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Synthesis and Biological Significance of β -D-Glucuronides

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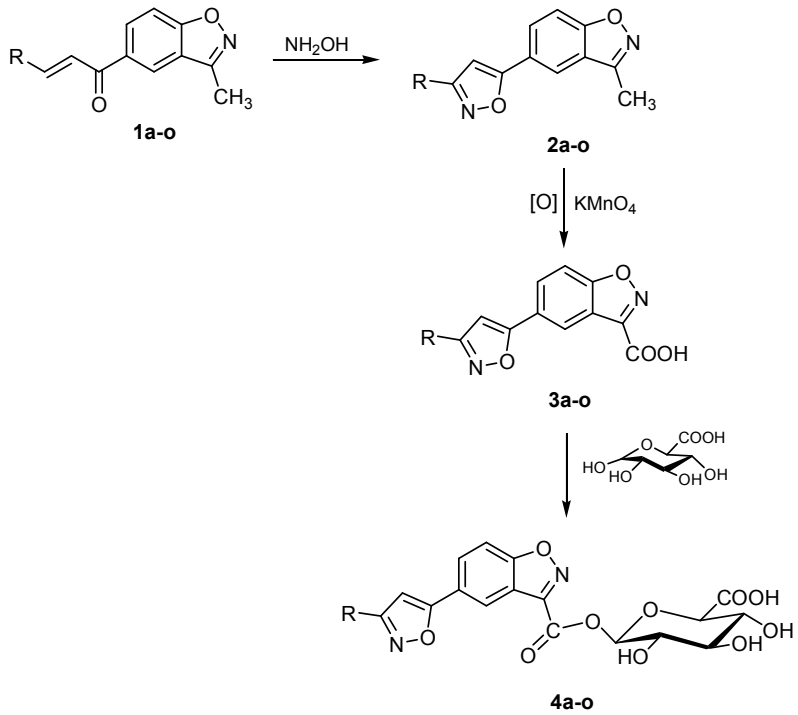
Abstract: 3-methyl-5-(3`-aryl prop-2`-enoyl)-1,2-benzisoxazoles **1a-o** undergoes interaction with hydroxyl amine hydrochloride to yield 3-methyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazoles **2a-o**, which on oxidation with $KMnO_4$ give 5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acids **3a-o**. Glucuronidation of these 5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acids with free glucuronic acid afforded β -D-Glucuronosyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylates **4a-o.** The structures of the products have been assigned on the basis of ^{1}H NMR, ^{13}C NMR, FAB-MS, optical activity and elemental analysis. The title compounds are found to have antibacterial and antifungal activities.
Keywords: Chalcones, Isoxazoles, carboxylic acids, β-D-glucuronides etc.

Introduction

In recent years isoxazoles have attracted much attention due to their diverse properties and wide spectrum of biological and pharmacological activities, e.g., anti-HIV, anti-inflammatory, anticancer and antidepressant properties[1-4]. 1,2-Benzisoxazole derivatives have been used as potential tuberculostatic, anti-inflammatory, analgesic, sedative etc agents[5-8]. β-D-Glucuronides are the conjugation products of compounds possessing a carboxylic acid functional group with free D-glucuronic acid. β-D-Glucuronides are polar and chemically reactive metabolites[9-10], it form covalent adduct with protein, generating increasing interest as potential mediator of hypersensitivity reaction, and it shows profound effect on drug metabolism[11-15].

Result and Discussion

Prompted by the above facts, some 5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acids **3a-o** and their β–D-glucuronides i.e., β–D-glucuronosyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylates **4a-o** have been synthesized with a view to study their biological profile by the glucuronidation of 5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acids **3a-o** with free D-glucuronic acid. The carboxylic acids **3a-o** were prepared by the oxidation of 3-methyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazoles **2a-o** with $KMnO_4$ and 3-methyl-5-(3`-aryl prop-2`-enoyl)-1,2-benzisoxazoles **1a-o** were cyclised to 3-methyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazoles **2a-o** by refluxing their alcoholic solution of hydroxylamine hydrochloride. Different chalcones **1a-o** have been prepared by Claisen-Schmidt condensation of 3-methyl-5-acetyl-1,2-benzisoxazole and aldehydes using piperidine[16-20].



Scheme

R = a; C_6H_5 f; *o*-ClC_6H_4 k; 3-C_5H_4N
b; *o*-OHC_6H_4 g; *p*-ClC_6H_4 l; 4-C_5H_4N
c; *p*-OHC_6H_4 h; *o*-$NO_2C_6H_4$ m; 3-C_4H_3O
d; 2,4-$(OH)_2C_6H_3$ i; *m*-$NO_2C_6H_4$ n; 3-C_8H_5N
e; *p*-OH-*m*-$OCH_3C_6H_3$ j; 2-C_5H_4N o; *p*-$N(CH_3)_2C_6H_4$

Conclusion

β-D-Glucuronides have been synthesized and shows profound effects on drug metabolism. Its easy method of preparation, mildness and efficacy in organic reactions such as cyclisation, oxidation and followed by glucuronidation shows that the reagent could be a useful addition to the existing lot of reagents.

Experimental

Chalcones **1a-o** were prepared as described in the literature[21]. Melting points were determined on a liquid paraffin bath in open capillaries and are uncorrected. FT-IR spectra were recorded using KBr disk on a Perkin-Elmer Infrared spectrometer and ^{1}H NMR spectra on Brucker AC-300F (300Hz) NMR spectrometer using CDCl3 and D_2O as a solvent and tetramethylsilane as internal standard. FAB-MS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using an *m*-nitrobenzyl alcohol (NBA) matrix and purity of compounds was checked on silica gel G-plate using iodine vapor as visualizing agent. Elemental analysis was determined by the FLASH EA 1112; C, H and N analyzer made by thermo Finnigen Italy.

3-Methyl-5-(3`-phenyl prop-2`-enoyl)-1,2-benzisox azole (1a). A mixture of 3-methyl-5-acetyl-1,2-benzisoxazole (0.1mol, 17.5g), benzaldehyde (15mL), ethyl alcohol (25mL) and a few drops of piperidine was warmed for 1hour. It was cooled to 0^0C, the yellow solid formed was filtered, washed with distilled water and dried. It was crystallized from distilled water (9.0g, 50.9%), m.p. 120^0C. It gave dark red color with conc. H_2SO_4. IR (KBr): 1715 (C=O str aryl), 1562 (C=C), 1362 (C-O), 3005 (Ar-H); ^{1}H-NMR signal at δ2.2 (s, CH_3), 7.4-9.3 (8H, m, aromatic protons), 6.0-6.7 (2H, d, CH=CH); FAB-MS: M^+ 264, m/z 248, m/z 185, m/z 174, 160 and m/z 132; Anal. Calcd. for C 77.55, H 4.98, N 5.32; Found: C 77.50, H 4.95, N 5.30%.

Similarly, other 3-methyl-5-(3`-aryl prop-2`-enoyl)-1,2-benzisixazoles **1a-o** were synthesized.

3-Methyl-5-(3`-phenyl isoxazol-5`-yl)-1,2-benzisox azole (2a). A mixture of 3-methyl-5-(3`-phenyl prop-2`-enoyl)-1,2-benzisoxazole **1a** (0.01mol, 2.6g), hydroxylamine hydrochloride (0.7g), ethyl alcohol (15mL) and KOH (0.4g) was refluxed on water bath for 4h. It was cooled and acidified with glacial acetic acid (1.5mL), and was poured on ice-cold water

(50mL). The colorless solid obtained was filter, washed with cold water (100mL), dried and crystallized with distilled water (1.5g, 57.1%), m.p. 114^0C. IR (KBr): 1615 (C=N str.), 1544 (C=C), 1363 (C=N ter amine), 3005 (C-H str $-CH_3$); ^{1}H-NMR signal at δ2.2 (s, CH_3), 6.7-9.1 (8H, m, aromatic protons), 6.4 (s, 1H for isoxazoles ring C_4-H); FAB-MS: M^+ 277, m/z 261, m/z 199 and m/z 144. Anal. Calcd. for C 73.90, H 4.38, N 10.14; Found: C 73.91, H 4.37, N 10.13%.

Following the above procedure, 3-methyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benzisixazoles **2a-o** were prepared (Table I).

3-Methyl-5-[3`-(4`-hydroxy)phenyl isoxazol-5`-yl]-1,2-benzisoxazole (2c). m.p. 98^0C (yield 61.0%); IR (KBr): 3420 (OH), 904 (isoxazoles ring streaching), 3305 (C-H, CH_3), 1560 (C=C), and 1718 cm^{-1} (C=N). ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 5.0 (C-OH,), 6.80 (C-H, isoxazoles), 2.34 (CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 122-146 (C-2, C-3), 188 (C-1), 156 (s, benzisoxazole), 98 (s, isoxazole), 15.6 (s, CH_3, singlet). Anal. Calcd. for C 69.86, H 4.14, N 9.58; Found: C 69.87, H 4.12, N 5.56%.

3-Methyl-5-[3`-(2`,4`-dihydroxy)phenyl isoxazol-5`-yl]-1,2-benzisoxazole (2d). m.p. 101^0C (yield 67.8%); IR (KBr): 3505 and 3485 (OH), 306 (isoxazole ring streaching), 3310 (C-H, CH_3), 1560 (C=C), and 1710 cm^{-1} (C=N). ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 4.9 and 5.5 (C-OH), 6.82 (C-H, isoxazole), 2.32 (CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 122-145 (C-2, C-3), 195 (C-1), 154 (s, benzisoxazole), 99 (s, isoxazole), 15.7 (s, CH_3, singlet). Anal. Calcd. for C 66.23, H 3.92, N 9.09; Found: C 66.21, H 3.91, N 9.07%.

3-Methyl-5-[3`-(4`-chloro)phenyl isoxazol-5`-yl]-1,2-benzisoxazole (2g). m.p. 219^0C (yield 68.0%); IR (KBr): 781 (C-Cl), 905 (isoxazoles ring streaching), 3305 (C-H, CH_3), 1560 (C=C), and 1710 cm^{-1} (C=N). ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 7.45 (C-Cl), 6.83 (C-H, isoxazole), 2.35 (CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 134.3 (C-Cl), 122 (C-H, benzisoxazole), 149 (isoxazole), 15.9 (s, CH_3, singlet). Anal. Calcd. for C 65.71, H 3.57, N 11.41; Found: C 65.70, H 3.54, N 11.40%.

5-(3`-phenyl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acid (3a). 3-methyl-5-(3`-phenyl isoxazol-5`-yl)-1,2-benzisoxazole **2a** (0.01mol, 2.8g), $KMnO_4$ (1.6g), sodium carbonate (1.5g) and water (100mL) was refluxed for 4hours until the purple color has disappeared. It was acidified with dil. H_2SO_4, The excess manganese dioxide was removed by sodium metabisulphite (0.1g), filtered and washed with distilled water and crystallized with distilled water (1.3g, 47.1%), m.p. 134^0C. IR (KBr): 3498 (OH), 1713 (C=O), 1363 (C=N ter amine), 905 (=N-O), 3005 (C-H str); ^{1}H-NMR signal at δ10.5-11.5 (s, Ar-COOH), 6.6-11.2 (8H, m, aromatic protons), 6.3 (s, 1H, C_4-H); FAB-MS: M^+ 306, m/z 261, m/z 247, m/z 229 and m/z 162. Anal. Calcd. for C 66.67, H 3.29, N 9.15; Found: C 66.65, H 3.28, N 9.13%.

In the same way, various carboxylic acids, 5-(3`-aryl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acids **3a-o** were synthesized.

5-[3`-(4`-hydroxy)phenyl isoxazol-5`-yl]-1,2-benziso xazole-3-carboxylic acid (3c). m.p. 154^0C (yield 44.54%); IR (KBr): 3422 (OH), 905 (isoxazole ring streaching), 1565 (C=C), and 1715 cm^{-1} (C=N). ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 5.1 (C-OH), 11.8 (COOH), 6.83 (C-H, isoxazole), ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 121-148 (C-2, C-3), 189 (C-1), 155 (s, benzisoxazole), 99 (s, isoxazole), 172 (carboxyl), 15.5 (s, CH_3, singlet). Anal. Calcd. for C 63.36, H 3.13, N 8.69; Found: C 63.32, H 3.14, N 8.67%.

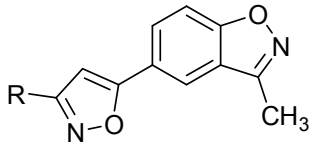
5-[3`-(2`,4`-dihydroxy)phenyl isoxazol-5`-yl]-1,2-benzisoxazole-3-carboxylic acid (3d). m.p. 156^0C (yield 48.7%); IR (KBr): 3500 and 3480 (OH), 308 (isoxazole ring streaching), 1560 (C=C), and 1710 cm^{-1} (C=N). ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 4.9 and 5.1 (C-OH,), 11.2 (COOH), 6.81 (C-H, isoxazole), ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 120-145 (C-2, C-3), 190 (C-1), 155 (s, benzisoxazole), 95 (s, isoxazole), 175 (carboxyl). Anal. Calcd. for C 60.0, H 3.55, N 8.23; Found: C 60.05, H 3.56, N 8.22%.

5-[3`-(4`-chloro)phenyl isoxazol-5`-yl]-1,2-benziso xazole-3-carboxylic acid (3g). m.p. 234^0C (yield 51.60%); IR (KBr): 782 (C-Cl), 908 (isoxazole ring streaching), 1565 (C=C), and 1742 cm^{-1} (C=N). ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 7.42 (C-Cl), 10.8 (COOH), 6.82 (C-H, isoxazole), ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 134.5 (C-Cl), 125 (C-H, benzisoxazole), 151 (isoxazole), 173 (carboxyl), 15.9 (s, CH_3, singlet). Anal. Calcd. for C 59.93, H 2.66, N 8.22. Found: C 59.91, H 2.64, N 8.19%.

β-D-Glucuronosyl-5-(3`-phenyl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylate (4a). To a solution of 5-(3`-phenyl isoxazol-5`-yl)-1,2-benzisoxazole-3-carboxylic acid **3a** (0.01 mol, 3.06g) in (4mL) dry pyridine, which was kept at 0^0C, D-glucuronic acid (1.94g) was added in portion with constant stirring.

The reaction mixture was left at room temperature for 18h, it was poured over crushed ice. The resulting white solid was filtered and washed with ice-cold water (yield 1.92g, 62.09%. IR (KBr): 3373 (OH), 911

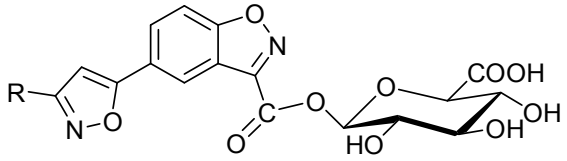
Table I: Characterization data of compound 2a-o.



2a-o

Product	R	Mol. Formula	mp (^{0}C)	Yield (%)	R_f	% Found (Calcd) C	H	N
2a	C_6H_5	$C_{17}H_{12}N_2O_2$	114	57.1	0.27	73.91 (73.90)	4.37 (4.38)	10.13 (10.14)
2b	*o*-OHC_6H_4	$C_{17}H_{12}N_2O_3$	124	40.0	0.31	69.85 (69.86)	4.12 (4.14)	9.57 (9.58)
2c	*p*-OHC_6H_4	$C_{17}H_{12}N_2O_3$	98	61.0	0.28	69.87 (69.86)	4.12 (4.14)	9.56 (9.58)
2d	2,4-$(OH)_2C_6H_3$	$C_{17}H_{12}N_2O_4$	100	67.8	0.40	66.21 (66.23)	3.91 (3.92)	9.07 (9.09)
2e	*p*-OH*m*-$OCH_3C_6H_3$	$C_{18}H_{14}N_2O_4$	209	80.0	0.26	67.05 (67.07)	4.38 (4.38)	8.65 (8.69)
2f	*o*-ClC_6H_4	$C_{17}H_{11}ClN_2O_2$	123	84.0	0.21	65.70 (65.71)	3.56 (3.57)	11.40 (11.41)
2g	*p*-ClC_6H_4	$C_{17}H_{11}ClN_2O_2$	219	68.0	0.32	65.70 (65.71)	3.54 (3.57)	11.40 (11.41)
2h	*o*-$NO_2C_6H_4$	$C_{17}H_{11}N_3O_4$	155	66.6	0.30	63.54 (63.55)	3.56 (3.45)	13.07 (13.08)
2i	*m*-$NO_2C_6H_4$	$C_{17}H_{11}N_3O_4$	110	71.5	0.24	63.53 (63.55)	3.43 (3.45)	13.05 (13.08)
2j	2-C_5H_4N	$C_{16}H_{11}N_3O_2$	188	67.9	0.22	69.30 (69.31)	3.98 (4.00)	15.13 (15.15)
2k	3-C_5H_4N	$C_{16}H_{11}N_3O_2$	115	83.0	0.31	69.33 (69.31)	4.12 (4.00)	15.16 (15.15)
2l	4-C_5H_4N	$C_{16}H_{11}N_3O_2$	198	75.7	0.27	69.32 (69.31)	4.09 (4.00)	15.16 (15.15)
2m	3-C_4H_3O	$C_{15}H_{10}N_2O_3$	179	60.5	0.29	67.65 (67.67)	3.75 (3.79)	10.49 (10.52)
2n	3-C_8H_5N	$C_{19}H_{13}N_3O_2$	256	73.5	0.25	72.35 (72.37)	4.15 (4.16)	13.30 (13.33)
2o	*p*-*N*$(CH_3)_2C_6H_4$	$C_{19}H_{17}N_3O_2$	209	82.0	0.29	71.40 (71.46)	5.39 (5.37)	13.15 (13.16)

Table II: Characterization data of compounds 4a-o.



4a-o

Product	R	Mol. Formula	$[\alpha]_D^{29}(^0)$	Yield (%)	R_f	% Found (Calcd) C	H	N
4a	C_6H_5	$C_{23}H_{18}N_2O_{10}$	43.2	63.7	0.30	57.24 (57.26)	3.74 (3.76)	5.80 (5.81)
4b	*o*-OHC_6H_4	$C_{23}H_{18}N_2O_{11}$	42.5	62.1	0.31	55.40 (55.42)	3.61 (3.64)	5.60 (5.62)
4c	*p*-OHC_6H_4	$C_{23}H_{18}N_2O_{11}$	48.1	59.9	0.25	55.43 (55.42)	3.65 (3.64)	5.62 (5.41)
4d	2,4-$(OH)_2C_6H_3$	$C_{23}H_{18}N_2O_{12}$	47.4	61.7	0.30	53.64 (53.70)	3.51 (3.53)	5.41 (5.45)
4e	*p*-OH*m*-$OCH_3C_6H_3$	$C_{24}H_{20}N_2O_{12}$	51.7	62.1	0.25	54.50 (54.55)	3.79 (3.82)	5.28 (5.30)
4f	*o*-ClC_6H_4	$C_{23}H_{17}ClN_2O_{10}$	55.9	52.9	0.21	53.43 (53.45)	3.30 (3.32)	5.41 (5.42)
4g	*p*-ClC_6H_4	$C_{23}H_{17}ClN_2O_{10}$	52.3	51.4	0.27	53.42 (53.45)	3.33 (3.32)	5.40 (5.42)
4h	*o*-$NO_2C_6H_4$	$C_{23}H_{17}N_3O_{12}$	39.8	48.4	0.30	52.30 (52.30)	3.24 (3.25)	7.96 (7.97)
4i	*m*-$NO_2C_6H_4$	$C_{23}H_{17}N_3O_{12}$	44.5	51.2	0.28	52.32 (52.30)	3.23 (3.25)	7.98 (7.97)
4j	2-C_5H_4N	$C_{22}H_{17}N_3O_{10}$	38.4	57.0	0.29	54.60 (54.66)	3.50 (3.55)	8.67 (8.69)
4k	3-C_5H_4N	$C_{22}H_{17}N_3O_{10}$	37.6	58.6	0.31	54.63 (54.66)	3.52 (3.55)	8.68 (8.69)
4l	4-C_5H_4N	$C_{22}H_{17}N_3O_{10}$	48.5	55.3	0.26	54.65 (54.66)	3.52 (3.55)	8.67 (8.69)
4m	3-C_4H_3O	$C_{21}H_{16}N_2O_{11}$	53.7	53.3	0.32	53.65 (53.39)	3.41 (3.66)	5.97 (5.93)
4n	3-C_8H_6N	$C_{25}H_{19}N_3O_{10}$	47.3	55.0	0.22	57.60 (57.58)	3.66 (3.67)	8.10 (8.06)
4o	*p*-*N*$(CH_3)_2C_6H_4$	$C_{25}H_{23}N_3O_{10}$	45.7	51.5	0.29	57.10 (57.14)	4.39 (4.41)	7.94 (8.00)

(isoxazole ring streaching), 1569 (C=C), and 1731 cm^{-1} (C=N). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 6.85 (C-H, isoxazole). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 121-148 (C-2, C-3), 187 (C-1), 155 (s, benzisoxazole), 97 (s, isoxazole). $[\alpha]^{25}_D$ (^{0}) +43.2; R_f 0.30; Anal. Calcd. for C 57.26, H 3.76, N 5.81; Found: C 57.24, H 3.74, N 5.80%. FAB-MS: M^+ 482, m/z 306 (due to loss of D-glucuronic acid), m/z 261 and m/z 229.

Following the above procedure, others β-D-glucuronosyl-5-(3`-aryl isoxazol-5`-yl)-1,2-benz isoxazole-3-carboxylates **4a-o** were prepared starting from the appropriate carboxylic acids **3a-o**. Compounds gave satisfactory C, H, and N analysis (Table II).

β-D-Glucuronosyl-5-[3`-(4`-hydroxy)phenyl isoxazol-5`-yl]-1,2-benzisoxazole-3-carboxylate (4c). Yield 59.93%; IR (KBr): 3422 (OH), 905 (isoxazole ring streaching), 1566 (C=C), and 1715 cm^{-1} (C=N). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 6.83 (C-H, isoxazole), 2.30 (CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 121-148 (C-2, C-3), 189 (C-1), 154 (s, benzisoxazole), 99 (s, isoxazole). $[\alpha]^{25}_D$ (^{0}) +48.1; R_f 0.25; Anal. Calcd. for C 55.42, H 3.64, N 5.62; Found: C 55.43, H 3.65, N 5.60%. FAB-MS: M^+ 498, m/z 322 (due to loss of D-glucuronic acid), m/z 262 and m/z 229.

β-D-Glucuronosyl-5-[3`-(2`,4`-dihydroxy)phenyl isoxazol-5`-yl]-1,2-benzisoxazole-3-carboxylate (4d). Yield 61.76%; IR (KBr): 3425 (OH), 904 (isoxazole ring streaching), 1566 (C=C), and 1716 cm^{-1} (C=N). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 6.82 (C-H, isoxazole). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 122-146 (C-2, C-3), 185 (C-1), 154 (s, benzisoxazole), 96 (s, isoxazole). $[\alpha]^{25}_D$ (^{0}) +47.4; R_f 0.30; FAB-MS: M^+ 514, m/z 338, m/z 263 and m/z 228; Anal. Calcd. for C 53.70, H 3.53, N 5.45; Found: C 53.64, H 3.51, N 5.41%.

β-D-Glucuronosyl-5-[3`-(4`-chloro)phenyl isoxazol-5`-yl]-1,2-benzisoxazole-3-carboxylate (4g). Yield 51.47%; IR (KBr): 780 (C-Cl), 3378 (OH), 912 (isoxazole ring streaching), 1568 (C=C), and 1730 cm^{-1} (C=N). ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): 7.46 (C-Cl), 6.84 (C-H, isoxazole). ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): 134 (C-Cl), 121-145 (C-2, C-3), 188 (C-1), 154 (s, benzisoxazole), 98 (s, isoxazole). $[\alpha]^{25}_D$ (^{0}) +52.3; R_f 0.27; FAB-MS: M^+ 516, m/z 340, m/z 262 and m/z 229; Anal. Calcd. for C 53.45, H 3.32, N 5.42; Found: C 53.42, H 3.33, N 5.40%.

Table III. Data for in vitro antibacterial and antifungal activity (in mm), minimum inhibitor concentration µg/mL.

Comp.	*E. coli*	*S. aureus*	*A. niger*	*C. albicans*
4a.	++	+	+++	+
4b.	+	N.A.	++	+++
4c.	++	+++	+	++
4d.	+	+++	+++	++
4e.	+++	++	+	+++
4f.	N.A.	+	+++	++
4g.	+++	+++	++	+++
4h.	++	+	+++	++
4i.	+++	+++	N.A.	++
4j.	++	+++	+++	+++
4k.	+++	+	++	++
4l.	+	+++	+	+++
4m.	+++	+++	+++	+
4n.	++	+	+	+++
4o.	+++	+++	+++	++

N.A. = Not Active, + = Less Active
++ = Moderately Active, +++ = Very Active
Norfloxacin 100µg/mL used as standard against *E. coli* and *S. aureus*.
Griseofulvin 100µg/mL used as standard against *A. niger* and *C. albicans*.

Biological screening

Biological screening of some newly synthesized compounds **4a-i** were tested at 100µg/mL concentration against *E. coli*, *S. aureus*, *A. niger* and *C. albicans* for its antibacterial and antifungal screening as shown in Table III.

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