Synthesis and Antimicrobial Evaluation of Some Novel Pyrido[2,3-*d*] Pyrimidine Derivatives and Their Ribofuranosides

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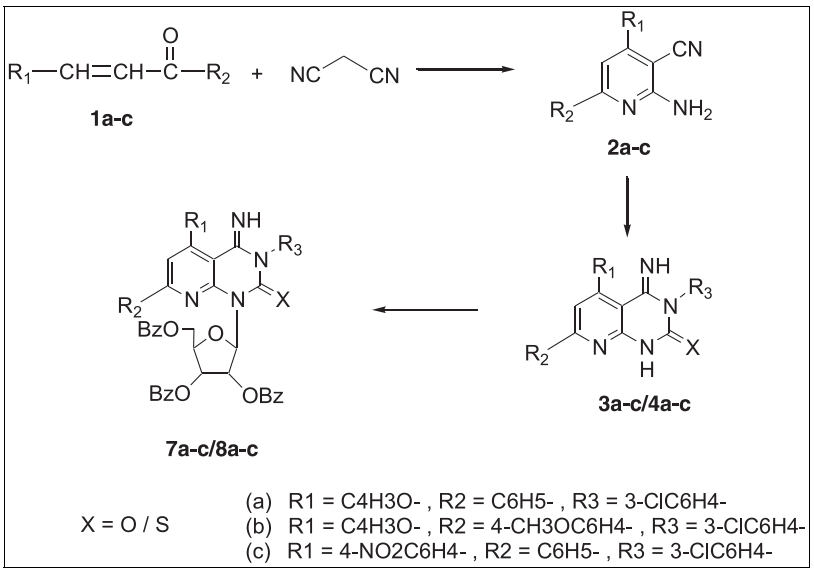

2-Amino-3-cyano-4,6-disubstituted pyridines **2a–c** on treatment with arylisocyanate and arylisothiocyanate afforded 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*] pyrimidin-2(1*H*)-ones **3a–c** and 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin-2(1*H*)-thiones **4a–c**, respectively. The ribofuranosides, namely, 4-imino-3,5,7-trisubstituted-1-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl) pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones **7a–c** and 4-imino-3,5,7-trisubstituted-1-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl) pyrido[2,3-*d*]pyri-midin-2(1*H*)-thiones **8a–c**, were synthesized by the condensation of trimethylsilyl derivatives of **3a–c** and **4a–c** with *β*-D-ribofuranosyl-1-acetate-2,3,5-tribenzoate. The structure of newly synthesized ribofuranosides and their precursors were established by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. All the synthesized compounds were screened for their antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus aureus*, *Aspergillus niger*, and *Aspergillus flavus*.

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INTRODUCTION

Pyrido[2,3-*d*]pyrimidines have attracted tremendous attention because of their diversified medicinal importance, for example, antibacterial [1–3], antitumor [4], antiviral [5], anticancer [6,7], antifungal [8,9], antiulcer [10], anticonvulsant [11,12], antihypertensive [13], and antineoplastic [14]. The ribofuranosides of pyrido[2,3-*d*] pyrimidines have been reported as antileukemic [15], anti-AIDS [16,17], antiherpes [18], hypnotic activity [19], and so forth. Some new pyrido[2,3-*d*]pyrimidines and their ribofuranosides have been synthesized in our previous laboratory work, which showed varying degrees of antimicrobial activity [20–22]. The manifold applications of pyrido[2,3-*d*]pyrimidines and their ribofuranosides have prompted us to target the synthesis of some novel 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin-2-(1*H*)-ones and 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*] pyrimidin-2-(1*H*)-thiones and their ribofuranosides **7a–c** and **8a–c**. Pyrido [2,3-*d*]pyrimidin-2-(1*H*)-ones/thiones and their ribofuranosides have been screened for antibacterial activities with *Escherichia coli and Staphylococcus aureus* and antifungal activity with *Aspergillus niger* and *Aspergillus flavus*.

RESULTS AND DISCUSSION

Chalcones **1a–c** and malononitrile on condensation in the presence of ammonium acetate and ethanol gave 2-amino-3-cyano-4,6-disubstituted pyridines **2a–c** via a Michael-type reaction. Compound **2a–c** on treating with aryl isocyanate/isothiocyanate afforded 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones **3a–c**/thiones **4a–c**. Compound **3a–c/4a–c** were treated with hexamethyldisilazane in toluene, gave the corresponding

trimethylsilyl derivatives **5a–c/6a–c**, which on stirring with *β*-D-ribofuranose-1-acetate-2,3,5-tribenzoate in *vacuo*, at 155–160°C for 10 h, and gave 4-imino-3,5,7-trisubstituted-1-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl) pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones **7a–c/**thiones **8a–c**, respectively (Scheme 1).

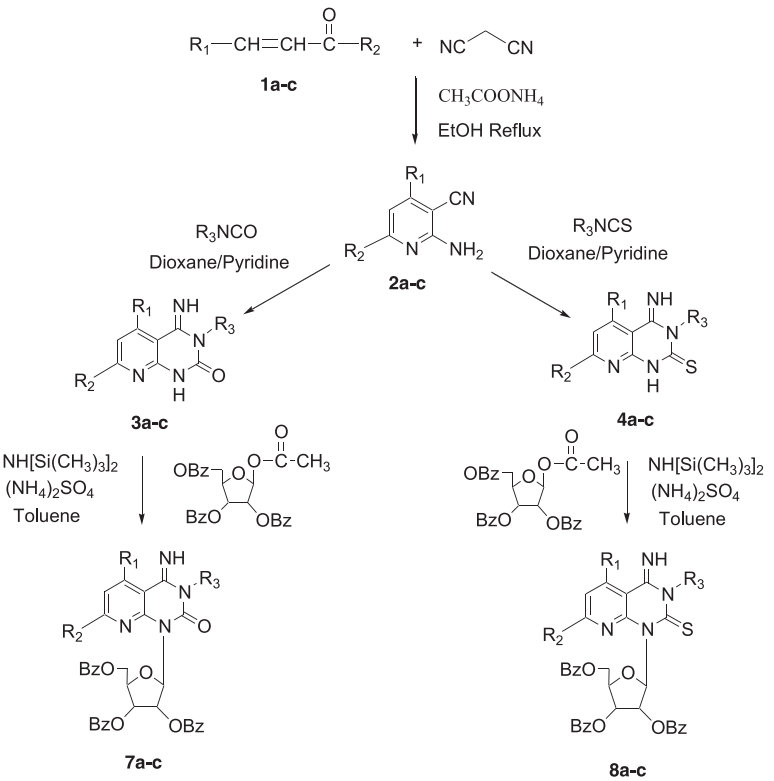
The IR spectra of compound **2a–c** showed a characteristic sharp band at 2210–2185 cm^{-1} indicating the presence of −C≡N group. Band in the region 3440–3305 cm^{-1} was assigned because of asymmetric and symmetric stretching vibrations of $-NH_2$ group. The disappearance of the characteristic absorption band in the region 2210–2185 cm^{-1} due to −C ≡ N group indicates the formation of heterocyclic ring in compounds **3a–c** and **4a–c**. Compounds **3a–c** and **7a–c** showed a characteristic absorption band in the region 1725–1685 cm^{-1} due to >C=O group. Compounds **4a–c** and **8a–c** showed an absorption band in the region 1235–1205 cm^{-1} due to >C=S group. Absorption bands due to >NH and >C=NH appeared in the regions 3375–3330 and 3180–3135 cm^{-1}, respectively, are supportive of the formation of **3a–c** and **4a–c**. Three characteristic bands of NHCS moiety in the region 1500–1355 cm^{-1} have also been observed in compound **4a–c**. Two sharp bands in the region 1545–1530 and 1370–1350 cm^{-1} were observed because of $-NO_2$ stretching vibrations in compounds **3c**, **4c**, **7c**, and **8c** showed.

The disappearance of the band due to >NH in compounds **7a–c** and **8a–c** revealed that N-1 substituted ribofuranosides are produced. The symmetric and asymmetric stretching vibrations due to C-O-C linkage of sugar moiety in compounds **7a–c** and **8a–c** have appeared in the regions 1185 and 1015 cm^{-1}.

^1H NMR spectra of all the synthesized compounds showed a multiplet of aromatic protons at 6.87–8.13 ppm. The >NH protons appeared as a singlet at 7.86–8.02 ppm in compounds **3a–c** and **4a–c**. The >C=NH protons in compounds **3a–c**, **4a–c**, **7a–c**, and **8a–c** appeared as a singlet at 8.71–8.95 ppm. Peak due to $-OCH_3$ protons appeared as a singlet at 3.77–3.90 ppm in compounds **3b**, **4b**, **7b**, and **8b**.

The disappearance of the peak due to >NH moiety in compounds **7a–c** and **8a–c** indicates the site of attachment of the sugar. In the sugar, proton at C_1'' caused a doublet at 6.52–6.63 ppm. C_2'', C_3'', and C_4'' protons

Scheme 1. Synthesis of 4-lmino-3,5,7-trisubstituted pyrido[2,3-*d*]pyramidines.



Wherein

(a) R_1= C_4H_3O- , R_2 = C_6H_5- , R_3 = 3-ClC_6H_4-
(b) R_1= C_4H_3O- , R_2 = 4-$CH_3OC_6H_4$- , R_3 = 3-ClC_6H_4-
(c) R_1= 4-$NO_2C_6H_4$- , R_2 = C_6H_5- , R_3 = 3-ClC_6H_4-

appeared as a multiplet at 4.81–4.96 ppm, and C_5'' protons caused a doublet in the region at 4.31–4.47 ppm. The characterization data of the synthesized compounds are given in Table 1.

Antimicrobial studies. All the synthesized compounds were screened for their antibacterial and antifungal activities against *E. coli* (Gram-negative bacteria), *S. aureus* (Gram-positive bacteria), *A. niger*, and *A. flavus* (Fungi) at the concentration of 100 μg/disc. Streptomycin and mycostatin were used as reference compounds, respectively.

The disc diffusion method developed by Varma *et al*. [23] has been followed. The results have been tabulated (Table 2) in the form of inhibition zones and activity indices. Although all the compounds show moderate to fairly good activities, a closer look at the activity indices reveals that the ribofuranosides are better antimicrobial agents than their bases.

Table 1

Characterization data of compounds **3a–c**, 4**a–c**, **7a–c**, and **8a–c**.

Compounds	R_1	R_2	R_3	Molecular formula	Yield %	M.P. °C	Found (%)/(cal.) C	H	N
3a	C_4H_3O-	C_6H_5-	3-ClC_6H_4-	$C_{23}H_{15}N_4O_2Cl$	64	>300	66.58 (66.60)	3.61 (3.64)	13.58 (13.51)
3b	C_4H_3O-	4-$CH_3OC_6H_4-$	3-ClC_6H_4-	$C_{24}H_{17}N_4O_3Cl$	67	274–76	64.72 (64.80)	3.87 (3.85)	12.61 (12.59)
3c	4-$NO_2C_6H_4-$	C_6H_5-	3-ClC_6H_4-	$C_{25}H_{16}N_5O_3Cl$	62	258–60	63.94 (63.94)	3.37 (3.43)	14.88 (14.90)
4a	C_4H_3O-	C_6H_5-	3-ClC_6H_4-	$C_{23}H_{15}N_4OSCl$	78	280–82	64.50 (64.11)	3.48 (3.52)	13.08 (13.00)
4b	C_4H_3O-	4-$CH_3OC_6H_4-$	3-ClC_6H_4-	$C_{24}H_{17}N_4O_2SCl$	69	244–46	62.57 (62.55)	3.76 (3.72)	12.12 (12.15)
4c	4-$NO_2C_6H_4-$	C_6H_5-	3-ClC_6H_4-	$C_{25}H_{16}N_5O_2SCl$	65	230–32	63.94 (63.910	3.37 (3.43)	14.88 (14.90)
7a	C_4H_3O-	C_6H_5-	3-ClC_6H_4-	$C_{49}H_{35}N_4O_9Cl$	75	288–90	68.48 (68.50)	4.07 (4.10)	6.58 (6.52)
7b	C_4H_3O-	4-$CH_3OC_6H_4-$	3-ClC_6H_4-	$C_{50}H_{37}N_4O_{10}Cl$	80	220–22	67.50 (67.54)	4.27 (4.19)	6.28 (6.30)
7c	4-$NO_2C_6H_4-$	C_6H_5-	3-ClC_6H_4-	$C_{51}H_{36}N_5O_{10}Cl$	71	208–10	67.04 (67.00)	3.97 (3.97)	7.62 (7.66)
8a	C_4H_3O-	C_6H_5-	3-ClC_6H_4-	$C_{49}H_{35}N_4O_8SCl$	68	227–29	67.28 (67.25)	4.07 (4.03)	6.35 (6.40)
8b	C_4H_3O-	4-$CH_3OC_6H_4-$	3-ClC_6H_4-	$C_{50}H_{37}N_4O_9SCl$	73	213–15	66.32 (66.33)	4.10 (4.12)	6.24 (6.20)
8c	4-$NO_2C_6H_4-$	C_6H_5-	3-ClC_6H_4-	$C_{51}H_{36}N_5O_9SCl$	71	196–98	65.84 (65.84)	3.92 (3.90)	7.52 (7.53)

Table 2

Antimicrobial activity of the synthesized compounds **3a–c**, **4a–c**, **7a–c**, and **8a–c**. Zone of inhibition in (mm) (activity index).

Compounds	Antibacterial activity *Escherichia coli*	Antibacterial activity *Staphylococcus aureus*	Antifungal activity *Aspergillus niger*	Antifungal activity *Aspergillus flavus*
3a	7.7 (0.83)	7.9 (0.87)	8.3 (0.95)	9.1 (0.93)
3b	8.1 (0.91)	8.2 (0.94)	8.8 (1.01)	9.7 (1.12)
3c	8.3 (0.88)	8.5 (0.96)	9.1 (1.06)	9.9 (1.15)
4a	8.4 (0.97)	8.8 (0.99)	9.3 (1.09)	9.3 (1.03)
4b	8.7 (1.03)	9.2 (0.98)	9.5 (1.14)	9.6 (1.09)
4c	8.9 (1.04)	9.4 (1.06)	9.6 (1.18)	9.8 (1.13)
7a	9.1 (1.06)	9.5 (1.09)	9.7 (1.21)	10.0 (1.15)
7b	9.2 (1.09)	9.7 (1.14)	10.0 (1.23)	10.1 (1.18)
7c	9.6 (1.12)	9.9 (1.17)	10.4 (1.25)	9.5 (1.08)
8a	9.9 (1.17)	10.1 (1.19)	10.1 (1.26)	10.3 (1.20)
8b	10.2 (1.21)	10.4 (1.22)	10.8 (1.29)	10.4 (1.22)
8c	10.4 (1.24)	10.7 (1.25)	11.0 (1.31)	10.8 (1.24)

Activity index = Inhibition area of the sample/Inhibition area of the standard.

CONCLUSION

In conclusion, we have described the synthesis of some novel pyrido[2,3-*d*]pyrimidine derivatives and their ribofuranosides; and antimicrobial screening against *E. coli* (Gram-negative bacteria), *S. aureus* (Gram-positive bacteria), *A. niger*, and *A. flavus* (Fungi). A closer observation reveals that most of the ribofuranosides exhibited fairly good activities as compared with their parent nucleus.

EXPERIMENTAL

Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. IR spectra were determined in KBr disc on SHIMADZU FT-IR spectrophotometer and ^{1}H NMR spectra on a JEOL AL-300 MHz NMR spectrophotometer in $CDCl_3$ using TMS as an internal standard; and ^{13}C NMR spectra on a JEOL AL-75 MHz NMR spectrophotometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were taken on a Thermoscientific TSQ 8000 triple quadrupole GC–MS/MS with pyroprobe 5000 mass spectrometer. The purity of compounds was checked by TLC using silica gel "G" as adsorbent and visualization was accomplished by UV light or iodine vapors in a chamber. Chalcones were synthesized by reported method [24].

Synthesis of 2-amino-3-cyano-4,6-disubstituted pyridine (2a–c). An appropriate chalcone (0.05 mol), malononitrile (0.05 mol), and ammonium acetate (0.4 mol) in ethanol (150 mL) was refluxed on a water bath for 13–15 h, and then the content of the flask was cooled and was poured onto crushed ice with constant shaking. The solid, thus obtained, was washed with water several times and finally with cold ethanol. The residue was recrystallized from ethanol.

Synthesis of 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*] pyrimidin-2(1*H*)-ones (3a–c). A mixture of compound **2a–c** (0.01 mol), 3-chlorophenylisocyanate (0.01 mol), dioxane (18.0 mL), and pyridine (2.0 mL) was refluxed at 150°C for about 14–16 h. After cooling, the crushed ice was added to it with constant stirring. The yellow solid mass, thus obtained, was washed with water. The dried crude product, so obtained, was recrystallized from DMF-ethanol (1:10). The spectral data of compound **3a–c** are presented in the following.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-phenylpyrido[2,3-d]pyrimidin-2(1H)-one (3a). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3355 (>NH), 3170 (>C=NH), 1695 (>C=O). ^{1}H NMR (300 MHz, $CDCl_3$) 6.96–7.87 (m, 13H, ArH), 7.96 (s, 1H, >NH), 8.85 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 164.40 (N-C=NH), 159.60 (N=C-NH), 157.70 (N-C=O), 156.60, 154.20, 152.40, 142.20, 139.60, 138.10, 134.10, 130.30, 129.40, 127.20, 124.10, 120.10, 118.20, 111.30, 110.40, 108.60, 105.10 (aromatic carbons); MS: *m*/*z* 412.9 [M + H]$^+$ for $C_{23}H_{15}N_4O_2Cl$.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-(4′-methoxyphenyl)-pyrido[2,3-d] pyrimidin-2(1H)-one (3b). Yellow solid, IR (KBr) (ν_{max}/cm^{-1}) 3335 (>NH), 3145 (>C=NH), 1685 (>C=O). ^{1}H NMR (300 MHz, $CDCl_3$) 3.83 (s, 3H, -OCH_3), 6.90–7.84 (m, 12H, ArH), 7.92 (s, 1H, >NH), 8.74 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 164.10 (N-C=NH), 160.60 (-C-OCH_3) 159.30 (N=C-NH), 158.80(N-C=O), 56.10 (-O-CH3), 156.90, 154.40, 144.40, 142.80, 138.50, 133.90, 130.10, 128.10, 125.10, 120.90, 117.90, 109.80, 110.0, 108.20, 105.40 (aromatic carbons); MS: *m*/*z* 443.7 [M + H]$^+$ for $C_{24}H_{17}N_4O_3Cl$.

4-Imino-3-(3′-chlorophenyl)-5-(4′-nitrophenyl)-7-phenylpyrido [2,3-d] pyrimidin-2(1H)-one (3c). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3375 (>NH), 3180 (>C=NH), 1710 (>C=O). ^{1}H NMR (300 MHz, $CDCl_3$) 7.03–8.11 (m, 14H, ArH), 8.02 (s, 1H, >NH), 8.90 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 164.80 (N-C=NH), 159.10 (N=C-NH), 158.30 (N-C=O), 157.35, 152.20, 149.60, 148.90, 144.50, 139.80, 139.10, 134.40, 130.60, 129.70, 127.50, 124.60, 118.70, 111.80, 108.80 (aromatic carbons); MS: *m*/*z* 466.3 [M + H]$^+$ for $C_{25}H_{16}N_5O_3Cl$.

Synthesis of 4-imino-3,5,7-trisubstituted pyrido[2,3-*d*] pyrimidin-2(1*H*)-thiones (4a–c). Compounds of **2a–c** (0.01 mol), 3-chlorophenylisothiocyanate (0.01 mol), dioxane (18.0 mL), and pyridine (2.0 mL) were refluxed at 150°C for about 14–16 h. After cooling, the contents of the flask were poured onto crushed ice with constant stirring. The yellow solid mass, thus obtained, was washed with water. The dried crude product was recrystallized form DMF-ethanol (1:10). Spectral data of compound **3a–c** are presented in the following.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-phenylpyrido[2,3-d]pyrimidin-2(1H)-thione (4a). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3340 (>NH), 3160 (>C=NH), 1220 (>C=S). ^{1}H NMR (300 MHz, $CDCl_3$) 6.94–7.82 (m, 13H, ArH), 7.90 (s, 1H, >NH), 8.82 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 179.40 (N-C=S), 163.20 (N-C=NH), 159.0 (N=C-NH), 158.10, 153.80, 142.10, 140.80, 139.10, 134.0, 130.0, 129.10, 127.0, 125.60, 124.90, 111.25, 110.20, 108.45 (aromatic carbons); MS: *m*/*z* 429.65 [M + H]$^+$ for $C_{23}H_{15}N_4OSCl$.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-(4′-methoxyphenyl)-pyrido[2,3-d] pyrimidin-2(1H)-thione (4b). Yellow solid, IR (KBr) (ν_{max}/cm^{-1}) 3330 (>NH), 3135 (>C=NH), 1205 (>C=S). ^{1}H NMR (300 MHz, $CDCl_3$) 3.77 (s, 3H, $-OCH_3$), 6.87–7.79 (m, 12H, ArH), 8.71 (s, 1H, >C=NH), 7.86 (s, 1H, >NH). ^{13}C NMR (75 MHz, $CDCl_3$) 179.15 (N-C=S), 163.05 (N-C=NH), 160.20 ($-$C-OCH_3) 159.0 (N=C-NH), 55.80 ($-$O-CH3), 157.90, 153.60, 142.50, 140.55, 133.75, 132.20, 129.95, 128.0, 125.05, 124.70, 114.80, 111.10, 109.65,

108.15, 105.0 (aromatic carbons); MS: *m*/*z* 458.9 $[M + H]^+$ for $C_{24}H_{17}N_4O_2SCl$.

4-Imino-3-(3′-chlorophenyl)-5-(4′-nitrophenyl)-7-phenyl-pyrido[2,3-d] pyrimidin-2(1H)-thione (4c). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3365 (>NH), 3175 (>C=NH), 1230 (>C=S). ^1H NMR (300 MHz, $CDCl_3$) 7.01–8.05 (m, 14H, ArH), 7.98 (s, 1H, >NH), 8.87 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 179.80 (N-C=S), 163.45 (N-C=NH), 159.60 (N=C-NH), 158.15, 149.20, 148.40, 144.0, 140.60, 139.50, 134.30, 130.20, 129.40, 127.90, 127.20, 125.10, 124.30, 123.40, 109.0, 107.80 (aromatic carbons); MS: *m*/*z* 483.45 $[M + H]^+$ for $C_{25}H_{16}N_5O_2SCl$.

Synthesis of 4-imino-3,5,7-trisubstituted-1-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl) pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones (7a–c). 4-Imino-3,5,7-trisubstituted pyrido[2,3-*d*] pyrimidin-2(1*H*)-ones **3a–c** (0.002 mol) in toluene (30 mL) were treated with hexamethyl disilazane (0.0124 mol) in the presence of few crystals of ammonium sulfate, and the contents were refluxed for 4 h. The clear-colored solution, thus obtained, was filtered, and the solvent was removed in *vacuo* at 100°C. The sugar *β*-D-ribofuranosyl-1-acetate-2,3,5-tribenzoate (0.02 mol) was added to the previous pasty mixture and then stirred at 140–145°C, under *vacuum* was regularly applied for 5 min, at the end of each hour. The melt, so obtained, was boiled in methanol for 10 min, cooled and filtered. The viscous mass of the ribofuranoside, so obtained, was recrystallized from diethyl ether. The spectral data of compound **7a–c** are presented in the following.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-phenyl-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-2(1H)-one (7a). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3160 (>C=NH), 1705 (>C=O). ^1H NMR (300 MHz, $CDCl_3$) 4.38 (d, 2H, C_5'' Sugar), 4.89–4.93 (m, 3H, C_2'', C_3'', and C_4'' Sugar), 6.60 (d, 1H, C_1'' Sugar), 7.35–8.15 (m, 15H, OBz), 7.65–7.90 (m, 13H, ArH), 8.89 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 167.80 (-OCO-Ph), 164.50 (N-C=NH), 159.20 (N=C-NH), 158.30 (N-C=O), 157.10, 154.10, 153.40, 144.90, 142.20, 139.80, 139.10, 134.60, 130.70, 129.60, 129.0, 128.50, 127.20, 124.40, 120.90, 118.40, 111.90, 110.20, 108.70 (aromatic carbons), 81.30, 74.80, 70.0, 68.90, 65.20 (C_1''- C_5'' Sugar); MS: *m*/*z* 858.1 $[M + H]^+$ for $C_{49}H_{35}N_4O_9Cl$.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-(4′-methoxyphenyl)-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyramidin-2(1H)-ones (7b). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3145 (>C=NH), 1700 (>C=O). ^1H NMR (300 MHz, $CDCl_3$) 3.90 (s, 3H, $-OCH_3$), 4.32 (d, 2H, C_5'' Sugar), 4.84–4.95 (m, 3H, C_2'', C_3'', and C_4'' Sugar), 6.54 (d, 1H, C_1'' Sugar), 7.32–8.19 (m, 15H, OBz), 7.55–7.80 (m, 12H, ArH), 8.80 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 167.20 (−OCO-Ph), 164.40 (N-C=NH), 160.60 (−C-OCH_3), 159.0 (N=C-NH), 158.50 (N-C=O), 157.80, 154.0, 153.20, 144.80, 142.10, 139.0, 134.40, 132.10, 130.70, 128.20, 129.10, 128.50, 124.30, 120.80, 118.20, 114.70, 111.50, 110.40, 108.60 (aromatic carbons), 81.10, 74.40, 70.10, 68.80, 65.0 (C_1''- C_5'' Sugar), 56.30 (−O-CH3); MS: *m*/*z* 887.6 $[M + H]^+$ for $C_{50}H_{37}N_4O_{10}Cl$.

4-Imino-3-(3′-chlorophenyl)-5-(4′-nitrophenyl)-7-phenyl-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-2(1H)-ones (7c). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3195 (>C=NH), 1725 (>C=O). ^1H NMR (300 MHz, $CDCl_3$) 4.47 (d, 2H, C_5'' Sugar), 4.91–4.96 (m, 3H, C_2'', C_3'', and C_4'' Sugar), 6.63 (d, 1H, C_1'' Sugar), 7.38–8.19 (m, 15H, OBz), 7.72–8.13 (m, 12H, ArH), 8.95 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 168.0 (−OCO-Ph), 164.80 (N-C=NH), 159.40 (N=C-NH), 158.50 (N-C=O), 158.20, 149.40, 148.50, 144.20, 140.70, 139.90, 134.80, 131.0, 129.90, 129.40, 127.50, 125.90, 124.80, 123.60, 118.60, 109.0, 107.80 (aromatic carbons), 81.50, 75.10, 70.2, 69.20, 65.40 (C_1''- C_5'' Sugar); MS: *m*/*z* 912.4 $[M + H]^+$ for $C_{51}H_{36}N_5O_{10}Cl$.

Synthesis of 4-Imino-3,5,7-trisubstituted-1-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidin-2(1*H*)-thiones (8a–c). 4-Imino-3,5,7-trisubstituted pyrido [2,3-*d*]pyrimidin-2(1*H*)-thiones **4a–c** (0.002 mol) in toluene (30 mL) was reacted with hexamethyldisilazane (0.0124 mol) in the presence of ammonium sulfate. The contents were refluxed for 4 h. The clear solution, thus obtained, was filtered, and the solvent was removed in *vacuo* at 100°C. The sugar *β*-D-ribofuranosyl-1-acetate-2,3,5-tribenzoate (0.02 mol) was added to the previous pasty mixture and then stirred at 140–145°C, under *vacuum* was regularly applied for 5 min, at the end of each hour. The melt was boiled in methanol for 10 min, cooled and filtered. The viscous mass of the ribofuranoside, so obtained, was recrystallized from diethyl ether. The spectral data of compound **8a–c** are presented in the following.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-phenyl-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-2(1H)-thione (8a). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3155 (>C=NH), 1225 (>C=S). ^1H NMR (300 MHz, $CDCl_3$) 4.36 (d, 2H, C_5'' Sugar), 4.87–4.92 (m, 3H, C_2'', C_3'', and C_4'' Sugar), 6.59 (d, 1H, C_1'' Sugar), 7.34–8.13 (m, 15H, OBz), 7.62–7.85 (m, 13H, ArH), 8.87 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 177.10 (N-C=S), 167.40 (−OCO-Ph), 164.30 (N-C=NH), 159.10 (N=C-NH), 158.25, 154.0, 153.10, 144.50, 142.40, 139.20, 138.90, 134.30, 130.10, 129.20, 128.40, 128.30, 127.0, 124.20, 120.80, 118.30, 111.20, 110.0, 108.50 (aromatic carbons), 81.20, 74.70, 70.1, 68.70, 65.10 (C_1''- C_5'' Sugar); MS: *m*/*z* 872.75 $[M + H]^+$ for $C_{49}H_{35}N_4O_8SCl$.

4-Imino-3-(3′-chlorophenyl)-5-furane-2-yl-7-(4′-methoxyphenyl)-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyramidin-2(1H)-thiones (8b). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3135(>C=NH), 1215 (>C=S). ^1H NMR (300 MHz, $CDCl_3$) 3.87 (s, 3H, -OCH_3), 4.31 (d, 2H, C_5'' Sugar),

4.81–4.90 (m, 3H, C_2'', C_3'', and C_4'' Sugar), 6.52 (d, 1H, C_1'' Sugar), 7.30–8.17 (m, 15H, OBz), 7.52–7.92 (m, 12H, ArH), 8.78 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 177.60 (N-C=S), 167.10 (-OCO-Ph), 164.20 (N-C=NH), 160.10 (−C-OCH_3), 158.80 (N=C-NH), 158.40, 154.10, 153.0, 144.50, 142.0, 138.80, 134.20, 132.0, 130.40, 128.0, 129.0, 128.20, 124.0, 120.50, 118.10, 114.30, 111.20, 110.20, 108.50 (aromatic carbons), 81.0, 74.20, 70.0, 68.60, 64.90 (C_1''- C_5'' Sugar);, 56.20 (−O-CH3); MS: *m/z* 903.8 $[M + H]^+$ for $C_{50}H_{37}N_4O_9SCl$.

4-Imino-3-(3′-chlorophenyl)-5-(4′-nitrophenyl)-7-phenyl-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidin-2(1H)-thiones (8c). Brown solid, IR (KBr) (ν_{max}/cm^{-1}) 3190 (>C=NH), 1235 (>C=S). ^{1}H NMR (300 MHz, $CDCl_3$) 4.39 (d, 2H, C_5'' Sugar), 4.90–4.94 (m, 3H, C_2'', C_3'', and C_4'' Sugar), 6.61 (d, 1H, C_1'' Sugar), 7.36–8.21 (m, 15H, OBz), 7.78–8.32 (m, 12H, ArH), 8.93 (s, 1H, >C=NH). ^{13}C NMR (75 MHz, $CDCl_3$) 178.30 (N-C=S), 167.90 (-OCO-Ph), 164.60 (N-C=NH), 159.20 (N=C-NH), 158.30, 149.30, 148.10, 144.0, 140.50, 139.70, 134.60, 131.10, 129.60, 129.0, 127.40, 125.70, 124.50, 123.20, 118.10, 108.80, 107.50, 81.40, 74.80, 70.10, 69.0, 65.30; MS: *m/z* 928.5 $[M + H]^+$ for $C_{51}H_{36}N_5O_9SCl$.

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