid leukemia cells with $IC_{50} = 1.07 \times 10^{-5}$ M, while 2′-deoxy analogue of (**1**) is active against lymphoid leukemia L1210 cells. Also, the acetyl derivative of (**1**) exhibits similar albeit less potent activities than (**1**).[4] Selective inhibitors for the human immunodeficiency virus type1 reverse transcriptase (HIV-RT) are derivatives of pyridine.[5] For example, 3-(4′,7′-dimethyl benzoxazol-2′-yl)-amino-5-ethyl-6-methyl pyridine-2(1*H*)-one

Received 25 August 2010; accepted 29 December 2010.
The authors thank the Deanship of the Graduate Studies, M.Sc. Program (Environmental Sciences) and the Department of Chemistry, UAE University for Shaikha S. Al-Neyadi's M.Sc. fellowship. This work was published in ICHC-22, St. Johns' NL, Canada, August 2009.
Address correspondence to Ibrahim M. Abdou, Department of Chemistry, Faculty of Science, UAE University, Al-Ain 17551, UAE. E-mail: i.abdou@uaeu.ac.ae

(**2**) and its 4,7-dichloro analogue have been reported to inhibit the spread of HIV-1 infection by 95% in MT4 cell culture and were selected for clinical trials as antiviral agents. 4-Benzylpyridone (**3**) has been shown to posses potent HIV-1 specific reverse transcriptase inhibitor properties.[5]

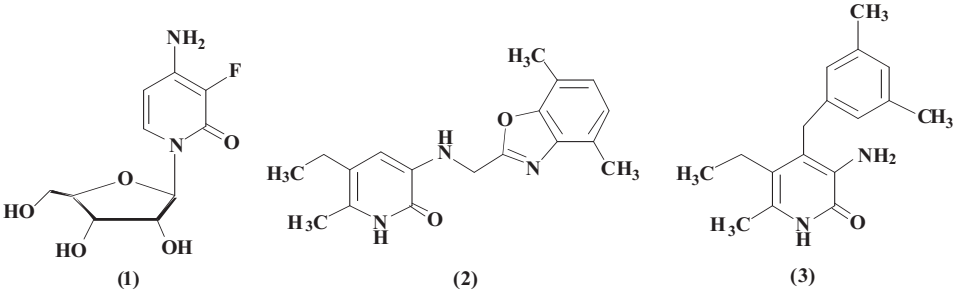


FIGURE 1 Microwave synthesis of 2(1H)-pyridone derivatives.

In our previous study,[6,17] we reported the synthesis and biological activities of pyrazolone and pyrimidine nucleosides.

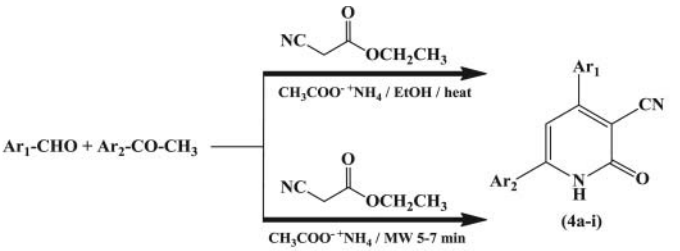
The goal of this work is to develop an environmental and friendly protocol for the synthesis of some new pyridone nucleosides. We synthesize series of pyridone and their nucleoside analogues using silica catalyzed microwave (MW) protocol. MW synthesizer has an advantage method for its practical cost and short reaction time. It is a new route with additional advantage to enhance the reaction rates and to improve the yield. The new obtained synthesized compounds will be used to study the cell proliferation effects and to establish their structure-activity relationships.

RESULTS AND DISCUSSION

Chemistry

The synthesis of 2(1*H*)-pyridone derivatives (**4a–i**) was performed as outlined in Scheme 1 and isolated in a crystalline form in 58–86% yields by using the methodology published previously.[7] Microwave synthetic protocol was used to obtain the target compounds (**4a–i**) in 90–95% yield. Their structures were unambiguously confirmed by one- and two-dimensional NMR spectroscopy and elemental analysis.[8] For example, the ^{1}H NMR spectrum of compound (**4d**) shows a singlet at δ 6.98 corresponding to the pyridine H-5. Protons at positions 3′, 4′, and 5′ of the thiophene show absorption pattern that is typical for the 2-thienyl group attached to an aromatic system.

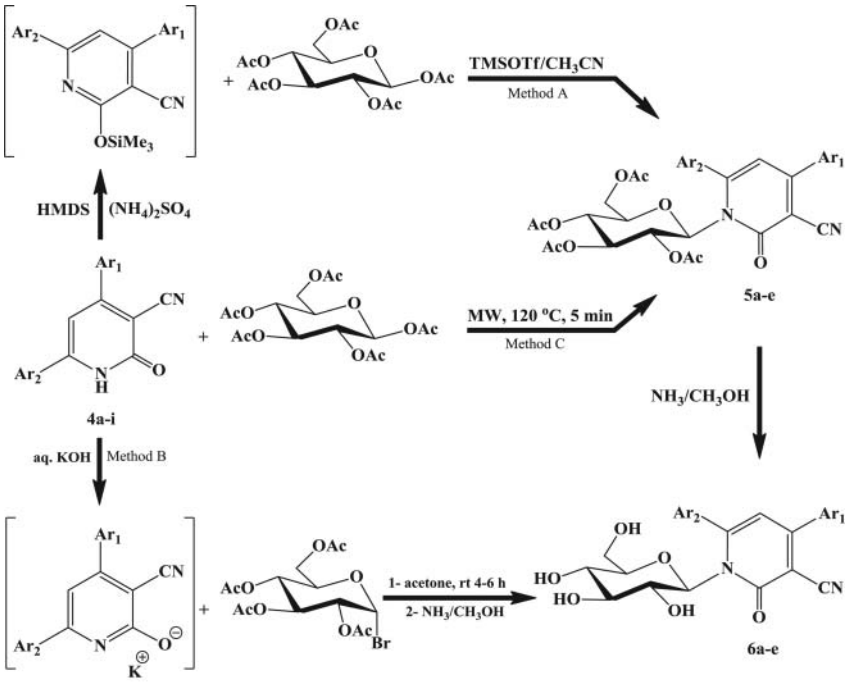
Three different protocols for the synthesis of the targeted nucleosides (**5a–e**)[9,13] were compared (Scheme 2). The silyl procedure (method A)[11–14] was used to synthesize nucleosides (**5a–e**). For example, a silyl derivative of 3-cyano-4-(thiophen-2′-yl)-6-(*p*-chlorophenyl)-2(*1H*)-pyridone (**4d**)



			Conventional		Microwave (MW)	
Compd.	Ar_1	Ar_2	Time (h)	Yield%	Time (min)	Yield%
4a	C_6H_5	C_6H_5	6	85	7	95
b	2-CH_3-C_6H_4	C_6H_5	6	67	5	90
c	2-thienyl	C_6H_5	6	73	5	93
d	2-thienyl	4-Cl-C_6H_4	6	82	5	95
e	2-CF_3-C_6H_4	C_6H_5	6	80	7	90
f	3-CH_3-C_6H_4	C_6H_5	6	76	5	95
g	4-CH_3-C_6H_4	4-Cl-C_6H_4	6	80	5	93
h	4-pyridyl	4-CH_3O-C_6H_4	6	80	5	95
i	C_6H_5	4-Cl-C_6H_4	6	80	5	91

SCHEME 1 Synthesis of 3-cyano-4,6-disubstituted pyridine-2(*1H*)-ones (**4a–i**).

was allowed to react with pentacetyl glucose in the presence of trimethylsilyltriflate (TMSOTf) in 1,2-dichloroethane to produce (**5d**) in 81% yield (Scheme 2). In method B,[9,10] the potassium salt of 2-pyridone (**4a–i**) was subjected to a reaction with an α-acetobromoglucose to produce the target nucleoside (**5a–e**). In method C,[17] microwave was used to simplify the formation of *N*-glucoside linkage in shorter time and in an accepted yield (63%). In particular, the β-structure of the obtained nucleoside (**5d**) was determined by using ^{1}H NMR. More specifically, the large spin-spin coupling constant ($J_{H1''\text{-}H2''} > 7$ Hz) for a diaxial interaction between H-1″ and H-2″ is fully consistent with the β-isomer.[15] Similar results were obtained for the remaining glucosides. The conformation of the resultant nucleosides was established using two-dimensional NMR analysis. The phase sensitive NOESY spectrum of (**6a**) was collected at 25°C. The inter-ring cross peaks were observed between the anomeric proton H-1″ and *ortho*-phenyl protons



Compd.	Ar_1	Ar_2
5,6a	C_6H_5	C_6H_5
b	2-CH_3-C_6H_4	C_6H_5
c	2-thienyl	C_6H_5
d	2-thienyl	4-Cl-C_6H_4
e	2-CF_3-C_6H_4	C_6H_5

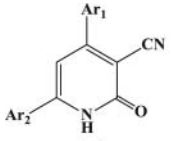
SCHEME 2 Synthetic pathways of pyridone glucosides (**5**,**6a–e**).

at the 6-position supporting the formation of *N*-glucosides as single isomer, not *O*-glucosides.[16]

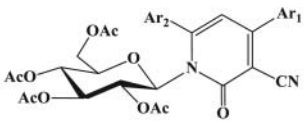
Antiproliferation Activity

Table 1 shows the in vitro antiproliferative activity of compounds (**4a–i**) and their glucoside derivatives (**5**,**6a–e**) on human promyelotic leukemia cells (HL-60) using the MTT cell proliferation assay. Introducing electron withdrawal groups at the 4- and 6-positions of the pyridine ring have shown

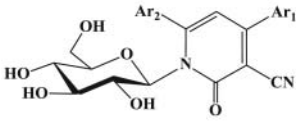
TABLE 1 The antiproliferation activity of HL-60 cells treated with compounds (**4–6$_{a\text{-}i}$**)



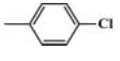
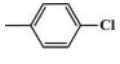
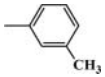
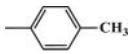
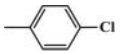
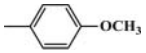
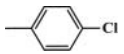
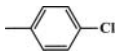
4a-i



5a-e



6a-e

Compd.	Ar_1	Ar_2	Inhibition (%) 100 μM	200 μM	Compd.	Ar_1	Ar_2	Inhibition (%) 100 μM	200 μM
4a			06%	03%	**5a**			08%	05%
b			05%	04%	**b**			25%	15%
c			40%	30%	**c**			29%	25%
d			37%	25%	**d**			32%	26%
e			32%	28%	**e**			38%	28%
f			04%	03%	**6a**			09%	10%
g			29%	21%	**b**			20%	19%
h			38%	30%	**c**			50%	49%
i			17%	18%	**d**			47%	43%
					e			40%	30%

significant increase in the antiproliferation activities. Glucoside (**6c**) with 2-thienyl group at the 4-position was found to have the highest ability to inhibit HL-60 proliferation among all synthesized compounds. The viability percentage of HL-60 cells treated with (**6c**) was reduced by 50% while that treated with the pyridine analogue (**4c**) showed 40% antiproliferation activity compared to the control. Glucoside (**6e**) substituted with trifluoromethyl group enhanced the potency in inhibiting HL-60 cell by 40% or 30% at concentration of 100 μM and 200 μM, respectively.

On the other hand, electron withdrawing substitutes in the 6-position of the pyridine ring were found to enhance the antiproliferation activity. Similar inhibitions in HL-60 cells were obtained by the acetylated compounds (**5c-e**) at 100 μM and 200 μM (Table 1). Pyridone analogues substituted with electron-donating groups (**4b**,**f**) showed no effect on HL-60 cell line compared with the control.

As results, the antiproliferation activity of the analogues having electron-withdrawing groups at positions 4- and 6- of the pyridine ring inhibited cell viability relative to the control. Consequently, structures (**6c-e**) offer an interesting model for the design of new glucosides endowed with antiproliferative activity. These preliminary results will be part of future investigations.

EXPERIMENTAL

General

All air sensitive materials were handled under a nitrogen atmosphere. Microwave synthesis was done using CEM discovery S-class (Matthews, NC, USA). Melting points were determined on (Pyrex capillary) Gallenkamp apparatus (Leicestershire, UK). Infrared spectra were recorded with a Thermo Nicolet Nexus 470 FT-IR spectrometer (Barrington, IL, USA) in the range 4000–400 cm^{-1} on samples in potassium bromide disks. ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (75 MHz) were obtained on Varian 200 MHz instrument (Crawley, West Sussex, UK); chemical shifts were recorded in δ (ppm) units, relative to Me_4Si as an internal standard. Optical rotations were measured with a Perkin-Elmer digital polarimeter at 589 nm (sodium D line) in a 1 dm cell (Fremont, CA, USA). Thin layer chromatography (TLC) was carried out on precoated Merck silica gel F_{254} plates and ultraviolet (UV) light was used for visualization (Gibbstown, NJ, USA). Column chromatography was performed on a Merck silica gel. Microanalytical data (C,H,N,S) were performed on a Flash–EA-1112 series analyzer (CLU, UAE University). The reagents were purchased from Aldrich and used without further purification (Sigma-Aldrich, LABCO, Dubai, UAE).

General Procedure for the Synthesis of (4a–i)

Conventional Method[7]

A mixture of an aromatic aldehyde (10 mmol), ethyl cyanoacetate (10 mmol), arylketone (10 mmol), and ammonium acetate (0.1 mol) in ethanol (50 mL) was heated under reflux for approximately 6 hours. The mixture was cooled, and the resultant precipitate was filtered, washed with cold water (3 × 50 mL), and crystallized from appropriate solvent to give the desired 2(1*H*)-pyridone derivatives (**4a–i**) in 67–86% yield.

Microwave Synthesis

Equimolar amounts of aromatic aldehyde (10 mmol), ethyl cyanoacetate (10 mmol), arylketone (10 mmol), and ammonium acetate (0.1 mol) were irradiated at 200 W for 5–7 minutes using microwave reactor CEM S-discovery. The obtained product was purified by crystallization from EtOH-DMF to afford 2(1*H*)-pyridone derivatives (**4a–i**) in 90–95% yields.

*3-Cyano-4,6-diphenyl-2(1H)-pyridone (**4a**).* Yellow crystals; m.p. 333°C; $R_f = 0.53$ (hexane/ethyl acetate, 6:4), IR (cm^{-1}): 1600 (CO), 2220 (CN), 3440 (NH); ^{1}H NMR (DMSO-d_6): δ 6.82 (s, 1H, H-5), 7.54–7.89 (m, 10H, aromatic), 12.81 (bs, 1H, NH, exchangeable in D_2O); ^{13}C NMR (DMSO-d_6): δ 106.3 (C-5), 116.5(CN), 116.0 (C-3), 127.8–136.0 (aromatic), 151.5 (C-6), 159.8 (C-2), 162.0 (C-4). Anal. Calcd. for $C_{18}H_{12}N_2O$ (272.30): C, 79.39; H, 4.44; N, 10.29. Found: C, 79.0; H, 4.46; N, 10.20.

*3-Cyano-6-phenyl-4-(2′-tolyl)-2(1H)-pyridone (**4b**).* Pale yellow crystals; m.p. 284°C; $R_f = 0.38$ (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1641 (CO), 2350 (CN), 3420 (NH); ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, *o*-CH_3), 6.71 (s, 1H, H-5), 7.31–7.89 (m, 12H, aromatic), 12.81 (bs, 1H, NH, exchangeable in D_2O); ^{13}C NMR (DMSO-d6): δ 107.5 (C-5), 116.6 (CN),116.0 (C-3), 126.7–137.1 (aromatic), 151.9 (C-6), 161.8 (C-2), 162.4 (C-4); Anal. Calcd. for $C_{19}H_{14}N_2O$ (286.33): C, 79.70; H, 4.93; N, 9.78; found: C, 79.9; H, 5.06; N, 9.87%.

*3-Cyano-6-phenyl-4-(thiophen-2′-yl)-2(1H)-pyridone (**4c**).* Yellow crystals; m.p. 315°C; $R_f = 0.62$ (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1643 (CO), 2220 (CN), 3425 (NH); ^{1}H NMR (DMSO-d_6): δ 6.90 (s, 1H, H-5), 7.31 (t, 1H, H-4′, $J = 5.0$ Hz), 7.55 (m, 3H), 7.58 (m,2H), 7.98 (d, 1H, H-5′, $J = 5.0$ Hz), 8.05 (d, 1H, H-3′, $J = 2.6$ Hz) 12.65 (bs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-*d6*): δ 95.3 (C3), 104.5 (C-5), 117.0 (CN), 127.8, 128.7, 128.9, 131.2, 131.4, 131.9, 132.2, 136.8, 150.8 (C6), 151.2 (C-2), 162.2 (C-4); Anal. Calcd. for $C_{16}H_{10}N_2OS$ (278.33): C, 69.04; H, 3.62; N, 10.06; S, 11.52%, found: C, 68.70; H, 3.63; N, 10.0; S, 11.50%.

*3-Cyano-6-(4′-chlorophenyl)-4-(thiophen-2′-yl)-2(1H)-pyridone (**4d**).* Pale yellow crystals; m.p. 342–343°C; $R_f = 0.32$ (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1660 (CO), 2220 (CN), 3430 (NH); ^{1}H NMR (DMSO-d_6): δ 6.98 (s, 1H, H-5), 7.32 (dd, 1H, H-4′, $J = 3.8, 5.0$ Hz), 7.62 (d, 2H, $J = 8.6$ Hz), 7.88–7.93 (d, 2H, $J = 8.6$ Hz), 7.98 (d, 1H, H-5′, $J = 5.0$ Hz), 8.01 (d, 1H, H-3′, $J =$

3.8 Hz) 12.74 (bs, 1H, NH, exchangeable with D_2O);^{13}C NMR (DMSO-d_6): δ 104.8 (C-5), 116.9 (CN), 116.0 (C-3),128.7–128.9, 129.7, 131.2, 131.6, 132.0, 136.1, 136.7 (aromatic), 150.2 (C-6),150.7 (C-2), 162.3 (C-4). Anal. Calcd. for $C_{16}H_9N_2OClS$ (312.77): C, 61.44; H, 2.90; N, 8.96; S, 10.25%.Found:C, 61.4; H, 2.9; N, 8.94; S, 10.3%.

*3-Cyano-6-phenyl-4-(2′-trifluoromethylphenyl)-2(1H)-pyridone (**4e**).* Yellow crystals; m.p. 306–307°C; R_f = 0.34 (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1637 (CO), 2349 (CN), 3446 (NH); ^{1}H NMR (DMSO-d_6): δ 6.84 (s, 1H, H-5), 7.50 (m, 3H), 7.89 (m, 6H), 12.81 (bs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d6): δ; 98.0 (CN), 106.3 (C-5), 116.2 (CN), 125.6, 125.7, 125.8, 126.7, 127.9, 129.0, 130.2, 130.8, 132.3, 150.2 (C-4), 158.4 (C-6), 161.8 (C-4), 161.9 (C-2). Anal. Calcd. for $C_{19}H_{11}N_2OF_3$ (340.30): C, 67.06; H, 3.26; N, 8.23%, found: C, 67.4; H, 3.30; N, 8.30%.

*3-Cyano-6-phenyl-4-(3′-tolyl)-2(1H)-pyridone (**4f**).* Yellow crystals; m.p. 263°C, Rf = 0.26 (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1650 (CO), 2229 (CN), 3442 (NH); ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H, *m*-CH_3), 6.78 (s, 1H, H-5), 7.34–7.55 (m, 7H), 7.86–7.88 (m, 2H), 12.81 (bs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6): δ 98.4 (C-3), 106.3 (C-5), 116.6 (CN), 125.4, 127.8, 128.8, 131.1, 131.3, 132.3, 136.1, 138.3, 151.4 (C-6), 159.9 (C-2), 162.2 (C-4); Anal. Calcd. for $C_{19}H_{14}N_2O$ (286.33): C, 79.70; H, 4.93; N, 9.78%, found: C, 79.71; H, 5.04; N, 9.77%.

*3-Cyano-6-(4′-chlorophenyl)-4-(4′-tolyl)-2(1H)-pyridone (**4g**).* Yellow crystals; m.p. 312–313°C; R_f = 0.180(6:4 hexane/ethyl acetate); IR (KBr, cm^{-1}) 2349 (CN), 1636 (CO), 3433 (NH), ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 6.83 (s, 1H, H-5), 7.34 (d, 2H, J = 8.2 Hz), 7.57 (d, 2H, J = 8.2 Hz), 7.62 (d, 2H, J = 8.6 Hz), 7.90 (d, 2H, J = 8.6 Hz), 12.38 (bs, 1H, NH, exchangeable with D_2O);^{13}C NMR (DMSO-d_6): δ 98.0 (C-5), 107.3 (C-3), 117.2 (CN), 128.9, 129.6, 130.0, 130.3, 132.0, 133.7, 136.6, 141.2 (C-6), 160.2 (C-2), 162.8 (C-4); Anal. Calcd. for $C_{19}H_{13}ClN_2O$ (320.77): C, 71.14; H, 4.08; N, 8.73% found: C, 71.2; H, 4.03; N, 8.67%.

*3-Cyano-6-(4′-methoxyphenyl)-4-(pyridin-4′-yl)-2(1H)-pyridone (**4h**).* Yellow crystals; m.p. 306–307°C; Rf = 0.34 (6:4 hexane/ethyl acetate), IR (KBr, cm-1)1637 (CO), 2349 (CN), 3446 (NH); ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, *p*-OCH3), 6.84 (s, 1H, H-5), 7.07 (d, 2H, J = 9.0 Hz), 7.67 (d, 2H, J = 4.4 Hz),7.87 (d, 2H, J = 9.0 Hz) 8.76 (d, 2H, J = 4.4 Hz), 12.81 (bs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6): δ 55.6 (*p*-OCH3), 104.8 (C-5), 114.4, 116.1 (CN), 122.6, 124.1, 129.6, 143.6, 150.2, 157.1, 161.8 (C-4), 161.9 (C-2); Anal. Calcd. for C18H13N3O$_2$ (303.30): C, 71.28; H, 4.32; N, 13.85%, found: C, 71.25; H, 4.35; N, 13.82%.

*3-Cyano-6-(4′-chlorophenyl)-4-phenyl-2(1H)-pyridone (**4i**):.* Yellow crystals; m.p. 305–306°C; R_f = 0.22 (6:4 hexane/ethyl acetate); IR (KBr, cm^{-1}) 2216 (CN), 1635 (CO), 3446 (NH); ^{1}H NMR (DMSO-d_6): δ 6.87 (s, 1H, H-5), 7.55 (m, 5H), 7.70 (d, 2H, J = 10.8 Hz), 7.91 (d, 2H, J = 10.8 Hz),

12.42 (bs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6): δ 98.5 (CN), 107.4 (C-5), 117.1 (C-3), 128.9, 129.4, 129.6, 130.3, 131.1, 132.0, 136.6, 136.7, 151.2 (C-6), 160.3 (C-2), 162.8 (C-4); Anal. Calcd. for $C_{18}H_{11}ClN_2O$ (306.75): C, 70.48; H, 3.61; N, 9.13%; found: C, 70.58; H, 3.62; N, 9.01%.

General Procedures for 3-Cyano-4,6-disubistituted-1-(2″,3″, 4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)- 2-pyridone (5a–e)

Method A

A mixture of 2-pyridone (**4a–e**) (0.01 mol), 1,1,1,3,3,3 hexamethyl disilazane (HMDS, 60 mL), ammonium sulfate (0.125 g) and few drops of chlorotrimethylsilane was heated under nitrogen for 2–6 hours. Excess HMDS was removed by distillation, and the residue was dried under a reduced pressure. The resulting silyl intermediate was dissolved in anhydrous MeCN (20 mL). A solution of a 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (3.91 g,0.01 mol) and TMSOTf (2.17 ml, 0.015 mol) in MeCN (20 mL) was added at 5°C with stirring. The stirring was continued at room temperature for 3–6 hours until the reaction was completed as observed by TLC analysis (chloroform/acetone, 1:1). The mixture was diluted with $CHCl_3$ (150 mL), and the organic solution was washed with a saturated $NaHCO_3$ solution (50 mL), and then with water (2 × 50 mL). After drying (anhydrous Na_2SO_4), the solvent was removed under a reduced pressure and a crude product thus obtained was purified by column chromatography ($CHCl_3$/ethyl acetate, 1:9) to give (**5a–e**) in 81–93% yield (Scheme 2).

Method B

To a solution of 4,6-disubstituted-2(1*H*)-pyridone (**4a–e**) (0.01 mol) in aqueous KOH [(0.56 g, 0.01 mol) in water (6 mL)], a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.12 g, 0.011 mol) in acetone (30 mL) was added. The mixture was stirred at room temperature until the reaction was judged completed by TLC (4–6 hours). The reaction mixture was diluted using 30 ml of CH_2Cl_2. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified using column chromatography ($CHCl_3$/ ethyl acetate, 1:9) to give after crystallization in ethanol the desired products (**5a–e**) in 58–69% yield (Scheme 2).

Method C[17]

A mixture of 3-cyano-4,6-diphenyl-2-pyridone (**4a**) (2.72 g, 0.01 mol) was suspended in anhydrous MeCN (20 mL). A solution of a 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (3.91 g, 0.01 mol) in MeCN (20 mL) was added with stirring at room temperature. A catalytic amount of silica gel (1.0 g) was

added. The solvent was removed and the mixture irradiated at 90°C (5–200 W) for 3–5 minutes in a 35 mL closed vial using CEM S-discovery microwave reactor. The mixture was suspended in $CHCl_3$ (150 mL), filtered and the organic solution was washed with a saturated $NaHCO_3$ solution (50 mL), and then with water (2 × 50 mL). After drying (anhydrous Na_2SO_4), the solvent was removed under a reduced pressure and the crude product obtained was purified by column chromatography ($CHCl_3$/ethyl acetate, 1:9) to give (**5a**) in 63% yield (Scheme 2).

*3-Cyano-4,6-diphenyl-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-2-pyridone (**5a**).* White crystals; yield 85% (method A), 66% (method B); (method C) 63%; m.p. 193°C, from ethanol; R_f = 0.48 (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1640 (C-2), 1752 (acetyl carbonyl CO), 2354 (CN); $[\alpha]^{25}$ = 25.4° (*c* = 4.92 mg/mL, chloroform);^{1}H NMR ($CDCl_3$): δ 1.91–2.07 (4s, 12H, $4CH_3CO$), 4.03–4.25(m, 3H, H-5′, H-6′a,H-6′b), 5.21–5.27 (dd, 1H, H-4′, *J* = 3.6 Hz, *J* = 7.8 Hz), 5.51–5.53 (t, 1H, H-3′, *J* = 3.6 Hz), 5.65–5.74 (t, 1H, H-2′, *J* = 3.6 Hz, *J* = 7.8 Hz), 6.27–6.31 (d, 1H, H-1′, $J_{1'\text{-}2'}$ = 7.8 Hz), 7.49–8.00 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$): δ 20.3–20.5 ($4CH_3$), 62.0 (C-6′), 68.3 (C-4′), 70.3 (C-2′), 72.6 (C-3′), 72.8(C-5′), 94.3 (C-1′), 94.3(C-5), 113.9 (C-3), 115.5 (CN), 127.2–136.8 (aromatic), 157.3 (C-6), 157.8 (C-2), 162.3 (C-4), 168.9–170.6 (four acetoxy carbonyl carbon). Anal. Calcd. for $C_{32}H_{30}N_2O_{10}$ (602.59): C, 63.78; H, 5.02; N, 4.65%, found: C, 64.01; H, 5.14; N, 4.61%.

*3-Cyano-6-phenyl-1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-4-(2′-tolyl)-2-pyridone (**5b**).* White crystals; yield 87% (method A), 69% (method B); m.p. 189–190°C, from ethanol; R_f = 0.38 (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1659 (C-2), 1765 (acetoxy carbonyl), 2352 (CN); $[\alpha]^{25}$ = 26.1° (*c* = 3.84 mg/ml, chloroform);^{1}H NMR ($CDCl_3$): δ 1.93–2.08 (4s, 12H, $4CH_3$), 2.28 (s, 3H, *o*-CH_3), 4.00 (m, 1H, H-5′), 4.25–4.27 (m, 2H, H-6″a,H-6″b), 5.23–5.47 (m, 3H, H-2″, H-3″, H-4″), 6.32–6.36 (d, 1H, H-1″, $J_{1''\text{-}2''}$ = 7.8 Hz), 7.25–8.05 (m, 10H, aromatic);^{13}C NMR ($CDCl_3$): δ 20.1 (*o*-CH_3), 20.8 (4 CH_3), 62.3 (C-6″), 68.6 (C-4″), 70.6 (C-2″), 72.9 (C-3″), 73.0 (C-5″), 94.7 (C-1″), 96.1 (C-5), 114.0 (C-3), 116.5 (CN), 126.4–136.9 (aromatic), 157.8 (C-6), 158.5 (C-2), 162.0 (C-4), 170.9 (four acetoxy carbonyl carbon); Anal.Calcd. for $C_{33}H_{32}N_2O_{10}$ (616.61): C, 64.28; H, 5.23; N, 4.54%, found: C, 64.50; H, 5.23; N, 4.47%.

*3-Cyano-6-phenyl-1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-4-(thiophen-2′-yl)-2-pyridone (**5c**).* White crystals; yield 93% (method A), 64% (method B); m.p. 188–189°C, from ethanol; R_f = 0.92 (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1680 (CO), 1752 (acetoxy carbonyl), 2354(CN); $[\alpha]^{25}$ = 7.1° (*c* = 4.28 mg/ml, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.92–2.07 (4s, 12H, $4CH_3$), 4.06 (m, 1H, H-5″), 4.21–4.22 (m, 2H, H-6″a, H-6″b) 5.18–5.50 (m, 3H, H-2″,H-3″, H-4″), 6.29 (d, 1H, H-1″, $J_{1''\text{-}2''}$ = 9.0 Hz), 7.20–7.56 (m, 5H, aromatic), 7.69 (s, 1H, H-5), 7.98–8.06 (m, 2H, H-3′, 4′); ^{13}C NMR ($CDCl_3$): δ 20.6–20.7 ($4CH_3$), 62.0 (C-6″), 68.4 (C-5″), 70.3 (C-4″), 72.98(C-3″), 73.0

(C-2″), 91.8 (C5), 94.4 (C-1″), 114.2 (C-3), 114.5 (CN), 127.3–137.2, 148.6 (thienyl C-2), 158.0 (C-6), 162.9 (C-2), 168.9, 170.9, 170.4, and 170.6 (four acetoxy carbonyl carbon); Anal.Calcd. for $C_{30}H_{28}N_2O_{10}S$ (608.62): C, 59.20; H, 4.64; N, 4.60; S, 5.27%, found: C, 59.02; H, 4.57; N, 4.63; S, 5.19%.

*3-Cyano-6-(p-chlorophenyl)-1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-4-(thiophen-2′-yl)-2-pyridone (**5d**).* White crystals; yield 81% (method A), 68% (method B); m.p. 155–156°C, from ethanol, Rf = 0.625(6:4 hexane/ethyl acetate),), IR (KBr, cm^{-1}) 1641 (C-2), 1752 (acetoxy carbonyl), 2330 (CN); $[\alpha]^{25} = 17.9°$ ($c = 9.2$ mg/ml, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.93–2.07 (4s, 12H, $4CH_3$), 4.00 (m, 1H, H-5″), 4.19–4.25 (m, 2H, H-6″a, H-6″b), 5.20–5.25 (m, 1H, H-4″), 5.39–5.45 (m, 2H, H-2″, H-3″), 6.25–6.30 (d,1H, H-1″, $J_{1''\text{-}2''} = 8.2$ Hz), 7.19–7.22 (d, 2H, $J = 4.2$ Hz), 7.45–7.51 (m, 1H, thienyl H-5′), 7.56–7.59 (d, 2H, $J = 8.2$ Hz), 7.63 (s, 1H, H-5), 7.94–7.99 (m, 2H, thienyl H-3′, H-4′); ^{13}C NMR ($CDCl_3$): δ 20.6–20.7 ($4CH_3$), 61.7 (C-6″), 67.1 (C-5″), 67.8 (C-4″), 70.9 (C-3″), 71.7 (C-2″), 95.0 (C-1″), 91.9 (C-5), 113.9 (C-3), 114.5 (CN), 128.5–137.2 (aromatic), 148.7 (C-6), 156.7 (C-2), 163.1 (C-4), 168.9, 170.2, 170.3 and 170.4 (four acetoxy carbonyl carbon). Anal.Calcd. for $C_{30}H_{27}ClN_2O_{10}S$ (643.06): C, 56.03; H, 4.23; N, 4.36; S, 4.99%, found: C, 56.0; H, 4.20; N, 4.21; S, 4.89%.

*3-Cyano-6-phenyl-1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-4-(2′-trifluoromethylphenyl)-2-pyridone (**5e**).* White crystals; yield 86% (method A), 58% (method B); m.p. 167–168°C, from ethanol, $R_f = 0.86$ (6:4 hexane/ethyl acetate), IR (KBr, cm^{-1}) 1660 (C-2), 1760 (acetoxy carbonyl), 2400 (CN); $[\alpha]^{25} = 9.5°$ ($c = 8.4$ mg/mL, chloroform);^{1}H NMR ($CDCl_3$): δ 1.91, 2.05, 2.06, 2.08 (4s, 12H, $4CH_3$), 4.05–4.11 (m, 1H, H-5″), 4.22–4.25 (m, 2H, H-6″a,H-6″b), 5.18–5.27 (m, 1H, H-4″), 5.42–5.47 (m, 2H, H-2″, H-3″), 6.33–6.37 (d, 1H, H-1″, $J_{1''\text{-}2''} = 8$ Hz), 7.51 (m, 3H), 7.59 (s, 1H, H-5), 7.77 (m, 4H), 8.05 (m, 2H);^{13}C NMR ($CDCl_3$): δ 20.5–20.6 (4s, $4CH_3$), 62.0 (C-6″), 68.3 (C-5″), 70.3 (C-4″), 72.7 (C-3″), 94.2 (C-2″), 94.4 (C-1″), 113.6 (C-5), 115.3 (C-3), 116.5 (CN), 126.1 (CF_3), 127.3–139.3 (aromatic), 162.3 (C-6), 155.7 (C-2), 158.4 (C-4), 168.9–170.6 (four acetoxy carbonyl carbon); Anal.Calcd. for $C_{33}H_{29}F_3N_2O_{10}$ (670.59): C, 59.11; H, 4.36; N, 4.18%, found: C, 59.18; H, 4.30; N, 4.12%.

*Ammonolysis of (**5a–e**).* Dry gaseous ammonia was passed through a solution of acetylated nucleoside (**5a–e**, 0.5 g) in dry methanol (10 mL) at 0°C for about 0.5 hours. The mixture was stirred at 0°C until the reaction was judged complete by TLC. Then the residue was purified using column chromatography eluting with 2% CH_3OH in CH_2Cl_2 to give after crystallization in MeOH a white crystalline product (**6a–e**).

*3-Cyano-1-(β-D-glucopyranosyl)-4-phenyl-2-pyridone (**6a**).* White crystals; yield 89%; m.p. 182°C, from methanol; $R_f = 0.35$ (CH_2Cl_2), IR (KBr, cm^{-1}) 1590 (CO), 2230 (CN), 3430 sugar-OH; $[\alpha]^{25} = 116.8°$ ($c = 10.4$ mg/ml, methanol);^{1}H NMR (DMSO-d_6): δ 3.26–3.67 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′a,H-6′b), 4.57, 5.08, 4.15, 5.43 (4 sugar OH, exchangeable with D_2O),

6.13–6.16 (d, 1H, H-1′, $J = 7.4$ Hz), 7.51–7.60 (m, 6H, aromatic), 7.73–7.76 (m, 2H), 7.88 (s, 1H, H-5), 8.22–8.27 (m, 2H);^{13}C NMR (DMSO-d_6): δ 60.6 (C-6′), 69.7 (C-5′), 72.9 (C-4′), 77 (C-3′), 78.0(C-2′), 96.6 (C-1″), 92.8 (C-5), 114.9 (C-3), 115.0 (CN), 127.6–136.5 (aromatic), 156.8 (C-6), 157.4 (C-2), 162.9(C-4). Anal. Calcd. for $C_{24}H_{22}N_2O_6$ (434.44): C, 66.35; H, 5.10; N, 6.45; found: C, 65.99; H, 4.98; N, 6.41%.

3-Cyano-1-(β-D-glucopyranosyl)-6-phenyl-4-(2′-tolyl-2-pyridone ***(6b)***. White crystals; yield 95%; m.p. 163°C, from methanol; $R_f = 0.51$ (CH_2Cl_2), IR (KBr, cm^{-1}) 1585 (CO), 2450 (CN), 3400 sugar-OH; $[\alpha]^{25} = 88°$ ($c = 6.52$ mg/ml, methanol);^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H, CH_3), 3.36–3.66 (m, 6H, H-2″ H-3″, H-4″, H-5″, H-6″a,H-6″b), 4.65, 4.95, 5.27(4 sugar OH, exchangeable with D_2O), 6.12–6.15 (d, 1H, H-1″, $J_{1''\text{-}2''} = 7.8$ Hz), 7.39–7.57 (m, 7H), 7.87 (s, 1H, H-5), 8.24–8.28 (m, 2H);^{13}C NMR (DMSO-d_6): δ 21.7 (s, CH3), 61.0 (C-6″), 68.8 (C-5″), 70.6 (C-4″), 74.2 (C-3″), 77.1 (C-2″), 93.4 (C-1″), 97.8 (C-5), 115.4 (C-3), 115.7 (CN), 126.4–139.0 (aromatic), 157.5 (C-6), 157.9 (C-2), 163.7 (C-4). Anal. Calcd. for $C_{25}H_{24}N_2O_6$ (448.47): C, 66.95; H, 5.39; N, 6.25%; found: C, 66.89; H, 5.37; N, 6.31%.

3-Cyano-1-(β-D-glucopyranosyl)-6-phenyl-4-(thiophen-2′-yl)-2-pyridone ***(6c)***. White crystals; yield 92%; m.p. 219°C, from methanol; $R_f = 0.34$ (CH_2Cl_2), IR (KBr, cm^{-1}) 1595 (CO), 2300 (CN), 3445 sugar-OH; $[\alpha]^{25} = 202°$ ($c = 8.4$ mg/ml, methanol); ^{1}H NMR (DMSO-d_6): δ 3.25–3.68 (m, 6H, H-2″, H-3″, H-4″, H-5″, H-6″a, H-6″b), 4.59, 5.09, 5.18, 5.42 (4 sugar OH, exchangeable with D_2O), 6.11–6.15 (d, 1H, H-1″, $J_{1''\text{-}2''} = 7.8$ Hz), 7.32–7.37 (dd, 1H, H-4′, $J = 5.0$ Hz, $J = 3.4$ Hz), 7.54–7.56 (m, 3H, aromatic), 7.97 (s, 1H, H-5), 7.98–7.99 (d, 1H, H-3′, $J = 3.4$ Hz), 8.03–8.06 (d, 1H, H-5′, $J = 5.0$ Hz), 8.22–8.27 (m, 2H, aromatic); ^{13}C NMR (DMSO-d_6): δ 60.5 (C-6″), 69.6 (C-5″), 72.7 (C-4″), 76.9 (C-3″), 78.0 (C-2″), 90.4 (C-3), 96.7(C-1″), 113.4 (C-5), 115.3 (CN), 127.6, 128.7, 129.0, 130.6, 130.9, 131.1, 136.3, 148.3 (C-6), 157.4 (C-2), 163.5 (C-4). Anal. Calcd. for $C_{22}H_{20}N_2O_6S$ (440.47): C, 59.99; H, 4.58; N, 6.36; S, 7.28%; found: C, 60.10; H, 4.59; N, 6.20; S, 7.32%.

3-Cyano-6-(4′-chlorophenyl)-1-(β-D-glucopyranosyl)-4-(thiophen-2′-yl)-2-pyridone ***(6d)***. White crystals; yield 86%; m.p. 250°C, from methanol; $R_f = 0.38$ (CH_2Cl_2), IR (KBr, cm^{-1}) 1645 (CO), 2240 (CN), 3440 sugar-OH; $[\alpha]^{25} = 331.2°$ ($c = 8.8$ mg/ml, methanol);^{1}H NMR (DMSO-d_6): δ 3.24–3.68 (m, 6H, H-2″ H-3″, H-4″, H-5″, H-6″a,H-6″b), 4.59, 5.13, 5.19, 5.44 (4 sugar OH, exchangeable with D_2O), 6.08–6.12 (d, 1H, H-1″, $J_{1''\text{-}2''} = 7.4$ Hz), 7.32–7.37 (dd, 1H, H-4′, $J = 5.0$ Hz, $J = 3.8$ Hz), 7.59–7.63 (d, 2H, $J = 10.6$ Hz), 7.98–8.05 (m, 3H, H-5, H-3′, H-5′), 8.26–8.28 (d, 2H, $J = 10.6$ Hz); ^{13}C NMR (DMSO-d_6): δ 60.6 (C-6″), 69.6 (C-5″), 72.8 (C-4″), 76.9(C-3″), 78.0 (C-2″), 90.7 (C-5), 96.8 (C-1″), 113.3(C-3), 115.2 (CN), 128.6, 129.1, 129.5, 130.8, 131.3, 135.2, 135.8, 136.4, 148.5 (C-6), 156.1 (C-2), 163.5 (C-4). Anal. Calcd. for $C_{22}H_{19}ClN_2O_6S$ (474.91): C, 55.64; H, 4.03; N, 5.90; S, 6.75%; found: C, 55.59; H, 3.99; N, 6.01; S, 6.64%.

*3-Cyano-1-(β-D-glucopyranosyl)-6-phenyl-4-(2′-trifluoromethylphenyl)-2-pyridone (**6e**).* White crystals; yield 88%; m.p. 168°C, from methanol; $R_f = 0.87$ (CH_2Cl_2), IR (KBr, cm^{-1}) 1650 (CO), 2220 (CN), 3445 sugar-OH; $[\alpha]^{25} = 100.6°$ ($c = 8$ mg/ml, methanol); ^{1}H NMR (DMSO-d_6): δ 3.24–3.69 (m, 6H, H-2″ H-3″, H-4″, H-5″, H-6″a,H-6″b), 4.58, 5.10, 5.18, 5.44 (4 sugar OH, exchangeable with D_2O), 6.15–6.18 (d, 1H, H-1″, $J_{1''\text{-}2''} = 7.4$ Hz), 7.54–7.55 (m, 3H), 7.97–7.99 (m, 5H, aromatic), 8.28–8.29 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 60.5 (C-6″), 69.6 (C-5″), 72.7 (C-4″), 76.9 (C-3″), 78.0(C-2″), 92.9 (C-3), 96.7(C-1″), 114.7(C-5), 115.0 (CN), 125.7–139.8 (aromatic), 155.3 (C-6′), 157.7 (C-2), 162.8 (C-4). Anal. Calcd. for $C_{25}H_{21}F_3N_2O_6$ (502.44): C, 59.76; H, 4.21; N, 5.58%; found: C, 59.65; H, 4.30; N, 5.59%.

Cell Viability Assay[18–21]

The human promyelocytic leukemia HL-60 cell line (ATCC, Manassas, VA, USA) was grown in the DMEM medium (Gibco) supplemented with 20% fetal calf serum (Gibco, Carlsbad, CA, USA), 100 units/ml penicillin-streptomycin (Gibco) and non-essential amino acid (Gibco). The cells were maintained at 37°C in 5% CO_2 incubator. After reaching confluency, the cells were subcultured into 96 wells culture plates, allowed to grow for 24 hours to a density of 4×10^3 cells and treated with different concentrations of compounds. The human promyelocytic leukemia HL-60 cells were propagated by spinning at 1500 rpm for 3 minutes, changing the old medium and then subcultured.

The effects of compounds (**4a–i**, **5a–d**, and **6a–d**) on cell viability was evaluated by the MTT [3-(4′,5′-dimethylthiazol-2′-yl)-2,5-diphenyltetrazolium bromide] assay as described previously[18–21] and according to the manufacturer (Promega, Madison, WI, USA) instructions. Cells were plated in 96-well plates at a density of 4×10^3 cells/well/100 μL and incubated overnight in DMEM medium with and without the compounds (**4a–i**, **5a-d**, and **6a–d**) at concentrations of 100 and 200 μM for 24 hours. In parallel, the cells were treated with 0.1% of SDS and DMSO as controls then, 10 nM of MTT (final concentration of 0.5 mg/ml) was added to each well and incubated for 2–4 hours at 37°C. This assay is a colorimetric assay for cell viability based on the cellular cleavage of the yellow tetrazolium salt, MTT, into the purple formazan crystals that is soluble in cell culture medium and the absorbance is measured at 550 nm. Absorbance is directly proportional to the number of living cells in culture. Cell viability was calculated as percent of the control (untreated) cells.

CONCLUSION

This work led us to investigate three different ways to obtain 4,6-disubistituted-3-cyano-2(1*H*)-pyridone and their glucosides (**4–6a–e**). We

have reported one-pot synthesis using microwave to produce pyridine analogues as an environmental and economically improved method. The silyated method was used to produce nucleosides in competitive yields and remains one of the best nucleosides' synthetic strategies. Spectroscopic techniques such as infrared and NMR were used to confirm structures of the obtained products. The biological results done in vitro and have shown that compounds containing trifluoromethyl or heteroaryl groups at the 4-position possessed the highest anti-proliferation activities among all synthesized analogues. In addition, different aryl groups at the 6-position had similar activities. For example, 3-cyano-6-phenyl-4-(thiophen-2′-yl)-2(1*H*)-pyridone (**4d**) and 3-cyano-6-(*p*-chlorophenyl)-4-(thiophen-2′-yl)-2(1*H*)-pyridone (**4e**) have shown similar activities on cell viability. In summary, the results presented in this paper indicate that compounds with heteroaryl or trifluoromethyl groups substituted at the 4-position of the pyridine ring may lead to a novel nucleosides with better bioactivity.

REFERENCES

1. Taliani, S.; La Motta, C.; Mugnaini, L.; Simorini, F.; Salerno, S.; Marini, A.; Da Settimo, F.; Cosconati, S.; Cosimelli, B.; Greco, G.; Limongelli, V.; Marinelli, L.; Novellino, E.; Ciampi, O.; Daniele, S.; Trincavelli, M.; Martini, C. Novel N2-substituted pyrazolo[3,4-d]pyrimidine adenosine A_3 receptor antagonists: Inhibition of A_3-mediated human glioblastoma cell proliferation. *J. Med. Chem.* **2010**, 53 (10), 3954–3963.
2. McNamara, D.J.; Cook, P.D. Synthesis and antitumor activity of fluorine-substituted 4-amino-2(1*H*)-pyridinones and their nucleosides. 3-Deazacytosines. *J. Med. Chem.* **1987**, 30, 340–347.
3. Nesnow, S.; Miyazaki, T.; Kawaja, T.; Meyer, B.; Heidelberger C. Pyridine nucleosides related to 5-fluorouracil and thymine. *J. Med. Chem.* **1973**, 16, 524–528.
4. Imai, K.I.; Nohara, A.; Honjo, M. Synthesis of purine nucleosides using iodine as catalyst. *Chem. Pharm. Bull.* **1966**, 14, 1377–1381.
5. Onodera, K.; Hirano, S.F. Nucleosides and related substances. *Agr. Biol. Chem.* **1964**, 28, 173–178.
6. Abdou, I.M.; Saleh, A.M.; Zohdi, H.F. Synthesis and antitumor activity of 5-trifluoromethyl-2,4-dihydropyrazol-3-one Nucleosides. *Molecules* **2004**, 9 (3), 109–116.
7. Abadi, A.; Al-Deeb, O.; Al-Afify, A.; El-Kashef, H. Synthesis of 4-alkyl (aryl)-6-aryl-3-cyano-2(1H)-pyridinones and their 2-imino isosteres as nonsteroidal cardiotonic agents. *Il Farmaco*, **1999**, 54 (4), 195–201.
8. Stout M.G.; Robins R.K. Synthesis of some quinazoline nucleosides. *J. Org. Chem.* **1968**, 33 (3), 1219–1225.
9. Elgemeie, G.H.; Attia, A.M.; Fathy, N.M. Glycosides of heterocycles: A direct route to 1-(β-D-glycopyranosyl)pyridinethione nucleosides. *Liebigs Ann. Chem.* **1994**, 955–958.
10. Attia, A.M.; Elgemeie, G.H. First glycoside synthesis via piperidinium salts of heterocyclic nitrogen bases: The synthesis of a new class of dihydropyridine thioglycosides. *J. Carbohydr. Chem.* **2002**, 21, 325–339.
11. Niedballa, U.; Vorbruggen, H. Synthesis of nucleosides. 10. General synthesis of *N*-glycosides. II. Synthesis of 6-methyluridines. *J. Org. Chem.*, **1974**, 39, 3660–3663.
12. Vorbrüggen, H.; Krolikiewicz, K. New catalysts for the synthesis of nucleosides. *Angew. Chem.* **1975**, 14, 421–422.
13. Niedballa, U.; Vorbruggen, H. Synthesis of nucleosides. 9. General synthesis of *N*-glycosides. I. Synthesis of pyrimidine nucleosides. *J. Org. Chem.* **1974**, 39, 3654–3660.
14. Niedballa, U.; Vorbruggen, H. Synthesis of nucleosides. 12. General synthesis of *N*-glycosides. Iv. Synthesis of nucleosides of hydroxy and mercapto nitrogen heterocycles. *J. Org. Chem.* **1974**, 39, 3668–3671.

15. Abdou, I.M.; Attia, A.M.; Strekowski, L. Glucopyranosides derived from 6-aryl-5-cyano-2-(methylthio)pyrimidin-4(3*H*)Ones. *Nucleosides, Nucleotides Nucleic Acids*, **2002**, 21, 15–21.
16. Abdou, I.M.; Strekowski, L. A facile synthesis of 6-Aryl-5-cyano-1-(β-D-pyranosyl or β-D-furanosyl)-2-thiocytosines. *Tetrahedron*, **2000**, 56, 8631–8636.
17. El-Sayed, H.A.; Moustafa, A.H.; Haikal, A.Z.; Abdou, I.M.; El-Ashry, E.S.H. Synthesis and evaluation of antimicrobial activity of some pyrimidine glycosides. *Nucleosides, Nucleotides Nucleic Acids*, **2008**, 27, 1061–1071.
18. Amatori, S.; Bagaloni, I.; Macedi, E.; Formica, M.; Giorgi, L.; Fusi, V.; Fanelli, M. Malten, A new synthetic molecule showing in vitro antiproliferative activity against tumour cells and induction of complex DNA structural alterations. *Br. J. Cancer*, **2010**, 103, 239–248.
19. Serova, M.; Galmarini, C.M.; Ghoul, A.; Benhadji, K.; Green, S.R.; Chiao, J.; Faivre, S.; Cvitkovic, E.; Tourneau, C.; Calvo, F.; Raymond, E. Antiproliferative effects of sapacitabine (CYC682), a novel 2′-deoxycytidine-derivative, in human cancer cells. *Br. J. Cancer*, **2007**, 97, 628–636.
20. Galmarini, C.M.; Mackey, J.R.; Dumontet, C. Nucleoside Analogues: Mechanisms of drug resistance and reversal strategies. *Leukemia*, **2001**, 15, 875–90.
21. Bhat, U.G.; Gartel, A.L. Nucleoside analog ARC targets Mcl-1 to induce apoptosis in leukemia cells. *Leukemia*, **2010**, 24, 851–855.