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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF BENZISOXAZOLE DERIVATIVES AND THEIR *N*-GLUCOSIDES

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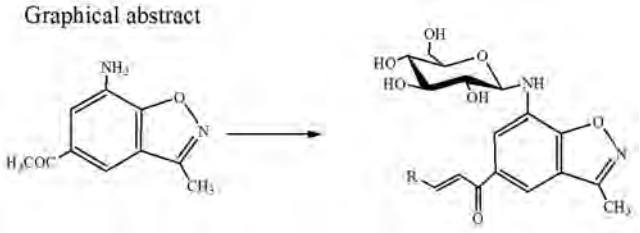
ABSTRACT Different 7-amino-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles were synthesized by the interaction of appropriate 5-acetyl-7-amino-3-methyl-1,2-benzisoxazole with different aromatic aldehydes using piperidine. Tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide was prepared by the reaction of powdered glucose pentaacetate and bromine in the presence of chloroform. Condensation of tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide with 7-amino-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles furnished 7-amino-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles which on deprotection gave 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles. Polarographic studies revealed the presence of reducible groups with distinguished $E_{1/2}$ values. All compounds were screened for antimicrobial activities, and some compounds showed potent antibacterial and antifungal activities.

Graphical abstract



KEYWORDS 1,2-Benzisoxazole, Nitro, Amino compounds, N-glucosides, Polarography.

INTRODUCTION

Heterocyclic compounds promote life on earth. Heterocyclic compounds such as isoxazole, pyrazoles, furans, pyrroles, thiazines, and oxazines exhibit diverse pharmacological activities such as anti-fungal,[1] antibacterial,[2-4] antiviral,[5] anti-inflammatory,[6,7] herbicidal,[8] anticancer,[9] cytotoxic,[10] anesthetics,[11] and insecticidal.[12] Chalcones are considered as precursors of flavonoids and isoflavonoids which are widely present in edible plants. Chemically, they consist of open chain flavonoids in which the two aromatic rings are joined together by a three carbon *α*, *β*-unsaturated carbonyl functional group. The presence of *α*, *β*-keto functional group in chalcone is responsible for antimicrobial activities[13,14] and has been used as intermediates for the preparation of compounds having therapeutic value. They are natural biocides and known intermediates in the synthesis of heterocyclic compounds exhibiting various biological activities. According to reported literature, chalcone derivatives exhibit potential pharmacological activities such as cytotoxic,[15] antimicrobial,[16,17] antiviral, anti-inflammatory, and anesthetic properties.[18-20] Heterocyclic system having benzisoxazoles moieties are well known for significant activities in pharmaceutical compounds.[21,22]

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1,2-benzisoxazole derivatives are potential antipsychotic agents with affinity for serotonergic and dopaminergic receptor.[23] The *N*-benzyl piperidine compounds are used for the palliative treatment of Alzheimer's disease, potential tuberculosis, hypertension, inflammation and also as sedative agents.[24] They have antidepressant, anticonvulsant,[25] and antifungal[26] properties.

Glucosylation improves the solubility of various drugs without affecting their activities. Impregnation of the glycosidic moiety into the molecules increases its hydrophilicity as compared to the respective aglycon. *β*-Glucosylation can improve the drug targeting to the cells due to their solubility in the membrane components.[27] The screening results indicate that glucosides show moderate to excellent antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* organisms and antifungal activity against *Candida albicans* and *Aspergillus niger*.[28]

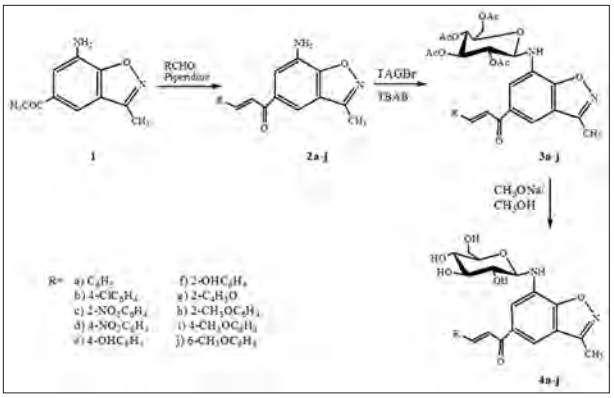
In the view of pronounced biological and pharmacological observations of chalcones, 1,2-benzisoxazoles, nitro, amine compounds, and *N*-glucosides, it was planned to synthesize new chemical entities having active pharmacological functions, namely, chalcones, benzisoxazoles, nitro, amine, and their *N*-glucosides moiety in a single molecular framework as a new biologically active compounds.

RESULTS AND DISCUSSION

5-Acetyl-7-amino-3-methyl-1,2-benzisoxazole **(1)** was synthesized by a literature multispecs process.[29-31,34] 7-Amino-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles **(2a-j)** were prepared by the interaction of 5-acetyl-7-Amino-3-methyl-1,2-benzisoxazole with different aromatic and heterocyclic aldehydes using suitable solvent.[32] 7-amino-(*β*-D-2,3,4,6-tetra-*O*-acetyl glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles **3a-j** were prepared by glucosylation of 7-amino-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles with tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide using tetrabutylammonium bromide and dichloromethane as a solvent. All the synthesized compounds were deprotected by sodium methoxide in methanol to obtained target molecules 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles **4a-j (Scheme 1)**.[33] Polarographic studies revealed the presence of reducible groups with distinguished $E_{1/2}$ values.

EXPERIMENTAL SECTION

Melting points were determined on amelting point apparatus in open capillaries. Fourier transform infrared (FT-IR) spectra were recorded on Bruker infrared spectrometer, ^{1}H-NMR,^{13}C-NMR spectra on Bruker Avance II 400 NMR spectrometer and FAB-MS spectra were recorded, elemental analyses were determined using Perkin-Elmer C, H, N analyzer and polarograms were recorded on Elico CL-362 polarograph. Purity of compounds was checked on silica gel plates using UV chamber for visualization.



Scheme 1: Synthesis of 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3'-aryl prop-2'-enoyl)-1,2-benzisoxazoles

Synthesis of 5-acetyl-7-amino-3-methyl-1,2-benzisoxazole, 1

It has been synthesized as per reported in literature.[34] (Yield 12.3 g, 64.73%), mp 136°C and functional group test, i.e., dye test was positive.

Synthesis of 7-amino-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole, (2a)

Condensation reaction occured in ethyl alcohol (25 mL) by taking 5-acetyl-7-amino-3-methyl-1,2-benzisoxazole (1.90 g, 0.01M), benzaldehyde (1.0 mL, 0.01M), and few drops of piperidine for 40 min. The reaction mixture was cooled to 0°C; yellow solid compound formed was washed. (Yield 2.10 g, 75.50%), mp 92°C and its alcoholic solution turned red with alkali and decolorized with bromine water, and it gave dark red color with concentrations H_2SO_4.

FT-IR: The infrared spectrum showed characteristic absorption bands, (υ_{max} cm^{-1}): 3359 (-NH_2), 3253 (-NH_2), 2840-3067 (C-H str. in benzene), 1734 (C=O str. aryl ketone). ^{1}H-NMR: The ^{1}H-NMR spectrum displayed signals at δ8.79-8.78 (d, *J* = 5.96 Hz, 1H, -CO-CH=CH-), δ8.43-8.41, (d, *J* = 8.08 Hz, 1H, C=O-C-H=C-H), δ8.21-8.19 (d, *J* = 8.08 Hz, 1H, Ar-H), δ8.07-8.04 (d, *J* = 9.84 Hz, 1H, Ar-H), δ7.45-7.82 (m, 4H, Ar-H), δ7.03-7.00 (d, *J* = 11.12 Hz,1H, Ar-H), δ4.22 (s, 2H, NH_2), δ2.69 (s, 3H, -CH_3). ^{13}C-NMR: The ^{13}C-NMR spectrum displayed signals δ198.31 (C=O), δ160.61 (C-3a), δ150.69 (C-7a), δ141.79 (ethylene CH), δ139.32 (C-1′), δ136.06 (C-5), δ133.96 (C-7), δ131.80 (C-3′), δ129.27 (C-5′), δ127.39 (C-4′), δ126.97 (C-2′), δ125.98 (C-6′), δ125.18 (C-9), δ123.09 (ethylene CH), δ119.03 (C-6), δ114.43 (C-4), δ14.78 (CH_3). FAB-MS: FAB-MS confirmed the molecular formula $C_{17}H_{14}N_2O_2$. It shows molecular ion peak at m/z 279 $[C_{17}H_{14}N_2O_2]^+$.

In the same way, other chalcones 7-amino-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles **(2b-j)** were prepared. The characterization data of these compounds are summarized in **Table 1**.

Synthesis of 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole, (4a)

To a solution of 7-amino-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole (2.78 g, 0.01M)

Table 1: Characterization data of 7-amino-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles (2a-j)

Compound	R	Molecular formula	Mol. Wt.	mp °C	Yield (%)	R_f value	Found (calculated) %		
							C	H	N
2a	C_6H_5	$C_{17}H_{14}N_2O_2$	278	92	75	0.15	73.37 (73.12)	5.07 (5.20)	10.07 (10.05)
2b	4-ClC_6H_4	$C_{17}H_{13}ClN_2O_2$	312.8	95	78	0.13	65.29 (65.35)	4.19 (4.21)	8.96 (9.05)
2c	2-$NO_2C_6H_4$	$C_{17}H_{13}N_3O_4$	323.3	131	65	0.18	63.16 (63.05)	4.05 (4.00)	13.0 (13.21)
2d	4-$NO_2C_6H_4$	$C_{17}H_{13}N_3O_4$	323.3	142	56	0.22	63.16 (63.05)	4.05 (4.00)	13.0 (13.21)
2e	4-OHC_6H_4	$C_{17}H_{14}N_2O_3$	294.3	135	67	0.15	69.38 (69.78)	4.79 (4.65)	9.52 (9.57)
2f	2-OHC_6H_4	$C_{17}H_{14}N_2O_3$	294.3	109	64	0.25	69.38 (69.78)	4.79 (4.65)	9.52 (9.57)
2g	2-C_4H_3O	$C_{15}H_{12}N_2O_3$	268.3	175	49	0.27	67.13 (63.13)	4.51 (4.60)	10.44 (10.36)
2h	2-$CH_3OC_6H_4$	$C_{18}H_{16}N_2O_3$	308.3	88	64	0.14	70.12 (70.26)	5.23 (5.10)	9.09 (9.09)
2i	4-$CH_3OC_6H_4$	$C_{18}H_{16}N_2O_3$	308.3	106	58	0.22	70.12 (70.26)	5.23 (5.10)	9.09 (9.09)
2j	6-$CH_3OC_6H_4$	$C_{18}H_{16}N_2O_3$	308.3	119	72	0.2	70.12 (70.26)	5.23 (5.10)	9.09 (9.09)

and 2,3,4,6-tetra-*O*-acetyl glucopyranosyl bromide (3.0 g, 0.01M) in dichloromethane (4 mL) was added tetrabutylammonium bromide) (0.32 g) with stirring at 5°C. The organic layer was separated, washed with water, 5% aqueous $NaHCO_3$, again with water and dried.

The tetra-acetyl derivative was deacetylated with 5% sodium methoxide solution. To a solution of 7-amino-(*β*-D-2,3,4,6-tetra-*O*-acetyl glucopyranosyl)-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole in absolute methanol (25 mL) was added (1.5 mL) of 5% of sodium methoxide solution and kept at room temperature for 45 min. The reaction mixture was neutralized with ion exchange resin (Amberlite IR 120, H^+, cation exchanger), filter and dried. A semi solid mass , thus obtained, was crystallized from ethanol as brown syrupy compound was obtained. The compound was found to be optically active and specific rotation $[\alpha]^{25}$ D in water was found to be +46.1°.

FT-IR: (υ_{max} cm^{-1}): 3348 (str. OH), 3110 (stretch N-H), 2961 (Ar-H str), 1672 (C=O), 1639 (C=N).[35]^{1}H-NMR: The ^{1}H-NMR spectrum displayed signals at^{1}H-NMR: δ8.69-8.67 (dd, *J* = 2.16 Hz, *J* = 2.00 Hz, 1H in ethylenic -CH=CH), δ8.47-8.46 (d, *J* = 1.08 Hz, 1H in ethylenic -CH=CH), δ8.29-7.96 (m, 6H, Ar-H), δ7.76-7.75 (d, *J* = 5.68 Hz, 1H, Ar-H), δ5.08 (s, 1H, -NH), δ4.59-4.58 (d, *J* = 4.0 Hz,1H, H-1 anomeric proton in glucose), δ4.22-4.07 (m, 2H, -CH_2 in glucose), δ3.88-3.80 (m, 1H, H-2 in glucose), δ 3.68 (s, 1H, H-5 in glucose), δ3.50 (s, 1H, H-3 in glucose), δ3.36-3.33 (d, 1H, H-4 in glucose), δ2.56 (s, 3H, -CH_3). Signals due to hydroxyl protons of the carbohydrate were not observed because of fast exchange of non-hydrogen bonded -OH groups and the acidic phenolic functions.[36] ^{13}C-NMR: The ^{13}C-NMR spectrum displayed signals δ194.96 (C=O), δ165.31 (C-3), δ155.79 (C-3a), δ146.69 (ethylene CH), δ137.08 (C-1′), δ132.21 (C-5), δ131.66 (C-3′), δ130.32 (C-5′), δ129.13 (C-4′), δ128.49 (C-2′), δ126.20 (C-6′), δ125.33 (C-7), δ125.00 (C-7a), δ122.79 (ethylene CH), δ119.42 (C-6), δ118.83 (C-4), δ109.83 (glucose C-1), δ80.16 (glucose C-5), δ75.00 (glucose C-3), δ72.10 (glucose C-4), δ62.09 (glucose C-2), δ59.64 (glucose C-6), δ13.98 (CH_3).[37] FAB-MS: FAB-MS confirmed the molecular formula $C_{23}H_{24}N_2O_7$. It showed molecular ion peak at m/z 440 $[C_{23}H_{24}N_2O_7]^+$. The base peak appeared at m/z 277 $[C_{17}H_{13}N_2O_2]^+$.[38]

In the same way, other *N*-glucosides 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles **(4b-j)** were prepared. The characterization data of these compounds are summarized in **Table 2.**

POLAROGRAPHIC STUDIES

Polarographic studies of 7-amino-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole and 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole were carried out using Elico CL-362 polarograph based on microprocessor operation. The electrode system consisted of dropping mercury electrode as working electrode, platinum wire as an auxiliary electrode and saturated calomel electrode as a reference electrode. The supporting electrolyte used was 0.1M KCl solution.

The supporting electrolyte solution was deaerated with nitrogen for 15 min and polarograms were recorded in DC and DPP modes. To this solution, various concentrations of ethanolic solutions of 7-amino-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole were added, and polarograms were recorded for each addition. The DC polarograms have been shown in **Figure 1a** while DP polarograms have been shown in **Figure 1b**.

The DC polarogram showed a distinct polarographic wave with half wave potential ($E_{1/2}$) -1.390V which matches with the literature value for methyl-*α*-*β*-unsaturated aryl ketone group.[39] The differential pulse polarogram shows a distinct peak with peak potential -1.388V.

The supporting electrolyte solution was deaerated with nitrogen for 15 min, and polarograms were recorded in DC and DPP modes. To this solution, various concentrations of ethanolic solutions of 7-amino-(*β*-D-glucopyranosyl)-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole were added, and polarograms were recorded for each addition. The DC polarograms have been shown in **Figure 1c** while DP polarograms have been shown in **Figure 1d**.

The DC polarogram showed a distinct polarographic wave with half wave potential ($E_{1/2}$) -1.491V which matches with the literature value for sugar group.[40] The differential

Table 2: Characterization data of 7-amino-(β-D-glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′-enoyl)-1,2-benzisoxazoles (4a-j)

Compound	R	Molecular formula	Mol. Wt.	[α] D (°C)	R_f value	Found (calculated) %		
						C	H	N
4a	C_6H_5	$C_{23}H_{24}N_2O_7$	440.4	+46.1	0.20	62.72 (62.70)	5.49 (5.56)	6.36 (6.40)
4b	4-ClC_6H_4	$C_{23}H_{23}ClN_2O_7$	474.9	+48.2	0.31	58.17 (58.23)	4.88 (4.88)	5.90 (5.95)
4c	2-$NO_2C_6H_4$	$C_{23}H_{23}N_3O_9$	485.4	+39.1	0.25	56.91 (56.80)	4.78 (4.80)	8.66 (8.96)
4d	4-$NO_2C_6H_4$	$C_{23}H_{23}N_3O_9$	485.4	+47.3	0.27	56.91 (56.80)	4.78 (4.80)	8.66 (8.96)
4e	4-OHC_6H_4	$C_{23}H_{24}N_2O_8$	456.4	+46.7	0.32	60.52 (60.92)	5.30 (5.30)	6.14 (6.21)
4f	2-OHC_6H_4	$C_{23}H_{24}N_2O_8$	456.4	+41.9	0.14	60.52 (60.92)	5.30 (5.30)	6.14 (6.21)
4g	2-C_4H_3O	$C_{21}H_{22}N_2O_8$	430.0	+38.6	0.16	58.60 (58.60)	5.15 (5.01)	6.51 (6.30)
4h	2-$CH_3OC_6H_4$	$C_{24}H_{26}N_2O_8$	470.5	+42.0	0.21	61.27 (61.05)	5.57 (6.00)	5.95 (5.98)
4i	4-$CH_3OC_6H_4$	$C_{24}H_{26}N_2O_8$	470.5	+50.1	0.23	61.27 (61.05)	5.57 (6.00)	5.95 (5.98)
4j	6-$CH_3OC_6H_4$	$C_{24}H_{26}N_2O_8$	470.5	+43.4	0.27	61.27 (61.05)	5.57 (6.00)	5.95 (5.98)

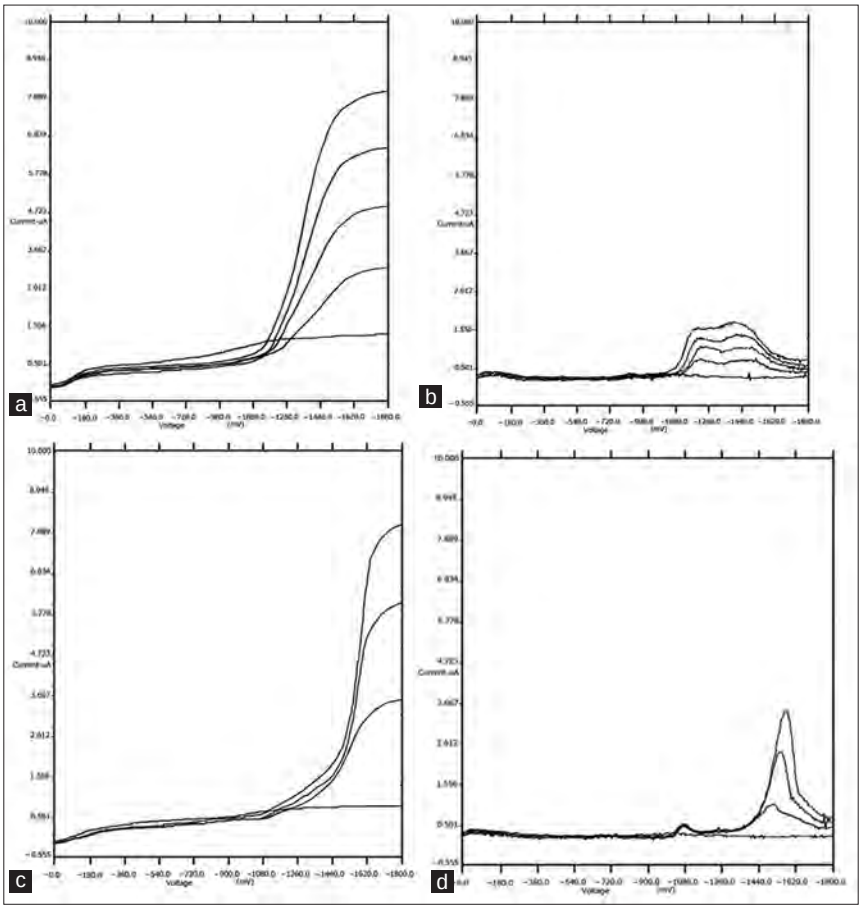


Figure 1: (a) DC polarograms of 0.1M KCl and with four additions of 7-amino-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole, (b) DP polarograms of 0.1M KCl and with four additions of 7-amino-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole, (c) DC polarograms of 0.1M KCl and with four additions of 7-amino-(β-D-glucopyranosyl)-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole, (d) DP polarograms of 0.1M KCl and with four additions of 7-amino-(β-D-glucopyranosyl)-3-methyl-5-(3′-phenyl prop-2′-enoyl)-1,2-benzisoxazole

pulse polarogram shows a distinct peak with peak potential −1.543V.

ANTIMICROBIAL ACTIVITY

The compounds **4a-j** were screened for their antibacterial activity against *E. coli* and *S. aureus* by disc diffusion method. The standard norfloxacin was used for the comparison of results. The screening result showed the entire compound active against both the bacteria tested at 800 µg/mL concentration. Compounds **4b, 4e, 4g**, and **4i** showed moderate activity against two bacteria and remaining compound showed less active. Similarly, antifungal screening of compounds **4a-j** was carried out against

Table 3: Antimicrobial activity of 7-amino-(β-D-glucopyranosyl)-3-methyl-5-(3′-aryl prop-2′enoyl)-1,2-benzisoxazoles (4a-j)

Zone of Inhibition (mm)				
Compound	Antibacterial activity		Antifungal activity	
	E. coli	*S. aureus*	*C. albicans*	*A. niger*
4a	7.3	16.0	11.6	10.4
4b	12.8	9.1	11.4	10.7
4c	7.4	11.2	11.8	8.5
4d	6.7	10.2	-	
4e	11.9	14.0	10.5	11.9
4f	7.3	10.4	10.8	10.1
4g	12.0	9.0	10.3	7.9
4h	7.9	10.4	9.8	8.9
4i	10.8	11.0	9.5	10.6
4j	7.9	11.0	11.1	10.2
	Norfloxacin		Nystatin	
	33 (100 µg/ml)	24	12.7 (25 µg/ml)	13.3

E. coli: Escherichia coli, S. aureus: Staphylococcus aureus, C. albicans: Candida albicans, Aspergillus niger: A. niger

two fungi, *viz*., *C. albicans* and *A. niger* adopting the disc diffusion method. The comparison of results was done using clotrimazole as a standard. The compounds **4a-c** and **4j** were active, **4e-i** were moderately active whereas **4d** was in active against *C. albicans* and *A. niger* at 800 µg/mL concentration **(Table 3)**.

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