Carbohydrates to Functionalized Pyridines: A New Synthetic Approach via Enol-Driven Ring Transformations

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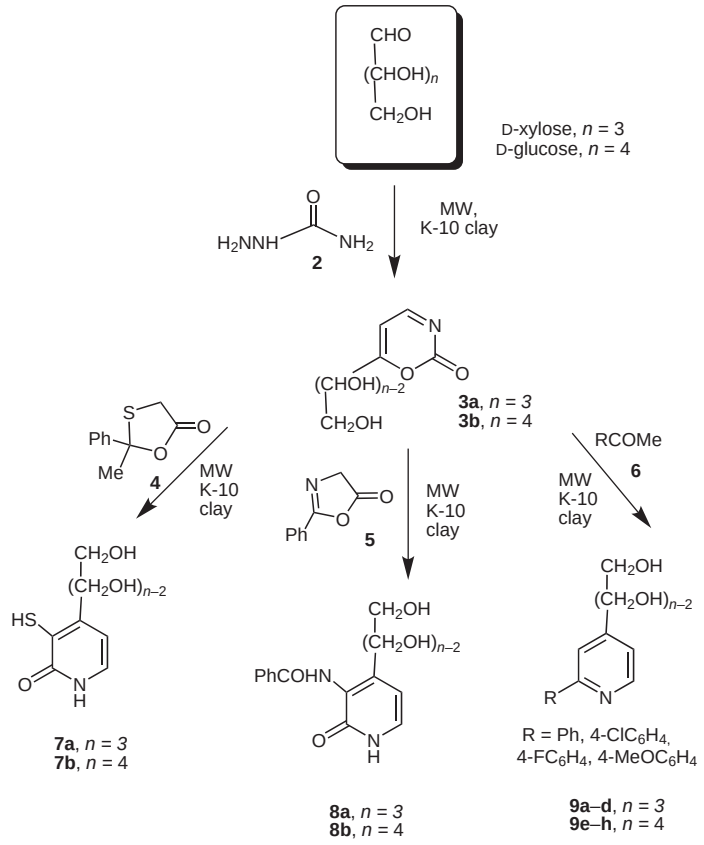
Abstract: An expeditious synthetic protocol for polyhydroxyalkylpyridines and their 3-amino/mercapto-2-pyridinone analogues using unprotected aldoses as biorenewable resources is reported. The synthesis involves enol-driven Michael-type addition of lactones/ketones to aldose-derived 1,3-oxazin-2-ones followed by decarboxylative ring transformation to yield various novel polyhydroxyalkylpyridines. This is a one-pot nanoclay (K-10 clay)-catalyzed process proceeding under conditions of solvent-free microwave irradiation.

Key words: carbohydrates, mineral-catalyzed, microwaves, 1,3-oxazin-2-ones, pyridines, solvent-free

Pyridines and pyridinones are basic structural motifs present in various useful medicinal products. Amlodipine (Norvasac®), a dihydropyridine (DHP) derivative belonging to a class of medications called calcium channel blockers, was approved by the FDA in 2004, and is presently in clinical use for the treatment of high blood pressure and angina. Other DHP derivatives, nifedipine[1] and nicardipine,[2] were also approved by the FDA in 1981 and 1988, respectively, for the same purpose. Isoniazid is being popularly used in tuberculosis therapy since its release in 1952. Recently, certain pyridine derivatives have been reported as a new class of unnatural anti-HIV agents with multiple mechanisms of antiviral action.[3] The amino and mercapto functions are synthetically and pharmacologically readily manipulable. Several molecules embedded with, or derived from, 3-amino/mercaptopyridine-2(1*H*)-one scaffolds have been found to be HIV-1 reverse transcriptase and thrombin inhibitors, and antihypertensive agents.[4,5]



Scheme 1 Formation of functionalized pyridines **7**–**9** from xylose/glucose

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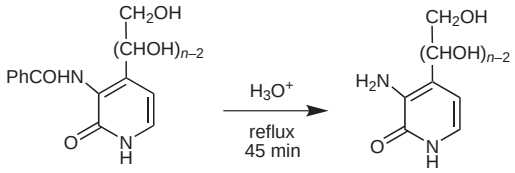
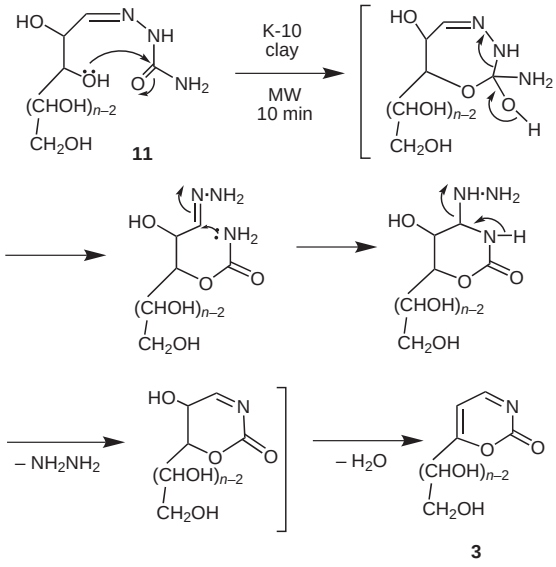


Scheme 2 Debenzoylation of **8** to the corresponding amino analogues **10**

Most of the best-established methods for the synthesis of pyridines are based on cyclization reactions, for example the venerable Hantzsch synthesis and its variants. An alternative method for forming the pyridine ring involves [4+2] cycloaddition reactions using azadienes, especially heterocyclic rather than acyclic, and electron-rich alkenes and alkynes.[6–8] In these reactions the initial cycloaddition is followed by a retro-Diels–Alder reaction in which a small stable molecule, such as HCN, CO_2, or N_2 is eliminated.

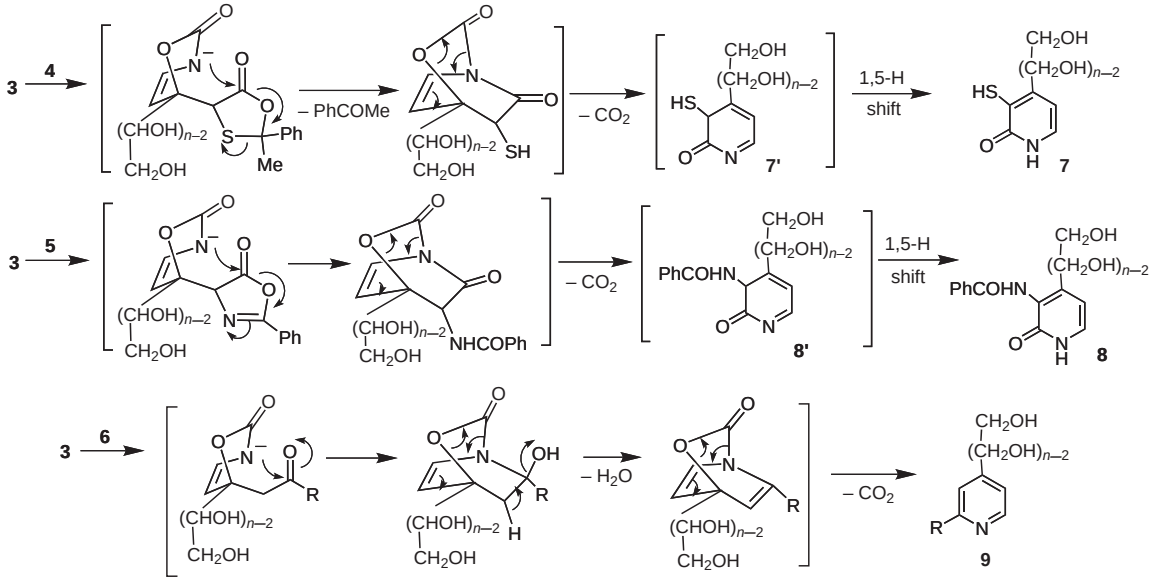
Use of biorenewable resources in organic syntheses is a promising approach as it is in accordance with the sustainable development. The polyhydroxyalkyl dihydropyridines incorporating the NH_2 and SH functions reported herein are hitherto unknown, and neither known synthetic approaches to pyridines nor functionalization reactions of heterocycles can be used for their synthesis, although they appear to be attractive scaffolds for exploiting chemical diversity and generating drug-like library to screen for lead candidates. Aside from the simple expectation that the presence of sugar residues with free hydroxyl groups in DHP should increase the water solubility and bioavailability, other interesting biological properties may arise owing to the extensive and essential role of carbohydrates in the complex machinery of various glycoconjugate biological activity.[9,10]



Scheme 3 Plausible mechanism for the formation of 1,3-oxazin-2-ones **3** from xylose/glucose semicarbazone **11**

In view of the above mentioned valid points and in continuation of our quest for novel microwave (MW)-assisted solvent-free heterocyclization processes,[11–15] especially using carbohydrates as starting material,[11,12] we report herein an unprecedented synthesis of functionalized pyridines **7**–**9** using D-xylose/D-glucose **1** as biorenewable resources (Scheme 1). In this protocol acid-catalyzed cyclization of D-glucose/D-xylose semicarbazones **11** yields the corresponding precursors 1,3-oxazin-2-ones **3**, which undergo enol-driven deacarboxylative ring transformation with enolic entities to furnish polyhydroxyalkyl pyridines **7**, **8**, and **9** (Scheme 4). Compounds **3** and **7**–**10** are hitherto unreported.

After considerable experimentation, it was found that the envisaged synthetic strategy was successful using 1,3-ox-



Scheme 4 Plausible mechanism for the formation of pyridines **7**–**9**

azin-2-ones **3**, which were obtained in 79–82% yields via Montmorillonite K-10 clay catalyzed domino cycloisomerization, dehydrazination, and dehydration of glucose/xylose semicarbazones **11** under solvent-free MW irradiation conditions in a one-pot procedure (Scheme 3).[16] The mechanism shown in Scheme 3 is supported by the formation of hydrazine during the reaction as detected by *p*-dimethylaminobenzaldehyde method.[17] It was noted that other mineral catalysts, viz. silica gel, neutral or basic alumina, were far less effective resulting in either no reaction (in the case of basic alumina) or relatively very low yields (15–28%) of **3** (in the cases of silica gel and neutral alumina). The solvent-free MW irradiation of an equimolar mixture of a 1,3-oxazin-2-one **3**, oxathiolanone **4**, azalactone **5**, or a ketone **6**, in the presence of Montmorillonite K-10 clay (particle size 32.7 nm) afforded the corresponding pyridine analogues **7**, **8**, or **9** in 83–94% yields (Scheme 1, Table 1).[18] Compounds **8** could be easily debenzoylated to furnish the corresponding amino analogues **10** (Scheme 2).[19] The use of other mineral catalysts, viz. silica gel, neutral or basic alumina, resulted in relatively very low yields of **7**, **8**, and **9** (19–35%).

The precursor 1,3-oxazin-2-ones **3** are endowed with two electrophilic centers, C-2 and C-6, in which the latter is highly prone to Michael-type nucleophilic attack due to the extended conjugation with electron-withdrawing N–C=O grouping. In the presence of an acid (K-10 clay), the reaction is possibly initiated by the enol form of the compounds **4**, **5**, and **6**, which acts as a nucleophile and preferentially attacks at the highly electrophilic center C-6 of the oxazine ring driving the decarboxylative ring transformation to yield **7**, **8**, and **9**, respectively (Scheme 4).

The same products **7**, **8**, and **9** were obtained even if 2-thione analogues of 1,3-oxazin-2-ones **3** were used. This supports the plausible mechanisms outlined in Scheme 4. It is noteworthy that we could isolate only aromatic 1,2-dihydropyrimidin-2-ones **7** and **8** instead of the nonaromatic 2,3-dihydropyrimidin-2-ones **7′** and **8′**, which are related to the former by a 1,5-proton shift.

Table 1 K-10 Clay Catalyzed Microwave-Activated Solvent-Free Synthesis of Functionalized Pyridines **7**–**9**

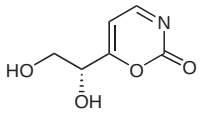
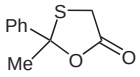
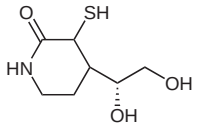
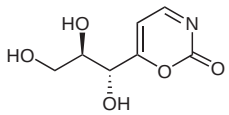
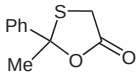
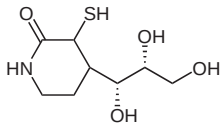
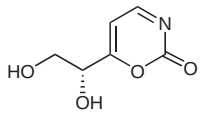
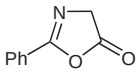
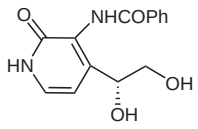
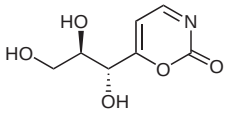
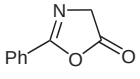
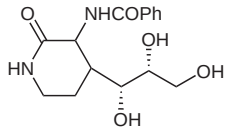
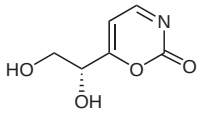
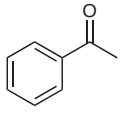
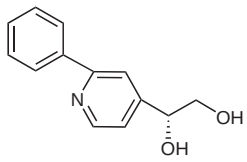
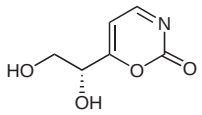
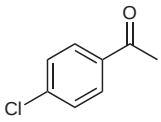
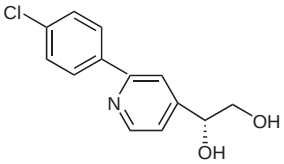
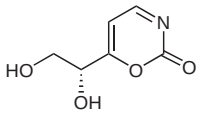
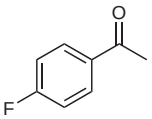
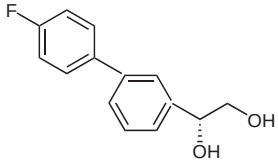
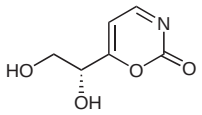
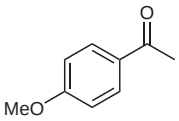
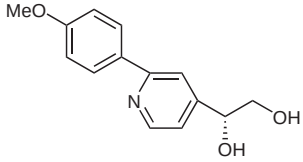
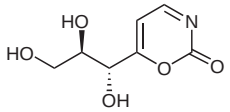
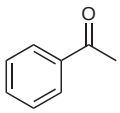
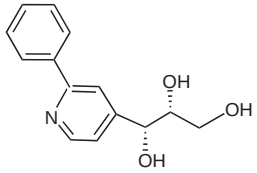
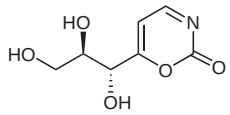
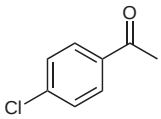
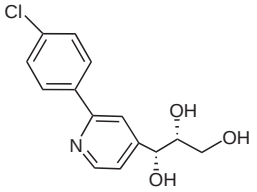
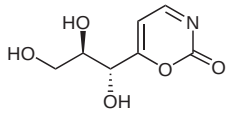
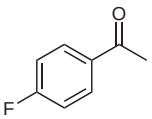
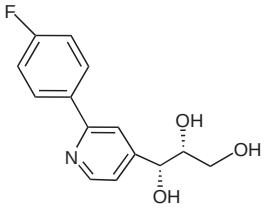
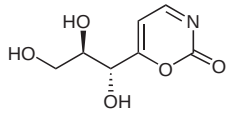
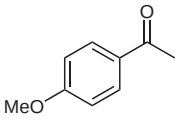
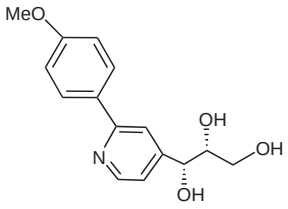
Entry	Oxazine	Lactone/ketone	Product	Time (min)[a]	Yield (%)[b,c]
1			 **7a**	9	89
2			 **7b**	10	91
3			 **8a**	10	94
4			 **8b**	1	92
5			 **9a**	7	83

Table 1 K-10 Clay Catalyzed Microwave-Activated Solvent-Free Synthesis of Functionalized Pyridines **7**–**9** (continued)

Entry	Oxazine	Lactone/ketone	Product	Time (min)[a]	Yield (%)[b,c]
6			 **9b**	9	85
7			 **9c**	8	91
8			 **9d**	10	87
9			 **9e**	8	88
10			 **9f**	10	92
11			 **9g**	10	4
12			 **9h**	11	90

[a] Microwave irradiation time at 90 °C.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H, and N analyses within ± 0.35% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

In conclusion, we have devised efficient routes for the synthesis of novel polyhydroxyalkylpyridines and their 3-amino/mercapto-2-pyridinone analogues of remarkable pharmacological potential from unprotected aldoses as

biorenewable resources. The synthesis is effected under conditions of K-10 clay catalysis and solvent-free microwave irradiation.

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(16) **General Procedure for the Synthesis of 6-Polyhydroxyalkyl-1,3-oxazin-2-ones 3**
Thoroughly mixed aldose semicarbazone **11** (2.0 mmol) and Montmorillonite K-10 clay (0.20 g) were taken in a 20 mL vial and subjected to MW irradiation in a CEM Discover Focused Microwave Synthesis System at 90 °C for 10 min. After completion of the reaction as indicated by TLC, H_2O (10 mL) was added to give the crude product, which was recrystallized from EtOH to obtain an analytically pure sample of **3** as a white solid.
Characterization Data for Synthesized Compounds
Compound **3a**: white solid; mp 145–148 °C. IR (KBr): 3392, 3386, 3011, 1692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 4.11 (dd, $J_{2'Ha,2'Hb}$ = 10.1 Hz, $J_{1'H,2'Ha}$ = 5.4 Hz, 1 H, 2′H_a), 4.30 (dd, $J_{1'H,2'Ha}$ = 5.4 Hz, $J_{1'H,2'Hb}$ = 2.9 Hz, 1 H, 1′H), 4.63 (dd, $J_{2'Ha,2'Hb}$ = 10.1 Hz, $J_{1'H,2'Hb}$ = 2.9 Hz, 1 H, 2′H_b), 4.93–5.21 (br s, 2 H, 2 × OH, exch. D_2O), 7.48 (d, $J_{4H,5H}$ = 8.1 Hz, 1 H, 5-H), 7.89 (d, $J_{4H,5H}$ = 8.1 Hz, 1 H, 4-H). ^{13}C NMR (100 MHz, DMSO-d_6/TMS): δ = 64.5, 65.3, 73.7, 86.2, 105.9, 174.5. MS (FAB): *m/z* = 158 [MH^+]. Anal. Calcd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.91. Found: C, 46.17; H, 4.58; N, 8.79.
Compound **3b**: white solid; mp 153–155 °C. IR (KBr): 3399–3382, 3008, 1689 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.88 (ddd, $J_{2'H,3'Ha}$ = 5.4 Hz, $J_{1'H,2'H}$ = 4.6 Hz, $J_{2'H,3'Hb}$ = 2.7 Hz, 1 H, 2′H), 4.03 (dd, $J_{3'Ha,3'Hb}$ = 10.5 Hz, $J_{2'H,3'Ha}$ = 5.4 Hz, 1 H, 3′H_a), 4.37 (d, $J_{1'H,2'H}$ = 4.6 Hz, 1 H, 1′H), 4.59 (dd, $J_{3'Ha,3'Hb}$ = 10.5 Hz, $J_{2'H,3'Hb}$ = 2.7 Hz, 1 H, 3′H_b), 5.01–5.37 (br s, 3 H, 3 × OH, exch. D_2O), 7.51 (d, $J_{4H,5H}$ = 8.1 Hz, 1 H, 5-H), 7.85 (d, $J_{4H,5H}$ = 8.1 Hz, 1 H, 4-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 64.3, 65.9, 71.7, 73.5, 86.5, 106.3, 174.8. MS–FAB: *m/z* = 188 [MH^+]. Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 44.69; H, 4.73; N, 7.73.
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(18) **General Procedure for the Synthesis of 4-Polyhydroxyalkyl-1*H*-pyridin-2-ones 7, 8, and 2-Aryl-4-polyhydroxyalkylpyridines 9**
An intimate solvent-free mixture of 1,3-oxazin-2-one **3** (2.4 mmol) and 1,3-oxathiolan-5-one **4** (2.4 mmol), or 1,3-oxazol-5-one **5** (2.4 mmol), or ketone **6** (2.4 mmol) in the presence of Montmorillonite K-10 clay (0.25 g) was taken in a 20 mL vial and subjected to MW irradiation in a CEM Discover Focused Microwave Synthesis System at 90 °C for 7–11 min. After completion of the reaction as indicated by TLC, H_2O (10 mL) was added to give the crude product, which was recrystallized from EtOH to obtain an analytically pure sample of **7**, **8**, or **9** as a white solid.
Characterization Data for Representative Compounds
Compound **7a**: white solid; mp 178–180 °C. IR (KBr): 3388–3361, 3015, 2550, 1692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.57 (s, 1 H, SH, exch. D_2O), 3.71 (dd, $J_{2'Ha,2'Hb}$ = 10.3 Hz, $J_{1'H,2'Ha}$ = 5.4 Hz, 1 H, 2′H_a), 4.19 (dd, $J_{2'Ha,2'Hb}$ = 10.3 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, 2′H_b), 4.27 (dd, $J_{1'H,2'Ha}$ = 5.4 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, 1′H), 4.97–5.06 (br s, 2 H, 2 × OH, exch. D_2O), 7.98 (d, $J_{5H,6H}$ = 7.8 Hz, 1 H, 5-H), 8.13 (d, $J_{5H,6H}$ = 7.8 Hz, 1 H, 6-H), 8.51 (br s, 1 H, NH, exch. D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 65.1, 74.2, 107.8, 124.9, 131.3, 136.4, 173.2. MS–FAB: *m/z* = 188 [MH^+]. Anal. Calcd for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48. Found: C, 44.79; H, 4.48; N, 7.73.
Compound **8a**: white solid; mp 156–158 °C. IR (KBr): 3398–3367, 3013, 1691, 1665, 1607, 1579, 1454 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.75 (dd, $J_{2'Ha,2'Hb}$ = 10.5 Hz, $J_{1'H,2'Ha}$ = 5.5 Hz, 1 H, 2′H_a), 4.17 (dd, $J_{2'Ha,2'Hb}$ = 10.5 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, 2′H_b), 4.31 (dd, $J_{1'H,2'Ha}$ = 5.5 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, 1′H), 5.03–5.12 (br s, 2 H, 2 × OH, exch. D_2O), 7.09–7.58 (m, 5 H_{arom}), 7.93 (d, $J_{5H,6H}$ = 7.2 Hz, 1 H, 5-H), 8.09 (d, $J_{5H,6H}$ = 7.2 Hz, 1 H, 6-H), 8.49–8.61 (br s, 2 H, 2 × NH, exch. D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 65.5, 73.6, 105.8, 124.9, 126.9, 128.7, 129.4, 130.5, 131.9, 136.7, 172.5, 173.3. MS–FAB: *m/z* = 275 [MH^+]. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.63; H, 5.35; N, 10.03.
Compound **9a**: white solid; mp 118–120 °C. IR (KBr): 3393, 3385, 3015, 1608, 1581, 1458 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.73 (dd, 1 H, $J_{2'Ha,2'Hb}$ = 10.2 Hz, $J_{1'H,2'Ha}$ = 5.2 Hz, 2′H_a), 4.05 (dd, 1 H, $J_{1'H,2'Ha}$ = 5.2 Hz, $J_{1'H,2'Hb}$ = 2.7 Hz, 1′H), 4.21 (dd, 1 H, $J_{2'Ha,2'Hb}$ = 10.2 Hz, $J_{1'H,2'Hb}$ = 2.7 Hz, 2′H_b), 4.95–5.13 (br s, 2 H, 2 × OH, exch. D_2O), 7.05–7.51 (m, 5 H_{arom}), 7.67–7.99 (m, 3 H_{arom}). ^{13}C NMR (DMSO-d_6/TMS): δ = 65.7, 67.1, 107.8, 126.8, 128.5, 129.7, 131.8, 133.6, 147.5, 149.2, 152.7. MS–FAB: *m/z* = 216 [MH^+]. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.25; H, 6.27; N, 6.69.
(19) **General Procedure for the Synthesis of 3-Amino-4-polyhydroxyalkyl-1*H*-pyridin-2-ones 10**
Compound **8** (2.0 mmol) was refluxed in H_2SO_4–H_2O (15 mL, 4:3, v/v) for 45 min in an oil bath. The reaction mixture was cooled, and the desired product **10** was precipitated by

adding concentrated NH_4OH (specific gravity 0.88) under ice cooling and recrystallized from EtOH to obtain an analytically pure sample of **10**.

Characterization Data for Synthesized Compounds

Compound **10a**: white solid; mp 141–143 °C. IR (KBr): 3391–3367, 3015, 1692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.77 (dd, $J_{2'Ha,2'Hb}$ = 10.3 Hz, $J_{1'H,2'Ha}$ = 5.5 Hz, 1 H, 2′H_a), 4.13 (dd, $J_{2'Ha,2'Hb}$ = 10.3 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, 2′H_b), 4.35 (dd, $J_{1'H,2'Ha}$ = 5.5 Hz, $J_{1'H,2'Hb}$ = 2.8 Hz, 1 H, 1′H), 4.96–5.18 (br s, 2 H, 2 × OH, exch. D_2O), 7.95 (d, $J_{5H,6H}$ = 7.5 Hz, 1 H, 5-H), 8.13 (d, $J_{5H,6H}$ = 7.5 Hz, 1 H, 6-H), 8.33–8.59 (br s, 3 H, 3 × NH, exch. D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 65.2, 73.6, 105.3, 124.9, 131.3, 136.4, 173.2. MS–FAB: *m/z* = 171 [MH^+]. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.72; H, 5.73; N, 16.19.

Compound **10b**: white solid; mp 127–128 °C. IR (KBr): 3398–3365, 3009, 1691 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.51 (ddd, $J_{2'H,3'Ha}$ = 5.3 Hz, $J_{1'H,2'H}$ = 4.2 Hz, $J_{2'H,3'Hb}$ = 2.4 Hz, 1 H, 2′H), 3.69 (dd, $J_{3'Ha,3'Hb}$ = 10.3 Hz, $J_{2'H,3'Ha}$ = 5.3 Hz, 1 H, 3′H_a), 4.06 (dd, $J_{3'Ha,3'Hb}$ = 10.3 Hz, $J_{2'H,3'Hb}$ = 2.4 Hz, 1 H, 3′H_b), 4.17 (d, $J_{1'H,2'H}$ = 4.2 Hz, 1 H, 1′H), 5.06–5.37 (br s, 3 H, 3 × OH, exch. D_2O), 7.99 (d, $J_{5H,6H}$ = 7.8 Hz, 1 H, 5-H), 8.12 (d, $J_{5H,6H}$ = 7.8 Hz, 1 H, 6-H), 8.29–8.65 (br s, 3 H, 3 × NH, exch. D_2O). ^{13}C NMR (100 MHz, DMSO-d_6/TMS): δ = 68.5, 71.1, 73.5, 112.9, 124.7, 129.9, 134.8, 172.9. MS–FAB: *m/z* = 201 [MH^+]. Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.21; H, 5.89; N, 14.16.