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Note

Efficient one-pot synthetic protocols for iminosugar-bearing imidazo[1,2-*a*]pyridines from carbohydrates

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ABSTRACT

This letter describes two unprecedented one-pot high yielding synthetic approaches to imidazo[1,2-*a*]pyridine scaffolds from carbohydrates. The first approach involves microwave-assisted acid-catalyzed domino reactions of unprotected D-glucose/D-xylose with ammonium acetate and benzoin to afford polyhydroxy iminosugar-bearing tetrahydroimidazo[1,2-*a*]pyridines. In the second approach, polyhydroxy iminosugar-bearing tetrahydrobenzimidazo[1,2-*a*]pyridines were synthesized by using unprotected D-glucose/D-xylose and 1,2-diamines in the presence of 10 mol % of oxalic acid under solvent-free microwave irradiation conditions.

Iminosugars are arousing a great interest as potential therapeutic agents against HIV infection,[1,2] cancer,[3,4] diabetes,[5,6] and other genetic and metabolic disorders[7] due to their powerful interference with glycosyltranferases. Recently published reviews clearly reveal the significance of iminosugars.[8–10] Imidazole- and pyridine-based structural scaffolds have been established as the essential part of many natural products. Synthetic compounds having these moieties exhibit a wide range of biological activities. Thus, tremendous efforts have been devoted to the synthesis of various imidazo[1,2-*a*]pyridines to explore their therapeutic potential.[11–15] Some of their derivatives act on the central nervous system[16,17] and have cardiotonic,[18] antiseptic, antiinflammatory,[19,20] and analgesic[21] effects, and also show activity against HIV infections.[22] They are α-amyloid formation inhibitors[23] and constitute a novel class of orally active nonpeptide bradykinin B_2 receptor antagonists.[24] Imidazo[1,2-*a*]pyridine compounds are presently in clinical use, for example, zolimidine (an antiulcer drug),[25] zolpidem (a hypnotic drug), and alpidem (a non-sedative anxiolytic drug).[26]

Among several methods available for the synthesis of imidazo[1,2-*a*]pyridines,[27–40] the most general involves the coupling of 2-aminopyridines with α-halocarbonyl compounds.[28] However, this approach does not readily lend itself to a diversity oriented synthesis. Recently more than a few synthetic methods for preparing these compounds based on multicomponent reactions have been reported by using Lewis acids as well as protic liquid and solid acids promoters such as scandium triflate,[32–34] $ZnCl_2$,[35] TsOH,[36] $HClO_4$,[37] HOAc,[38] montmorillonite K-10 clay,[39] and silica–sulfuric acid.[40] However, in spite of the potential utility of aforementioned routes for the synthesis of imidazo[1,2-*a*]pyridine derivatives, many of these reactions suffer from limitations such as introduction of substituents at specific positions and functional group intolerance of the conditions required. Many of these methods involve expensive reagents, long reaction times, low yields, and use of toxic organic solvents. However, to the best of our knowledge, there has been no report on the microwave-assisted synthesis of iminosugar-bearing tetrahydroimidazo[1,2-*a*]pyridines starting from D-glucose and D-xylose although they appear to be utilized for exploiting chemical diversity and generating a drug-like library to screen for potential new leads. Aside from the simple expectation that the presence of sugar residues with free hydroxyl groups in these heterocylic systems should increase the water solubility and bioavailability, other interesting biological properties may arise owing to the complex machinery of various glycoconjugate biological activities.[41]

On the basis of the above-mentioned points and our ongoing efforts to devise new MW-assisted solvent-free cyclization processes,[42–44] especially using carbohydrates as starting material,[45–49] we describe herein two synthetic approaches for an acid-catalyzed unprecedented synthesis of biologically important iminosugar-bearing tetrahydroimidazo[1,2-*a*]pyridines **4**, **5**, **7**, and **8** using D-glucose and D-xylose as biorenewable resources under solvent-free microwave irradiation conditions (Scheme 1).

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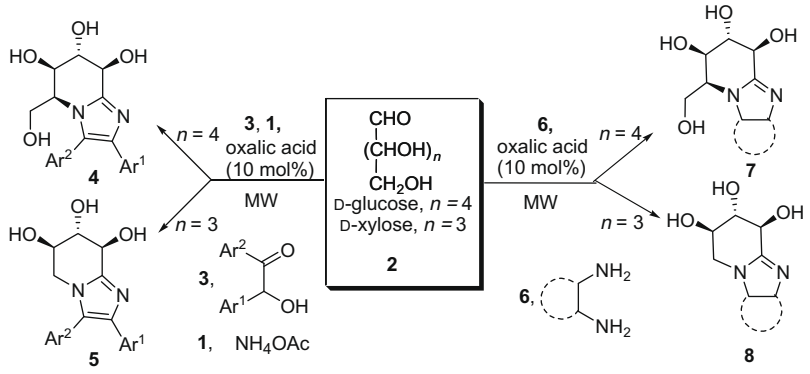


Scheme 1. Formation of iminosugar-bearing imidazo[1,2-*a*]pyridines **4**, **5**, **7,** and **8**.

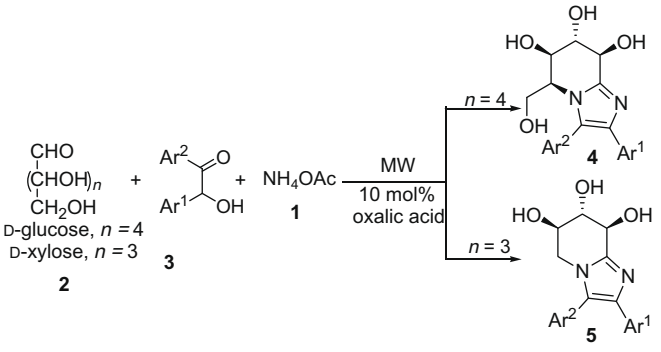
Advantageously, the present methodology avoids tedious protection–deprotection operations.

In order to probe the desired products we performed some preliminary experimentations when it was found that the synthesis of tetrahydroimidazo[1,2-*a*]pyridines **4** and **5** could be effected by MW-activated solvent-free reactions of D-glucose/D-xylose, benzoin **3**, and ammonium acetate mediated by 10 mol % oxalic acid (Scheme 2).

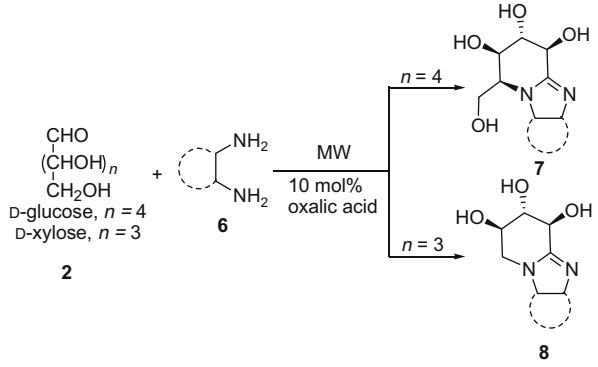
Inspired by the above-mentioned synthesis we have also successfully synthesized iminosugar-bearing tetrahydrobenzimidazo[1,2-*a*]pyridines **7** and **8** in excellent yields by using 1,2-diamine and D-glucose/D-xylose as starting substrates in the presence of 10 mol % oxalic acid via amine-driven domino reactions (Scheme 3).

It was noted that other catalysts' silica gel, montmorillonite K-10 clay, acidic, neutral or basic Al_2O_3, I_2, $CeSO_4{\cdot}8H_2O$, $CeCl_3{\cdot}7H_2O$ were far less effective (Table 1) resulting in either no reaction (in case of basic alumina) or relatively very low yields of products (**4a** and **7a** of Tables 2 and 3, respectively). To optimize catalyst loading, we carried out the reactions using 5, 10, and 15 mol % of oxalic acid and the highest yields were obtained with 10 mol % (Table 1, entry 7). Moreover, when the reaction was performed at 80 °C using conventional heating, significantly lower yields of **4a** and **7a** were obtained in relatively longer reaction times (Table 1).

First approach: The strategy followed for the envisaged synthesis of tetrahydroimidazo[1,2-*a*]pyridines **4** and **5** consisted of MW irradiation of a solvent-free intimate mixture of benzoin **3**, ammonium acetate **1**, and D-glucose/D-xylose **2** in the presence of 10 mol % oxalic acid, at 80 °C for 9–13 min in a Chemical Laboratory Microwave Oven (Model: BP-310/50, 230 V, 50 Hz power input) (Table 2). After isolation and purification by recrystallization



Scheme 2. Formation of iminosugar-bearing tetrahydroimidazo[1,2-*a*]pyridines **4** and **5**.



Scheme 3. Formation of iminosugar-bearing tetrahydrobenzimidazo[1,2-*a*]pyridines **7** and **8**.

Table 1
Optimization of reaction conditions for compounds **4a** and **7a**

Entry	Catalyst system	MW				Oil bath			
		Time[a] (min)		Yield[b] (%)		Time[a] (h)		Yield[b] (%)	
		4a	**7a**	**4a**	**7a**	**4a**	**7a**	**4a**	**7a**
1	K-10 clay	10	12	93	89	6	7	38	36
2	$CeCl_3{\cdot}7H_2O$–NaI	12	14	92	89	7	8	36	32
3	Silica gel	13	15	69	62	9	8	20	18
4	Neutral alumina	14	13	17	18	10	10	11	12
5	Acidic alumina	13	13	17	16	9	10	13	12
6	5 mol % oxalic acid	14	13	33	30	6	5	49	48
7	10 mol % oxalic acid	12	14	70	68	5	4	50	53
8	15 mol % oxalic acid	13	13	73	75	6	5	51	48

[a] Time for the completion of the reaction at 80 °C as indicated by TLC.
[b] Yield of isolated and purified products **4a** and **7a**.

from ethanol multifunctionalized tetrahydroimidazo[1,2-*a*]pyridines **4** and **5** were obtained in 80–96% yields.

Second approach: In the second synthetic route, iminosugar-bearing tetrahydrobenzimidazo[1,2-*a*]pyridines **7** and **8** were synthesized in 79–91% yields by MW irradiation of a solvent-free intimate mixture of D-glucose/D-xylose **2**, 1,2-diamine **6** and 10 mol % oxalic acid, at 80 °C for 8–14 min in a Chemical Laboratory Microwave Oven (Model: BP-310/50, 230 V, 50 Hz power input) (Table 3), which were isolated and purified by recrystallization from ethanol.

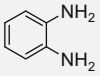
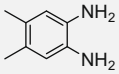
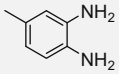
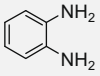
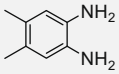
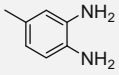
The formation of target compounds **4** and **5** may be tentatively rationalized by oxalic acid-catalyzed condensation of aldoses (D-glucose/D-xylose) **2**, 2-hydroxyketone **3** with ammonia (in situ

Table 2
Microwave-assisted synthesis of iminosugar-bearing tetrahydroimidazo[1,2-*a*]pyridines **4** and **5**

Product	Ar^1	Ar^2	Time[a] (min)	Yield[b,c] (%)
4a	C_6H_5	C_6H_5	10	93
4b	*p*-ClC_6H_4	C_6H_5	9	94
4c	*p*-$MeOC_6H_4$	C_6H_5	11	88
4d	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	12	83
5a	C_6H_5	C_6H_5	11	95
5b	*p*-ClC_6H_4	C_6H_5	9	96
5c	*p*-$MeOC_6H_4$	C_6H_5	10	89
5d	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	13	80

[a] Microwave irradiation time at 80 °C.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H, and N analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.

Table 3
Microwave-assisted synthesis of iminosugar-annulated tetrahydrobenzimidazo[1,2-*a*]pyridines **7** and **8**

Product	Diamine **6**	Time[a] (min)	Yield[b,c] (%)
7a		12	89
7b		8	79
7c		9	84
7d		14	82
8a		11	91
8b		10	83
8c		9	87
8d		13	90

[a] Microwave irradiation time at 80 °C.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H, and N analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.

generated from ammonium acetate) to form 2-aminoketone **12** and imino-derivative **13**, respectively. The adduct **14**, formed from **12** and **13**, underwent intramolecular dehydrative cyclization followed by dehydrogenation to afford the intermediate **17** which cyclodehydrated to give the products **4** and **5** in 80–96% yields (Scheme 4).

A plausible mechanistic pathway for the formation of products **7** and **8** allowing the second synthetic strategy is depicted in Scheme 5. The oxalic acid-catalyzed condensation of aldose (D-glucose/D-xylose) **2** with 1,2-diamine **6** gives imine **18** which undergoes intramolecular cyclization, dehydrogenation, and cyclodehydration cascade to afford products **7** and **8** in 79–91% yields.

In summary, we have developed two routes for an unprecedented one-pot synthesis of polyfunctionalized iminosugar-bearing imidazo[1,2-*a*]pyridine scaffolds using unprotected D-glucose and D-xylose as biorenewable resources under solvent-free MW irradiation conditions. The protocols are generally high yielding and offer an easy access to chemically and pharmaceutically relevant products.

1. Experimental

1.1. General

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in DMSO-d_6 and TMS was used as an internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. A Chemical Laboratory Microwave Oven (Model; BP-310/50, 230 V, 50 Hz power input) was used for all experiments. All chemicals used were reagent grade and were used as received without further purification. Silica Gel-G was used for TLC.

1.2. (5*S*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-5-(hydroxymethyl)-2,3-disubstituted-imidazo[1,2-*a*]pyridines-6,7,8-triol (4) and (6*R*,7*S*,8*S*)-5,6,7,8-tetrahydro-2,3-disubstituted-imidazo[1,2-*a*]pyridine-6,7,8-triol (5): general procedure

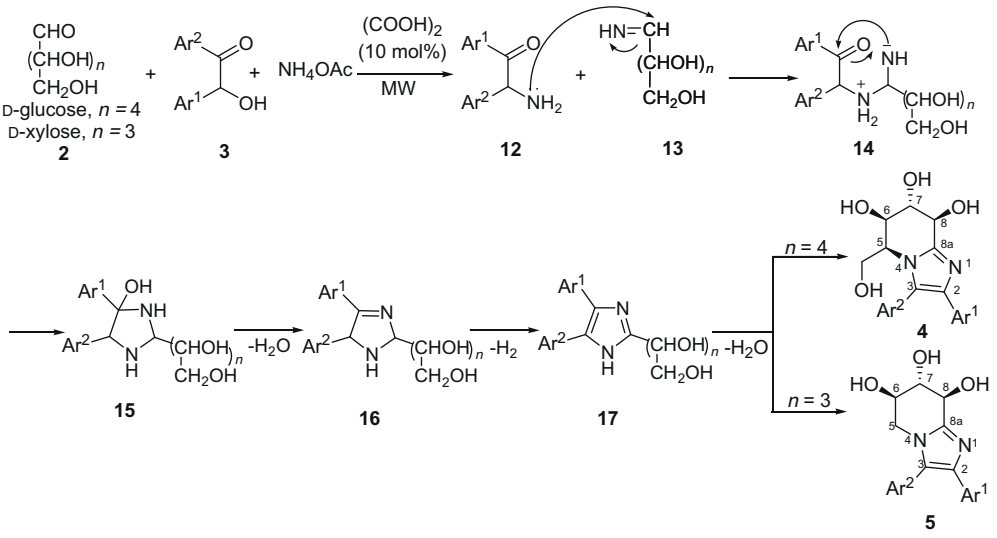
An intimate solvent-free mixture of benzoin **3** (1 mmol), ammonium acetate (2 mmol), and aldose **2** (1 mmol) in the presence of 10 mol % of oxalic acid was taken in a 20 mL vial and subjected to MW irradiation in a Chemical Laboratory Microwave Oven (Model: BP-310/50, 230 V, 50 Hz power input) at 80 °C for 9–13 min (Table 2). After completion of the reaction as indicated by TLC, water (10 mL) was added to precipitate the crude product, which was recrystallized from ethanol to give an analytically pure sample of **4** and **5** as a yellow solid.

1.2.1. 5-Hydroxymethyl-2,3-diphenyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6,7,8-triol (4a)

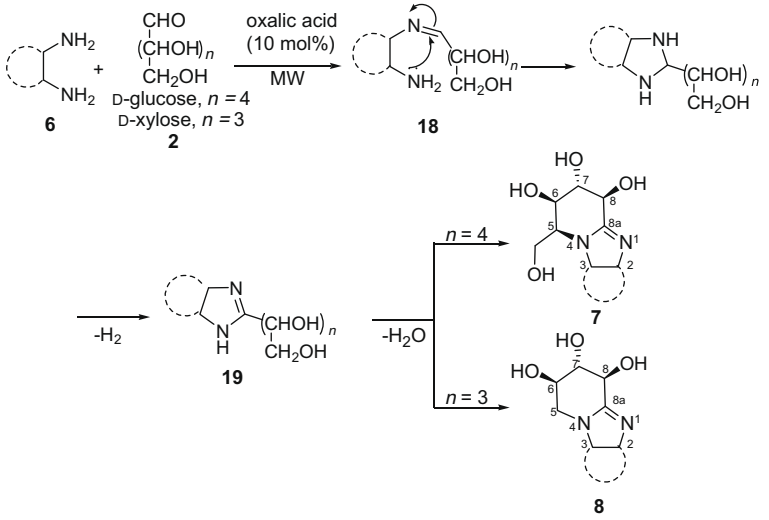
Yellow solid; yield 93%, mp 197–199 °C. IR (KBr) ν_{max} 3344, 3010, 2856, 1606, 1582, 1456 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.58 (dd, 1H, $J_{6H,7H}$ = 9.3 Hz, $J_{5H,6H}$ = 9.4 Hz, 6-H), 3.78 (ddd, 1H, $J_{1'Ha,5H}$ = 3.1 Hz, $J_{1'Hb,5H}$ = 6.7 Hz, $J_{5H,6H}$ = 6.0 Hz, 5-H), 3.85 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.7 Hz, $J_{1'Ha,5H}$ = 3.1 Hz, 1′-H_a), 3.97 (dd, 1H, $J_{7H,8H}$ = 9.6 Hz, $J_{6H,7H}$ = 9.3 Hz, 7-H), 4.00 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.7 Hz, $J_{1'Hb,5H}$ = 6.7 Hz, 1′-H_b), 4.88 (d, 1H, $J_{7H,8H}$ = 9.6 Hz, 8-H), 4.89–5.21 (br s, 4H, 4 × OH, exchangeable with D_2O), 7.20–7.54 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.5, 60.1, 68.3, 69.8, 81.2, 120.1, 122.4, 125.0, 125.7, 126.3, 126.9, 127.6, 128.2, 134.2, 135.0, 152.2. MS-FAB: *m/z* = 353 [MH$^+$]. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.22; H, 5.72; N, 7.95. Found: C, 67.98; H, 5.52; N, 8.26.

1.2.2. 2-(4-Chloro-phenyl)-5-hydroxymethyl-3-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol (4b)

Yellow solid; yield 94%, mp 183–185 °C. IR (KBr) ν_{max} 3345, 3011, 2858, 1607, 1583, 1456 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.60 (dd, 1H, $J_{6H,7H}$ = 9.2 Hz, $J_{5H,6H}$ = 9.3 Hz, 6-H), 3.79 (ddd, 1H, $J_{1'Ha,5H}$ = 3.0 Hz, $J_{1'Hb,5H}$ = 6.7 Hz, $J_{5H,6H}$ = 5.9 Hz, 5-H), 3.87 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.6 Hz, $J_{1'Ha,5H}$ = 3.0 Hz, 1′-H_a), 3.98 (dd, 1H, $J_{7H,8H}$ = 9.5 Hz, $J_{6H,7H}$ = 9.2 Hz, 7-H), 4.02 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.5 Hz, $J_{1'Hb,5H}$ = 6.7 Hz, 1′-H_b), 4.86 (d, 1H, $J_{7H,8H}$ = 9.5 Hz, 8-H), 7.19–8.00 (m, 9H_{arom}), 4.92–5.18 (br s, 4H, 4 × OH, exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.8, 60.7, 68.5, 70.0, 82.1,



Scheme 4. A plausible mechanism for the formation of iminosugar-bearing tetrahydroimidazo[1,2-*a*]pyridines **4** and **5**.



Scheme 5. A plausible mechanism for the formation of iminosugar-bearing tetrahydrobenzimidazo[1,2-*a*]pyridines **7** and **8**.

120.2, 122.2, 125.7, 126.3, 126.9, 127.6, 128.5, 131.7, 133.0, 135.2, 152.4. MS-FAB: *m/z* = 388 [MH$^+$]. Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.22; H, 4.96; N, 7.25. Found: C, 62.56; H, 4.66; N, 7.05.

1.2.3. 5-Hydroxymethyl-2-(4-methoxy-phenyl)-3-phenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol (4c)

Yellow solid; yield 88%, mp 176–178 °C. IR (KBr) ν_{max} 3343, 3010, 2984, 2856, 1605, 1584, 1455 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.57 (dd, 1H, $J_{6H,7H}$ = 9.2 Hz, $J_{5H,6H}$ = 9.3 Hz, 6-H), 3.71 (s, 3H, OCH_3), 3.77 (ddd, 1H, $J_{1'Ha,5H}$ = 3.0 Hz, $J_{1'Hb,5H}$ = 6.6 Hz, $J_{5H,6H}$ = 9.3 Hz, 5-H), 3.85 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.6 Hz, $J_{1'Ha,5H}$ = 3.0 Hz, 1′-H_a), 3.95 (dd, 1H, $J_{7H,8H}$ = 9.5 Hz, $J_{6H,7H}$ = 9.2 Hz, 7-H), 4.01 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.6 Hz, $J_{1'Hb,5H}$ = 6.6 Hz, 1′-H_b), 4.84 (d, 1H, $J_{7H,8H}$ = 9.5 Hz, 8-H), 4.97–5.17 (br s, 3H, 3 × OH, exchangeable with D_2O), 6.98–7.85 (m, 9H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.0, 54.1, 61.1, 67.9, 70.5, 81.8, 111.7, 120.1, 123.0, 125.1, 126.0, 126.9, 127.0, 127.6, 135.0, 152.1, 161.1. MS-FAB: *m/z* = 383 [MH$^+$]. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.00; H, 5.80; N, 7.33. Found: C, 65.73; H, 6.34; N, 7.11.

1.2.4. 5-Hydroxymethyl-2,3-bis-(4-methoxy-phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol (4d)

Yellow solid; yield 83%, mp 161–163 °C. IR (KBr) ν_{max} 3342, 3009, 2982, 2854, 1604, 1583, 1455 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.58 (dd, 1H, $J_{6H,7H}$ = 9.1 Hz, $J_{5H,6H}$ = 9.2 Hz, 6-H), 3.72 (s, 6H, OCH_3), 3.79 (ddd, 1H, $J_{1'Ha,5H}$ = 3.0 Hz, $J_{1'Hb,5H}$ = 6.5 Hz, $J_{5H,6H}$ = 9.2 Hz, 5-H), 3.82 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.7 Hz, $J_{1'Ha,5H}$ = 3.0 Hz, 1′-H_a), 3.94 (dd, 1H, $J_{7H,8H}$ = 9.5 Hz, $J_{6H,7H}$ = 9.2 Hz, 7-H), 3.99 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.7 Hz, $J_{1'Hb,5H}$ = 6.5 Hz, 1′-H_b), 4.85 (d, 1H, $J_{7H,8H}$ = 9.5 Hz, 8-H), 4.95–5.12 (br s, 4H, 4 × OH, exchangeable with D_2O), 6.97–7.52 (m, 8H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.8, 53.9, 54.2, 60.8, 68.0, 70.2, 81.7, 111.8, 112.0, 120.0, 122.8, 126.2, 126.8, 127.8, 128.5, 152.0, 161.1, 161.3. MS-FAB: *m/z* = 413 [MH$^+$]. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.11; H, 5.87; N, 6.79. Found: C, 63.79; H, 5.66; N, 6.45.

1.2.5. 2,3-Diphenyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol (5a)

Yellow solid; yield 95%, mp 180–182 °C. IR (KBr) ν_{max} 3343, 3009, 2852, 1603, 1580, 1455 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-

d_6): δ = 3.48 (ddd, 1H, $J_{6H,7H}$ = 9.1 Hz, $J_{5Ha,6H}$ = 9.7 Hz, $J_{5Hb,6H}$ = 3.5 Hz, 6-H), 3.51 (dd, 1H, $J_{5Ha,5Hb}$ = 12.9 Hz, $J_{6Ha,6H}$ = 9.7 Hz, 5-H_a), 3.89 (dd, 1H, $J_{5Ha,5Hb}$ = 12.9 Hz, $J_{5Hb,6H}$ = 3.5 Hz, 5-H_b), 3.94 (dd, 1H, $J_{7H,8H}$ = 9.5 Hz, $J_{6H,7H}$ = 9.1 Hz, 7-H), 4.82 (d, 1H, $J_{7H,8H}$ = 9.5 Hz, 8-H), 4.97–5.19 (br s, 4H, 4 × OH, exchangeable with D_2O), 7.18–7.51 (m, 10H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.3, 68.0, 71.0, 84.2, 120.1, 121.9, 125.0, 125.7, 126.8, 127.2, 127.7, 128.0, 134.3, 134.7, 152.1. MS-FAB: *m/z* = 323 [MH$^+$]. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.84; H, 5.63; N, 8.7. Found: C, 70.64; H, 5.51; N, 9.00.

1.2.6. 2-(4-Chloro-phenyl)-3-phenyl-5,6,7,8-tetrahydro imidazo[1,2-*a*]pyridine-6,7,8-triol (5b)

Yellow solid; yield 96%, mp 165–167 °C. IR (KBr) ν_{max} 3344, 3011, 2853, 1605, 1581, 1455 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.58 (ddd, 1H, $J_{6H,7H}$ = 9.1 Hz, $J_{5Ha,6H}$ = 9.6 Hz, $J_{5Hb,6H}$ = 3.4 Hz, 6-H), 3.83 (dd, 1H, $J_{5Ha,5Hb}$ = 12.8 Hz, $J_{5Ha,6H}$ = 9.6 Hz, 5-H_a), 3.92 (dd, 1H, $J_{5Ha,5Hb}$ = 12.8 Hz, $J_{5Hb,6H}$ = 3.4 Hz, 5-H_b), 3.95 (dd, 1H, $J_{7H,8H}$ = 9.4 Hz, $J_{6H,7H}$ = 9.1 Hz, 7-H), 4.83 (d, 1H, $J_{7H,8H}$ = 9.4 Hz, 8-H), 4.99–5.20 (br s, 3H, 3 × OH, exchangeable with D_2O), 7.17–7.93 (m, 9H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.1, 68.5, 71.2, 83.9, 120.4, 121.5, 125.1, 126.1, 126.7, 127.4, 128.2, 130.9, 133.2, 135.0, 151.8. MS-FAB: *m/z* = 357 [MH$^+$]. Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 64.09; H, 4.80; N, 7.86. Found: C, 64.40; H, 5.08; N, 7.53.

1.2.7. 2-(4-Methoxy-phenyl)-3-phenyl-5,6,7,8-tetrahydro imidazo[1,2-*a*]pyridine-6,7,8-triol (5c)

Yellow solid; yield 89%, mp 169–171 °C. IR (KBr) ν_{max} 3341, 3008, 2985, 2855, 1604, 1584, 1455 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.46 (ddd, 1H, $J_{6H,7H}$ = 9.0 Hz, $J_{5Ha,6H}$ = 9.5 Hz, $J_{5Hb,6H}$ = 3.4 Hz, 6-H), 3.50 (dd, 1H, $J_{5Ha,5Hb}$ = 12.8 Hz, $J_{5Ha,6H}$ = 9.5 Hz, 5-H_a), 3.70 (s, 3H, OCH_3), 3.85 (dd, 1H, $J_{5Ha,5Hb}$ = 12.8 Hz, $J_{5Hb,6H}$ = 3.4 Hz, 5-H_b), 3.92 (dd, 1H, $J_{7H,8H}$ = 9.4 Hz, $J_{6H,7H}$ = 9.0 Hz, 7-H), 4.82 (d, 1H, $J_{7H,8H}$ = 9.4 Hz, 8-H), 4.90–5.09 (br s, 3H, 3 × OH, exchangeable with D_2O), 6.95–7.49 (m, 9H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.4, 54.2, 68.8, 71.0, 83.7, 112.0, 119.9, 122.2, 125.6, 126.2, 126.9, 127.6, 128.4, 135.0, 152.0, 160.8. MS-FAB: *m/z* = 353 [MH$^+$]. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.22; H, 5.72; N, 7.95. Found: C, 68.11; H, 5.98; N, 8.26.

1.2.8. 2,3-Bis-(4-methoxy-phenyl)-5,6,7,8-tetrahydro imidazo[1,2-*a*]pyridine-6,7,8-triol (5d)

Yellow solid; yield 80%, mp 141–143 °C. IR (KBr) ν_{max} 3342, 3009, 2856, 1604, 1583, 1454 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.45 (ddd, 1H, $J_{6H,7H}$ = 8.9 Hz, $J_{5Ha,6H}$ = 9.4 Hz, $J_{5Hb,6H}$ = 3.3 Hz, 6-H), 3.49 (dd, 1H, $J_{5Ha,5Hb}$ = 12.7 Hz, $J_{5Ha,6H}$ = 9.4 Hz, 5-H_a), 3.71 (s, 6H, OCH_3), 3.88 (dd, 1H, $J_{5Hb,6H}$ = 3.3 Hz, $J_{5Ha,5Hb}$ = 12.7 Hz, 5-H_b), 3.91 (dd, 1H, $J_{7H,8H}$ = 9.4 Hz, $J_{6H,7H}$ = 8.9 Hz, 7-H), 4.80 (d, 1H, $J_{7H,8H}$ = 9.4 Hz, 8-H), 4.96–5.10 (br s, 3H, 3 × OH, exchangeable with D_2O), 6.95–7.51 (m, 8H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.0, 53.8, 54.6, 68.4, 71.3, 83.9, 111.5, 112.7, 119.0, 122.6, 126.2, 127.2, 127.9, 128.8, 152.3, 161.2, 161.4. MS-FAB: *m/z* = 383 [MH$^+$]. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.00; H, 5.80; N, 7.33. Found: C, 66.28; H, 5.47; N, 6.99.

1.3. (1*S*,2*R*,3*S*,4*S*)-1-hydroxymethyl-1,2,3,4-tetrahydro benzimidazo[1,2-*a*]pyridine-2,3,4-triol (7) and (2*R*,3*S*,4*S*)-1,2,3,4-tetrahydrobenzimidazo[1,2-*a*]pyridine-2,3,4-triol (8): general procedure

An intimate solvent-free mixture of diamine **6** (1 mmol), aldose **2** (1 mmol), and 10 mol % of oxalic acid was taken in a 20 mL vial and subjected to MW irradiation in a Chemical Laboratory Microwave Oven (Model: BP-310/50, 230 V, 50 Hz power input) at 80 °C for 8–14 min (Table 3). After completion of the reaction as indicated by TLC, water (10 mL) was added to precipitate the crude product, which was recrystallized from ethanol to give an analytically pure sample of **7** and **8** as a yellow solid.

1.3.1. 1-Hydroxymethyl-1,2,3,4-tetrahydrobenzo [4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol (7a)

Yellow solid; yield 89%, mp 206–208 °C. IR (KBr) ν_{max} 3343, 3009, 2857, 1603, 1581, 1455 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.58 (dd, 1H, $J_{6H,7H}$ = 9.2 Hz, $J_{5H,6H}$ = 9.1 Hz, 6-H), 3.66 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.8 Hz, $J_{1'Ha,5H}$ = 3.2 Hz, 1′-H_a), 3.79 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.8 Hz, $J_{1'Hb,5H}$ = 6.5 Hz, 1′-H_b), 3.91 (ddd, 1H, $J_{1'Ha,5H}$ = 3.2 Hz, $J_{1'Hb,5H}$ = 6.5 Hz, $J_{5H,6H}$ = 9.1 Hz, 5-H), 3.95 (dd, 1H, $J_{7H,8H}$ = 9.7 Hz, $J_{6H,7H}$ = 9.2 Hz, 7-H), 4.85 (d, 1H, $J_{7H,8H}$ = 9.7 Hz, 8-H), 4.88–5.04 (br s, 4H, 4 × OH, exchangeable with D_2O), 7.21–7.54 (m, 4H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.9, 58.6, 68.7, 70.0, 72.1, 114.7, 114.9, 122.6, 122.9, 132.9, 135.8, 159.4. MS-FAB: *m/z* = 251 [MH$^+$]. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.62; H, 5.64; N, 11.20. Found: C, 57.31; H, 5.89; N, 11.49.

1.3.2. 1-Hydroxymethyl-7,8-dimethyl-1,2,3,4-tetrahydro benzo[4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol (7b)

Yellow solid; yield 79%, mp 192–194 °C. IR (KBr) ν_{max} 3341, 3008, 2984, 2856, 1602, 1580, 1454 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 6H, CH_3), 3.53 (dd, 1H, $J_{2H,3H}$ = 9.3 Hz, $J_{1H,2H}$ = 9.0 Hz, 2-H), 3.69 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.9 Hz, $J_{1'Ha,1H}$ = 3.3 Hz, 1′-H_a), 3.81 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.9 Hz, $J_{1'Hb,1H}$ = 6.5 Hz, 1′-H_b), 3.93 (ddd, 1H, $J_{1'Ha,1H}$ = 3.3 Hz, $J_{1'Hb,1H}$ = 6.5 Hz, $J_{1H,2H}$ = 9.0 Hz, 1-H), 3.99 (dd, 1H, $J_{3H,4H}$ = 9.6 Hz, $J_{2H,3H}$ = 9.3 Hz, 3-H), 4.86 (d, 1H, $J_{3H,4H}$ = 9.6 Hz, 4-H), 4.90–5.12 (br s, 4H, 4 × OH, exchangeable with D_2O), 7.21 (s, 1H_{arom}), 7.29 (s, 1H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.8, 17.1, 51.2, 57.7, 67.6, 69.7, 114.9, 115.2, 127.8, 128.0, 130.9, 134.9, 161.8. MS-FAB: *m/z* = 279 [MH$^+$]. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.45; H, 6.52; N, 10.08. Found: C, 60.78; H, 6.16; N, 10.43.

1.3.3. 1-Hydroxymethyl-7-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol (7c)

Yellow solid; yield 84%, mp 186–188 °C. IR (KBr) ν_{max} 3341, 3008, 2984, 2856, 1602, 1580, 1454 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 3.51 (dd, 1H, $J_{6H,7H}$ = 9.1 Hz, $J_{5H,6H}$ = 9.0 Hz, 6-H), 3.71 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.7 Hz, $J_{1'Ha,5H}$ = 3.1 Hz, 1′-H_a), 3.85 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.7 Hz, $J_{1'Hb,5H}$ = 6.4 Hz, 1′-H_b), 3.92 (dd, 1H, $J_{7H,8H}$ = 9.6 Hz, $J_{6H,7H}$ = 9.1 Hz, 7-H), 3.97 (ddd, 1H, $J_{1'Ha,5H}$ = 3.1 Hz, $J_{1'Hb,5H}$ = 6.4 Hz, $J_{5H,6H}$ = 9.1 Hz, 5-H), 4.87 (d, 1H, $J_{7H,8H}$ = 9.6 Hz, 8-H), 4.93–5.14 (br s, 4H, 4 × OH, exchangeable with D_2O), 7.25–7.60 (m, 3H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.0, 50.8, 58.2, 68.1, 69.7, 71.9, 115.0, 115.3, 123.9, 129.9, 130.8, 135.8, 162.4. MS-FAB: *m/z* = 265 [MH$^+$]. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.12; H, 6.1; N, 10.61. Found: C, 59.31; H, 6.31; N, 10.97.

1.3.4. 5-Hydroxymethyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-6,7,8-triol (7d)

Yellow solid; yield 82%, mp 161–163 °C. IR (KBr) ν_{max} 3343, 3009, 2858 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.28 (dd, 1H, $J_{7H,8H}$ = 9.5 Hz, $J_{6H,7H}$ = 9.1 Hz, 7-H), 3.60 (dd, 1H, $J_{6H,7H}$ = 9.1 Hz, $J_{5H,6H}$ = 8.9 Hz, 6-H), 3.72 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.6 Hz, $J_{1'Ha,5H}$ = 3.2 Hz, 1′-H_a), 3.84 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.6 Hz, $J_{1'Hb,5H}$ = 6.2 Hz, 1′-H_b), 3.98 (ddd, 1H, $J_{1'Ha,5H}$ = 3.2 Hz, $J_{1'Hb,5H}$ = 6.2 Hz, $J_{5H,6H}$ = 8.9 Hz, 5-H), 4.87 (d, 1H, $J_{7H,8H}$ = 9.5 Hz, 8-H), 4.96–5.17 (br s, 4H, 4 × OH, exchangeable with D_2O), 6.29 (d, 1H, $J_{2H,3H}$ = 1.2 Hz, 2H), 6.40 (d, 1H, $J_{2H,3H}$ = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 48.6, 58.1, 68.1, 68.8, 71.2, 117.0, 121.2, 146.1. MS-FAB: *m/z* = 201 [MH$^+$]. Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.03; H, 6.04; N, 14.0. Found: C, 47.73; H, 5.92; N, 14.22.

1.3.5. 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol (8a)

Yellow solid; yield 91%, mp 197–199 °C. IR (KBr) ν_{max} 3342, 3006, 2855, 1605, 1579, 1454 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.45 (dd, 1H, $J_{5Ha,5Hb}$ = 12.7 Hz, $J_{5Ha,6H}$ = 9.6 Hz, 5-H_a), 3.60 (ddd, 1H, $J_{5Ha,6H}$ = 9.6 Hz, $J_{5Hb,6H}$ = 3.3 Hz, $J_{6H,7H}$ = 9.0 Hz, 6-H), 3.82 (dd, 1H, $J_{5Ha,5Hb}$ = 12.7 Hz, $J_{5Hb,6H}$ = 3.3 Hz, 5-H_b), 3.92 (dd, 1H, $J_{7H,8H}$ = 9.4 Hz, $J_{6H,7H}$ = 9.0 Hz, 7-H), 4.81 (d, 1H, $J_{7H,8H}$ = 9.4 Hz, 8-H), 4.91–5.19 (br s, 3H, 3 × OH, exchangeable with D_2O), 7.19–7.47 (m, 4H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 46.6, 66.0, 69.7, 72.9, 114.3, 114.6, 122.5, 122.7, 132.1, 135.4, 158.8. MS-FAB: m/z = 221 [MH^+]. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.03; H, 5.49; N, 12.73. Found: C, 60.39; H, 5.28; N, 12.43.

1.3.6. 7,8-Dimethyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol (8b)

Yellow solid; yield 83%, mp 145–147 °C. IR (KBr) ν_{max} 3340, 3007, 2981, 2853, 1602, 1580, 1454 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 6H, CH_3), 3.44 (dd, 1H, $J_{5Ha,5Hb}$ = 12.6 Hz, $J_{5Ha,6H}$ = 9.5 Hz, 5-H_a), 3.50 (ddd, 1H, $J_{5Ha,6H}$ = 9.5 Hz, $J_{5Hb,6H}$ = 3.1 Hz, $J_{6H,7H}$ = 8.9 Hz, 6-H), 3.81 (dd, 1H, $J_{5Ha,5Hb}$ = 12.6 Hz, $J_{5Hb,6H}$ = 3.1 Hz, 5-H_b), 3.96 (dd, 1H, $J_{7H,8H}$ = 9.4 Hz, $J_{6H,7H}$ = 8.9 Hz, 7-H), 4.83 (d, 1H, $J_{7H,8H}$ = 9.4 Hz, 8-H), 4.98–5.26 (br s, 3H, 3 × OH, exchangeable with D_2O), 7.18 (s, 1H_{arom}), 7.27 (s, 1H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.7, 17.0, 46.1, 65.9, 68.1, 73.7, 114.7, 114.9, 127.3, 127.5, 130.5, 134.2, 161.1. MS-FAB: m/z = 249 [MH^+]. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.93; H, 6.5; N, 11.29. Found: C, 62.82; H, 6.70; N, 11.11.

1.3.7. 7-Methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol (8c)

Yellow solid; yield 87%, mp 150–152 °C. IR (KBr) ν_{max} 3343, 3007, 2979, 2856, 1604, 1580, 1453 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3H, CH_3), 3.47 (dd, 1H, $J_{5Ha,5Hb}$ = 12.6 Hz, $J_{5Ha,6H}$ = 9.5 Hz, 5-H_a), 3.58 (ddd, 1H, $J_{5Ha,6H}$ = 9.5 Hz, $J_{5Hb,6H}$ = 3.2 Hz, $J_{6H,7H}$ = 9.0 Hz, 6-H), 3.86 (dd, 1H, $J_{5Ha,5Hb}$ = 12.6 Hz, $J_{5Hb,6H}$ = 3.2 Hz, 5-H_b), 3.97 (dd, 1H, $J_{7H,8H}$ = 9.3 Hz, $J_{6H,7H}$ = 9.0 Hz, 7-H), 4.85 (d, 1H, $J_{7H,8H}$ = 9.3 Hz, 8-H), 4.90–5.21 (br s, 3H, 3 × OH, exchangeable with D_2O), 6.91–7.45 (m, 3H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.7, 46.8, 66.1, 69.0, 73.9, 114.2, 114.7, 123.8, 129.2, 130.5, 135.3, 161.8. MS-FAB: m/z = 235 [MH^+]. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.57; H, 6.02; N, 11.97. Found: C, 61.80; H, 6.30; N, 11.82.

1.3.8. 5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyridine-6,7,8-triol (8d)

Yellow solid; yield 90%, mp 137–139 °C. IR (KBr) ν_{max} 3343, 3007, 2979, 2856, 1604, 1580, 1453 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.23 (ddd, 1H, $J_{5Ha,6H}$ = 9.4 Hz, $J_{5Hb,6H}$ = 3.3 Hz, $J_{6H,7H}$ = 9.1 Hz, 6-H), 3.27 (dd, 1H, $J_{7H,8H}$ = 9.2 Hz, $J_{6H,7H}$ = 9.1 Hz, 7-H), 3.49 (dd, 1H, $J_{5Ha,5Hb}$ = 12.5 Hz, $J_{5Ha,6H}$ = 9.4 Hz, 5-H_a), 3.86 (dd, 1H, $J_{5Ha,5Hb}$ = 12.5 Hz, $J_{5Hb,6H}$ = 3.3 Hz, 5-H_b), 4.31 (d, 1H, $J_{7H,8H}$ = 9.2 Hz, 8-H), 4.97–5.20 (br s, 3H, 3 × OH, exchangeable with D_2O), 6.30 (d, 1H, $J_{2H,3H}$ = 1.3 Hz, 3-H), 6.40 (d, 1H, $J_{2H,3H}$ = 1.3 Hz, 2-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.8, 66.2, 68.3, 70.1, 116.3, 120.8, 145.5. MS-FAB: m/z = 171 [MH^+]. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.44; H, 5.92; N, 16.47. Found: C, 49.11; H, 5.62; N, 16.83.

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