

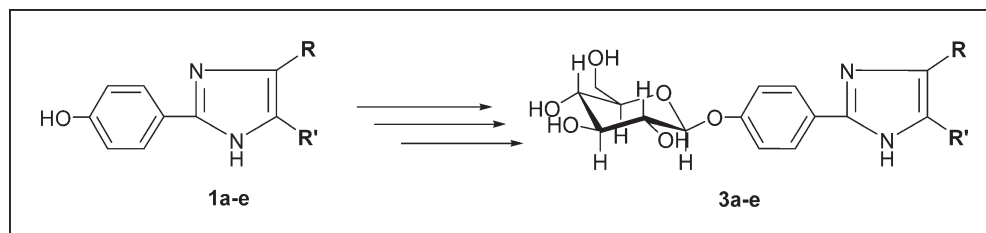
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A series of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles (**1a-e**) prepared from α -diketones, ammonium acetate, and *p*-hydroxybenzaldehyde, which were glucosylated by using α -acetobromoglucose to form 2-(4-*o*- β -D-2,3,4,6-tetra-*o*-acetyl-glucosidoxyphenyl)-4,5-disubstituted imidazoles (**2a-e**) which on catalytic deacetylation with CH₃ONa in methanol afforded the title compound 2-(4-*o*- β -D-glucosidoxyphenyl)-4,5-disubstituted imidazoles (**3a-e**). Compounds were characterized by elemental analysis and by instrumental technique, similarly the title compounds were investigated for antimicrobial and antifungal activity.

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INTRODUCTION

In continuation of our work [1] with imidazole ring which were very important in living systems like vitamin B₁₂. Imidazole also forms a part of some important compounds such as purine, adenine, xanthine, guanine, co-enzyme-a. It is also distributed in essential amino acid, e.g., 1-histidine. Imidazoles possess, various biological activities, *viz.*, antibacterial [2,3], antifungal [4], anti-inflammatory [5], antihistaminic [6], and hypertensive [7]. Glucoconjugate and the carbohydrate containing structure [8,9] exhibit a variety of biological and therapeutic properties [10]. As a result, the formation of glucosidic linkage continues to be a dominant theme in carbohydrate chemistry [11,12]. The attached sugar molecules increase water solubility and tissue penetration. In addition to acting as a modifier, carbohydrate can induce biological activity. In view of various biological activities of imidazoles and the importance of glucose moiety in the metabolism, several compounds containing imidazole and glucose moiety have been synthesized. Herein, we reported the synthesis of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles and 2-(4-*o*- β -D-glucosidoxyphenyl)-4, 5-disubstituted imidazoles.

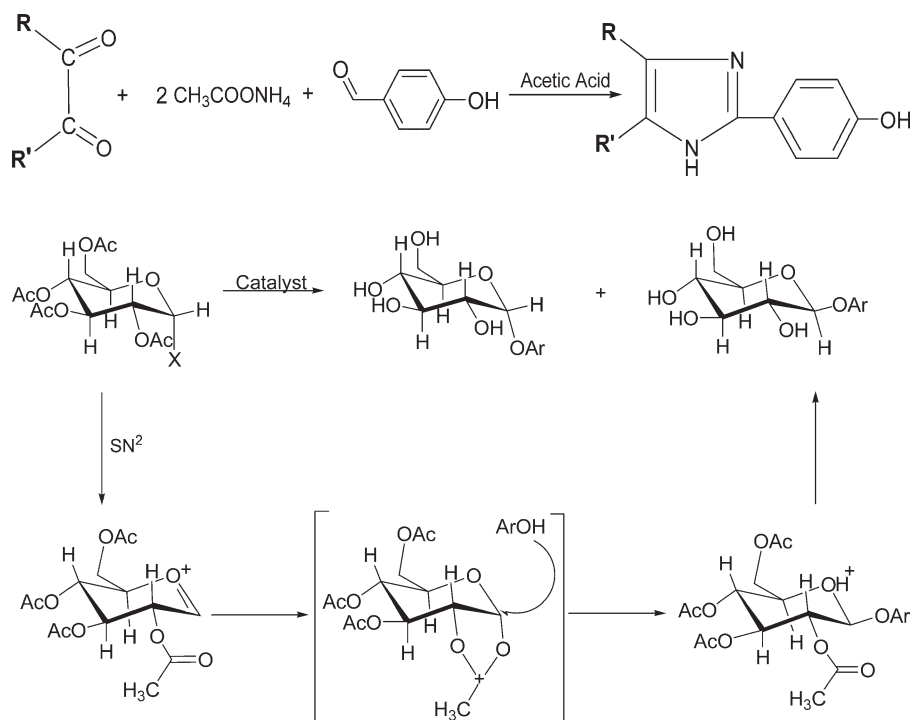
RESULTS AND DISCUSSION

Our general synthetic route starts with the aglycon synthesis **1** it was prepared by condensation between α -diketones, *p*-hydroxybenzaldehyde, and ammonium acetate in the acetic acid medium [13]. The series of these aglycon prepared by changing substitutions at 4,5 positions (**1a-e**). The glucosylation is carried out by using modified Koenigs-Knorr method [14] (Scheme 1).

The mechanism of *o*-glucosylation reaction gained immense importance due to its stereo- and regioselective nature. Glucosylation of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazole with α -acetobromoglucose (ACBG) followed by deacetylation leads to the desired *o*-glucoside with distereoselectivity in favors of β -anomer. *o*-Glucosylation takes place *via* S_N1 and S_N2 mechanism. In the absence of heavy metal salts or Lewis acid catalyst mostly follows S_N2 mechanism which mainly leads to β -anomer as the preferred product. In contrast, the presence of Lewis acid catalyst follows S_N1 mechanism and is less distereoselective and regioselective.

This leads to the formation of α - and β -anomers. An ester protecting group on the 2-hydroxyl group of the donor will lead to the neighboring group participation during *o*-glucosylation reaction and only the 1,2-trans-diaxial glucoside (β -anomer) is the preferred product.

Scheme 1



Glucosylation of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles with acetobromoglucose (ACBG) followed by deacetylation leads the desired *o*-glucoside FT-IR data of the *o*-glucoside are in agreement with the assigned structure. Anomeric configuration confirmed by ^1H NMR since the coupling constant of the compound 8.5 Hz was observed between H-1 and H-2 proton. ^{13}C NMR spectrum, C-1 resonated downfield of the other glucosyl carbon at δ 100.26 consistent with the formation of *o*- β -glucosides. $\text{S}_{\text{N}}2$ mechanism for 1,2-trans glucoside formation 1,2-dioxyacylcarbonium ion (Scheme 2).

BIOLOGICAL ASSAY

Antibacterial activity. The compounds (**3a–e**) were screened for their antibacterial activities against various pathogenic bacteria *Escherichia coli*, *Klebisilla aerogens*, *Staphylococcus aureus*, and *Bacillus subtilis* by the cup plate diffusion of 100 $\mu\text{g/mL}$ by using standard ciprofloxacin and sulphacetamide (100 $\mu\text{g/mL}$) for bacteria. The zone of inhibition after 24 h of incubation at 37°C was compared with standard drugs (Table 1).

Antifungal activity. The compounds (**3a–e**) were screened for antifungal activity tasted at 100 $\mu\text{g/mL}$ concentration in methanol against *Aspergillus niger* and

Candida albicans by adopting cup plate diffusion method. The zone of inhibition after 7 days at 37°C was compared with standard drugs gentamycin and clotrimazole (100 $\mu\text{g/mL}$).

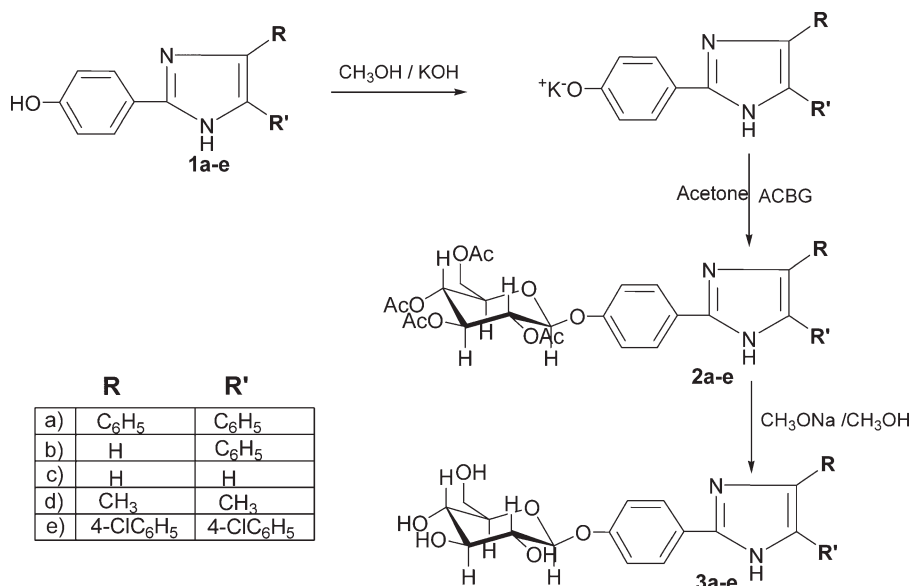
EXPERIMENTAL

The melting points (mp) are taken by using open capillary method and are uncorrected. The FT-IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr disc. The ^1H NMR spectra are recorded on Bruker DRX-300 (300 MHz FT-NMR) instrument using DMSO- d_6 as a solvent and TMS as internal standard, and the chemical shift are expressed in δ ppm values. EI-MS were recorded by direct insertion technique with a Hitachi Perkin Elmer RMU 6D mass Spectrophotometer. Elemental analysis was determined by the FLASH EA 1112 CHN analyzer, Thermo Finigin, Italy.

General procedure for 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles (1a–e**).** A mixture of 4-hydroxy benzaldehyde (5 mmol), α -diketones (5 mmol), ammonium acetate (10 mmol), and glacial acetic acid (50 mL) was refluxed for 2 h. It was poured on to cold water (200 mL) and neutralized with NH_4OH . The solid obtained was filtered, washed with water, and crystallized from alcohol.

2-(4-Hydroxyphenyl)-4,5-diphenyl imidazole (1a**).** Yield 1.4 g (75%), mp 260°C, $R_f = 0.78$, FT-IR spectrum showed the 3569.4 ($-\text{OH}$, broad) due to the presence of free phenolic hydroxyl group and 1608 ($\text{C}=\text{N}$, str.), 3165.3–2793.3 cm^{-1}

Scheme 2



(aromatic ring, str.), 1235.6 (C—O bend), 3466.6 (—NH); ¹H NMR: δ 7.2–7.5 (m, 14H, Ar—H), 6.8 (s, 1H, OH), 7.9 (1H, —NH, D₂O exchangeable) Anal. Calcd. for C₂₁H₂₆N₂O (312): C, 80.75; H, 5.16; N, 8.97; Found: C, 80.65; H, 5.11; N, 8.85.

2-(4-Hydroxyphenyl)-5-phenyl imidazole (1b). Yield 54%; mp 175°C (ethanol); R_f = 0.70, FT-IR: 3510 (—OH, broad), 3345.5 (—NH), 1612 (C=N, str.), 1218 (C—O bend), 3165.3–2790.3 cm⁻¹ (aromatic ring, str.). ¹H NMR: δ = 6.8 (s, 1H, OH), 10.2 (1H, —NH, exchangeable with D₂O), 6.5–7.3 (m, 9H, aromatic). Anal. Calcd. for C₁₅H₁₂N₂O (236): C, 76.25; H, 5.12; N, 11.86; Found: C, 76.18; H, 5.20; N, 11.82.

2-(4-Hydroxyphenyl)-imidazole (1c). Yield 72%; mp 190°C (ethanol); R_f = 0.68, FT-IR: 3585 (—OH, broad), 3358.0 (—NH), 1618 (C=N, str.), 1220 (C—O bend), 3105.5–2788.0 cm⁻¹ (aromatic ring, str.). ¹H NMR: δ = 5.6 (s, 1H,

OH), 9.5 (1H, —NH, exchangeable with D₂O), 6.2–7.4 (m, 4H, aromatic). Anal. Calcd. for C₉H₈N₂O (160): C, 67.49; H, 5.03; N, 17.49; Found: C, 67.56; H, 5.10; N, 17.45.

2-(4-Hydroxyphenyl)-4,5-dimethyl imidazole (1d). Yield 62%; mp 135°C (ethanol); R_f = 0.54, FT-IR: 3424 (—OH, broad), 3269.0 (—NH), 1614 (C=N, str.), 1224 (C—O bend), 3015.5–2712. cm⁻¹ (aromatic ring, str.). ¹H NMR: δ = 5.5 (s, 1H, OH), 9.4 (1H, —NH, exchangeable with D₂O), 6.2–7.8 (m, 4H, aromatic). Anal. Calcd. for C₁₁H₁₂N₂O (188): C, 70.19; H, 6.43; N, 14.88; Found: C, 70.25; H, 6.40; N, 14.90.

2-(4-Hydroxyphenyl)-4,5-bis-(4-chlorophenyl)-imidazole (1e). Yield 60%; mp 245°C (ethanol); R_f = 0.73, FT-IR: 3520 (—OH, broad), 3370.0 (—NH), 1624 (C=N, str.), 1222 (C—O bend), 3085–2712 cm⁻¹ (aromatic ring, str.). ¹H NMR δ = 5.8 (s, 1H, OH), 8.5 (1H, —NH, exchangeable with D₂O), 6.1–7.5

Table 1

Antimicrobial activity 4,5-diaryl-2-(4-*o*- β -D-glucosidoxyphe-nyl) imidazoles (**3a-e**).

Compd. No. ^b	Zone of inhibition ^a (mm) (activity index) ^{std}					
	Antibacterial activity				Antifungal activity	
	Gram-positive		Gram-negative			
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>K. aerogens</i>	<i>C. albicans</i>	<i>A. niger</i>
3a	19(0.55) ^c (0.61) ^d	25(0.86) ^c (0.96) ^d	18(0.51) ^c (0.62) ^d	19(0.83) ^c (0.90) ^d	21(1.00) ^c (0.91) ^d	23(0.92) ^c (1.00) ^d
3b	25(0.73) ^c (0.80) ^d	17(0.58) ^c (0.65) ^d	26(0.74) ^c (0.89) ^d	16(0.72) ^c (0.76) ^d	25(1.19) ^c (1.09) ^d	17(0.68) ^c (0.71) ^d
3c	30(0.88) ^c (0.96) ^d	19(0.65) ^c (0.73) ^d	22(0.62) ^c (0.75) ^d	20(0.90) ^c (0.95) ^d	17(0.80) ^c (0.73) ^d	19(0.76) ^c (0.79) ^d
3d	22(0.64) ^c (0.70) ^d	14(0.48) ^c (0.53) ^d	16(0.45) ^c (0.55) ^d	14(0.63) ^c (0.66) ^d	18(0.85) ^c (0.78) ^d	20(0.80) ^c (0.83) ^d
3e	16(0.47) ^c (0.51) ^d	20(0.68) ^c (0.76) ^d	19(0.54) ^c (0.65) ^d	18(0.81) ^c (0.85) ^d	20(0.95) ^c (0.86) ^d	14(0.56) ^c (0.58) ^d
Std. 1	34	29	35	22	21	25
Std. 2	31	26	29	21	23	24

^a Average zone of inhibition in mm.

^b Concentration of test compounds and standard 100 μ g/mL. (Activity index) = Inhibition zone of the sample/inhibition zone of the standard.

^c Activity index against std. 1.

^d Activity index against std. 2. For antibacterial activity: Std. 1 = Ciprofloxacin and Std. 2 = Sulphacetamide, for antifungal activity: Std. 1 = Gen-tamycin and Std. 2 = Clotrimazole.

(m, 12H, aromatic). Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O$ (380): C, 66.16; H, 3.70; N, 7.35; Found: C, 66.32; H, 3.76; N, 7.32.

General procedure for 2-(4- α - β -D-2,3,4,6-tetra-*o*-acetyl-glucosidoxyphenyl)-4,5-disubstituted imidazoles (2a-e). A solution of 3 g potassium salt of 4,5-disubstituted-2-(4-hydroxyphenyl)-imidazole in 10 mL of 5% methanolic KOH was added drop wise to a solution of 5 g of a acetobromoglucose in 20 mL of dry acetone. The resulting mixture was stirred at 0°C for 2 h. The reaction was allowed to proceed for an additional 24 h and the solvent remove under reduced pressure. The reaction was monitored by TLC, A brown syrupy mass of 4,5-disubstituted-2-(4- α - β -D-2,3,4,6-tetra-*o*-acetyl glucosidoxyphenyl)imidazoles were obtained.

2-(4- α - β -D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-4,5-diphenyl imidazole (2a). Yield 3.57 g (65%). R_f = 0.28. The compound was found to be optically active and the specific rotation $[\alpha]_D^{30}$ in DMSO was found to be -8.12. FT-IR spectrum of the compound showed following characteristic bands at ν_{max} 3424 (—NH), 1607 (C=N), and 1074 (C—O) cm^{-1} . The characteristic band due to phenolic hydroxyl group (3300–3500 cm^{-1}) was absent and the band due to C—O—C which appear at 1231 cm^{-1} confirms the formation of *o*-glucoside. 1H NMR: 2.02, 1.95, 1.97, 2.01 (s, 3H) (COCH₃), 4.8 (d, 1H, anomeric proton), 6.4–7.1 (m, 14H, Ar—H), 10.5 (s, 1H, —NH). Anal. Calcd. for $C_{35}H_{34}N_2O_{10}$ (642): C, 65.41; H, 5.33; N, 4.36; Found: C, 65.35; H, 5.30; N, 4.38.

2-(4- α - β -D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-5-phenyl imidazole (2b). Yield 72%; $[\alpha]_D^{30}$ = -12.56 (c, 0.1, DMSO); brown syrup; R_f = 0.12; FT-IR: 3420 (—NH), 2855 (glucosidic CH), 2420 (Ar—CH), 1610 (C=N), 1089 (C—O), and 1225 cm^{-1} (C—O—C). 1H NMR: 2.02, 1.94, 1.97, 2.01 (s, 3H) (COCH₃), 5.1 (d, 1H, anomeric proton), 6.2–7.0 (m, 9H, Ar—H), 9.6 (s, 1H, —NH). Anal. Calcd. for $C_{29}H_{30}N_2O_{10}$ (566): C, 61.48; H, 5.34; N, 4.94; Found: C, 61.42; H, 5.30; N, 4.93.

2-(4- α - β -D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl) imidazole (2c). Yield 82%; $[\alpha]_D^{30}$ = -2.24 (c, 0.1, DMSO); brown syrup; R_f = 0.22; FT-IR: 3428 (—NH), 2828 (glucosidic CH), 2610 (Ar—CH), 1618 (C=N), 1085 (C—O), and 1210 cm^{-1} (C—O—C). 1H NMR: 2.02, 1.90, 1.96, 2.01 (s, 3H) (COCH₃), 5.4 (d, 1H, anomeric proton), 6.0–7.3 (m, 4H, Ar—H), 9.8 (s, 1H, —NH). Anal. Calcd. for $C_{23}H_{26}N_2O_{10}$ (490): C, 56.32; H, 5.34; N, 5.71; Found: C, 56.38; H, 5.32; N, 5.76.

2-(4- α - β -D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-4,5-dimethyl imidazole (2d). Yield 78%; $[\alpha]_D^{30}$ = -8.16 (c, 0.1, DMSO); brown syrup; R_f = 0.21; FT-IR (KBr): 3430 (—NH), 2832 (glucosidic CH), 2612 (Ar—CH), 1625 (C=N), 1087 (C—O), and 1218 cm^{-1} (C—O—C). 1H NMR: 2.00, 1.92, 1.98, 2.01 (s, 3H) (COCH₃), 5.1 (d, 1H, anomeric proton), 6.2–6.9 (m, 4H, Ar—H), 10.2 (s, 1H, —NH). Anal. Calcd. for $C_{25}H_{30}N_2O_{10}$ (518): C, 57.91; H, 5.83; N, 5.40; Found: C, 57.95; H, 5.84; N, 5.42.

2-(4- α - β -D-2,3,4,6-Tetra-*o*-acetyl glucosidoxyphenyl)-4,5-bis-(4-chlorophenyl) imidazole (2e). Yield 75%; $[\alpha]_D^{30}$ = -4.10 (c, 0.1, DMSO); brown syrup; R_f = 0.28; FT-IR (KBr): 3440 (—NH), 2795 (glucosidic CH), 2610 (Ar—CH), 1620 (C=N), 1090 (C—O), and 1215 cm^{-1} (C—O—C). 1H NMR: 2.00, 1.94, 1.96, 2.02 (s, 3H) (COCH₃), 5.5 (d, 1H, anomeric proton), 6.2–6.8 (m, 12H, Ar—H), 11.4 (s, 1H, —NH). Anal. Calcd. for $C_{35}H_{32}Cl_2N_2O_{10}$ (710): C, 59.08; H, 4.53; N, 3.94; Found: C, 59.05; H, 4.56; N, 3.96.

General procedure for 2-(4- α - β -D-glucosidoxyphenyl)-4,5-disubstituted imidazoles (3a-e). A solution of 4,5-disubstituted-2-(4- α - β -D-2,3,4,6-tetra-*o*-acetyl glucosidoxyphenyl) imidazole (2 g) in 25 mL of dry methanol was added 1.5 mL of 5% CH₃ONa solution. The reaction mixture was kept at room temperature for additional 24 h. It was neutralized with ion-exchange resin (Amberlite IR 120, s.d. fine, H⁺ form) filtered and concentrated in vacuum to afford viscous, strongly hygroscopic brown colored syrupy.

2-(4- α - β -D-Glucosidoxyphenyl)-4,5-diphenyl imidazole (3a). Yield 65%; $[\alpha]_D^{30}$ = -9.88 (c, 0.1, DMSO); brown syrup; R_f = 0.12; FT-IR: 3200–3391.7 (—OH, broad, stretching), 2361.9 (aromatic str.), 1073.7 (C—O—C), 1609.9 cm^{-1} (C=N). 1H NMR: 6.8–7.7 Hz (H, Ar—H), 10.5 (s, —NH), 4.8 (d, 1H, $J_{1,2}$ = 8.5 Hz, 1'H) anomeric proton, 3.9 (1H, 2'H), 3.4 (dd, 1H, 3'H), 3.7 (1H, 4'H), 3.2 (1H, 5'H). ^{13}C NMR: δ 115–128 (Ar—C), sugar moiety: δ 100.26 (s, C-1') anomeric carbon, 81 (s, C-6'), 77 (s, C-5'), 72 (s, C-4'), 70.5 (s, C-3'), 62 (s, C-2'). EI-MS the molecular ion peak were observed at 474 (M + 1) (46%) base peak observed at 312 (100 %), 118 (10 %), 77 (08 %). Anal. Calcd. for $C_{27}H_{26}N_2O_6$ (474): C, 68.34; H, 5.52; N, 5.90; Found: C, 68.37; H, 5.50; N, 5.86.

2-(4- α - β -D-Glucosidoxyphenyl)-5-phenyl imidazole (3b). Yield 58%; $[\alpha]_D^{30}$ = -15.20 (c, 0.1, DMSO); brown syrup; R_f = 0.8; FT-IR: 3300 (—OH, broad), 2718.1 cm^{-1} (aromatic str.), 1079.2 (C—O—C), 1620.6 cm^{-1} (C=N). 1H NMR: 6.8–7.8 (m, 9H, Ar—H), 10.4 (s, 1H, —NH), 3.3 (1H, 5'H), 3.5 (1H, 4'H), 3.4 (1H, 3'H), 3.8 (1H, 2'H), 5.0 (dd, 1H, $J_{1,2}$ = 8.8 Hz, 1'H). ^{13}C NMR: δ 115–128 (Ar—C), sugar moiety: δ 108 (s, C-1') anomeric carbon, 80 (s, C-6'), 76 (s, C-5'), 71.5 (s, C-4'), 70.5 (s, C-3'), 60 (s, C-2'). EI-MS: 398 (M) (20%), 220 (58%) 116 (100%) base peak, 105 (10%), 78 (4%). Anal. Calcd. for $C_{21}H_{22}N_2O_6$ (398): C, 63.31; H, 5.57; N, 7.03; Found: C, 63.34; H, 5.50; N, 7.06.

2-(4- α - β -D-Glucosidoxyphenyl) imidazole (3c). Yield 60%; $[\alpha]_D^{30}$ = -5.22 (c, 0.1, DMSO); brown syrup; R_f = 0.15; FT-IR: 3400 (—OH, broad), 2818.1 (aromatic str.), 1088.2 (C—O—C) glucosidic linkage, 1624 cm^{-1} (C=N). 1H NMR: 6.5–7.9 (m, Ar—H), 11.4 (s, 1H, —NH), 3.2 (1H, 5'H), 3.4 (1H, 4'H), 3.5 (1H, 3'H), 3.9 (1H, 2'H), 5.5 (dd, 1H, $J_{1,2}$ = 10.2 Hz, 1'H) anomeric proton. ^{13}C NMR: δ 116–130 (Ar—C), sugar moiety: δ 110 (s, C-1') anomeric carbon, 82 (s, C-6'), 77 (s, C-5'), 72.5 (s, C-4'), 71.5 (s, C-3'), 63 (s, C-2'). EI-MS: 322 (M) (28 %), 160 (100 %) base peak 146 (15 %), 77 (4 %). Anal. Calcd. for $C_{15}H_{18}N_2O_6$ (322): C, 55.90; H, 5.63; N, 8.69; Found: C, 55.88; H, 5.60; N, 8.65.

2-(4- α - β -D-Glucosidoxyphenyl)-4,5-dimethyl imidazole (3d). Yield 68%; $[\alpha]_D^{30}$ = -11.10 (c, 0.1, DMSO); brown syrup; R_f = 0.16; FT-IR: 3380 (—OH, broad), 2910 (aromatic str.), 1085.0 (C—O—C) glucosidic linkage, 1630 cm^{-1} (C=N). 1H NMR: 6.0–7.4 (m, Ar—H), 10.2 (s, 1H, —NH), 3.0 (1H, 5'H), 3.2 (1H, 4'H), 3.5 (1H, 3'H), 3.7 (1H, 2'H), 5.6 (dd, 1H, $J_{1,2}$ = 9.8 Hz, 1'H) anomeric proton. ^{13}C NMR: δ 120–136 (Ar—C), sugar moiety: δ 115 (s, C-1') anomeric carbon, 88 (s, C-6'), 86 (s, C-5'), 76 (s, C-4'), 70. (s, C-3'), 65 (s, C-2'). EI-MS: 350 (M) (25 %), 170 (100 %) base peak 118 (12 %), 78 (8 %). Anal. Calcd. for $C_{17}H_{22}N_2O_6$ (350): C, 58.28; H, 6.33; N, 8.00; Found: C, 58.32; H, 6.36; N, 8.05.

2-(4- α - β -D-Glucosidoxyphenyl)-4,5-bis-(4-chlorophenyl) imidazole (3e). Yield 62%; $[\alpha]_D^{30}$ = -6.80 (c, 0.1, DMSO); brown syrup; R_f = 0.20; FT-IR: 3420 (—OH, broad), 3015 (aromatic str.), 1088.0 (C—O—C) glucosidic linkage, 1630 cm^{-1} (C=N).

^1H NMR: 6.0–7.3 (m, Ar—H), 10.5 (s, 1H, —NH), 3.0 (1H, 5'H), 3.4 (1H, 4'H), 3.5 (1H, 3'H), 3.8 (1H, 2'H), 5.2(dd, 1H, $J_{1,2} = 9.0$ Hz, 1'H) anomeric proton. ^{13}C NMR: δ 114–136 (Ar—C), sugar moiety: δ 103 (s, C-1') anomeric carbon, 78 (s, C-6'), 77 (s, C-5'), 75 (s, C-4'), 73 (s, C-3'), 67 (s, C-2'). EI-MS: 542 (M) (32 %), 380 (10 %) 246 (100 %) base peak, 163 (24 %), 137 (12 %), 77 (32 %). Anal.Calcd. for $\text{C}_{27}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_6$ (542): C, 59.68; H, 4.45; N, 5.16; Found: C, 59.72; H, 4.48; N, 5.15.

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