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SYNTHESIS, EVALUATION AND ANTIMICROBIAL ACTIVITY OF 5-METHYL DISUBSTITUTED BENZOXAZOLE DERIVATIVES

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ABSTRACT

New 5methyl substituted phenol benzoxazoles derivatives were synthesized by the reaction of 5-methyl 2- amino phenol with various aldehydes in the presence of ethyl alcohol and lead tetra acetate. All the compounds were characterized by their analytical and spectral (IR, 1HNMR and Mass) data. Synthesized compounds have been evaluated for their antimicrobial (gram +ve and gram –ve) and antifungal activities (C. Albicans) by standard method at 50µg/ml and 100µg/ml concentration. Benzoxazole derivatives (DS-1 to DS-8) shown significant activity as compared to Griseofulvin standard drugs.

Key words: *Antimicrobial activity, Antifungal activity, Benzoxazole.*

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INTRODUCTION

The rising prevalence of multi drug resistant microbial strains such as methicillin-resistant staphylococcus aureus and staphylococcus epidermis and vancomycin-resistant Enterococcus is a problem of ever increasing significance [1-4]. Although antimicrobial-resistance was recognized soon after the development of sulphonamide and penicillin [5-8].

Benzoxazoles ring is one of the most common heterocyclic in medicinal chemistry .Previous reported revealed that substituted benzoxazoles possess diverse chemotherapeutic activity including antibiotic [9], antimicrobial [10-14],and antiviral [15-17]

In previous studies some compounds which bearing hydrogen, chlorine, methyl and nitro substitution at the 5th position on the benzoxazoles ring and their antimicrobial activity in some gram positive and gram negative bacteria and Candida albicans [18-20] were carried out.

Recently reported the synthesis and antimicrobial activity of various 5 – or 6 - methyl -2 – (p-substituted benzyl), 2- (p-substituted phenoxy methyl), and 2–thio phenoxy methyl benzoxazoles and or benzimimidazoles[21].

The present work aimed to synthesize a new series of 5-methyl-2 amino phenol Benzoxazoles derivatives in order to determine their antimicrobial activities and feasible structure activity relationship.

On the basis of above description we have synthesized a different series of benzoxazoles derivative substituted at 2, 3 and 4th position and evaluated for their antimicrobial activity at different gram positive, gram negative and fungus. Comparisons of these compounds have done with control and different standard drugs.

EXPERIMENTAL WORK

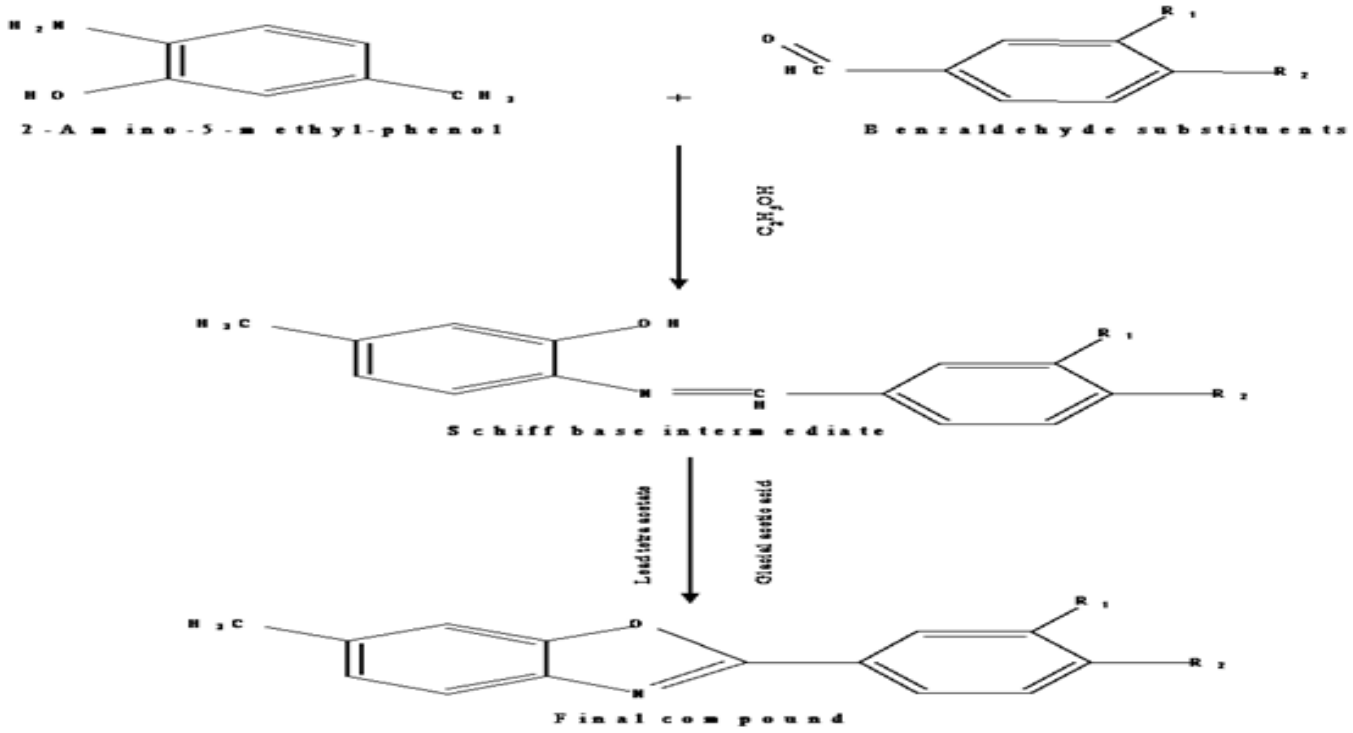
Chemistry

The starting materials were commercially available. The general synthetic strategy employed to prepare the benzoxazole derivatives was based on Schiff-base dehydrogenation. Melting points were measured on a veego Amp-1 melting point apparatus. Thin layer chromatography (TLC, silica gel-G) was used to monitor reactions and check product homogeneity. IR spectra were recorded in KBr pellets using a shimadzu model 470 spectrometer. 1H-NMR spectra were recorded on a JEOL GSX 270 MHz spectrometer (tetramethylsilane as internal standard). Splitting patterns are described as singlet (s), doublet (d) and multiplet (m). NMR values are given in δ units relative to CDCl3. Mass spectroscopy (m/z) spectra were obtained using a Hewlett Packard HP 5971A with mass selective Detector.

General Synthesis Procedure of DS-1 to DS-8

Aldehydie substituent's (0.01 mol) was added to mixture of 5-methyl 2-amino phenol (0.01mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed acetate (0.01mol) was added to the mixture of corresponding Schiff base (0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol final compound was obtained (Figure 1).

Figure 1. General synthesis scheme of compounds DS-1 to DS-8



Synthesis of 6-methyl-2-phenyl benzoxazole (compd. DS-1)

Benzaldehyde (1.2ml, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol) was added to the mixture of corresponding Schiff base (1.28g,0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-1 was obtained (Figure 1). The purity of synthesized compounds determined by TLC using silica gel-G as stationary phase and chloroform as mobile phase and iodine vapour was used as determine agent. Yield 78%; m.p. 162-164°C; λmax 367.5 nm; IR (KBr): 3015 cm-1 (C-H Ar), 2905 cm-1 (C-H Aliphatic), 162 cm-1 (C=C), 1520 cm-1 (N-H), 1014 cm-1 (C-N, Aliphatic); 1H NMR (CDCl3) δ: 8.1-8.6 (m, 2H), 7.1-7.8 (m, 3H), 6.5-6.9 (m, 3H), 2.33(s, 1H); Mass (m/z): 286.0

Synthesis of 6 methyl-2-p-tolyl-benzoxazole (compd. DS-2)

4 Methyl-benzaldehyde (1.28g, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol) was added to the mixture of corresponding Schiff base (1.30g, 0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-2 was obtained (Figure 1).Yield 82%; m.p. 175 -177°C; λmax 352nm; IR(KBr): 3402cm-1 (O-H), 3032cm-1 (C-H, Ar), 2988cm-1 (C-H, Aliphatic), 1627cm-1 (C=C, Ar), 1580cm-1 (N-H), 1043 cm-1 (C-N), 815cm-1 (C-H); 1H NMR (CDCl3) δ: 8.1-8.6 (m, 2H), 7.1-7.8 (m, 3H), 6.6-6.8 (m, 3H), 2.2-2.5 (s, 1H); Mass (m/z): 326.

Synthesis of 4-(6-Methyl benzoxazoles-2-yl) phenol (compd. DS-3)

4-Hydroxy-benzaldehyde(1.28g, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol) was added to the mixture of corresponding Schiff base (1.26g, 0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-3 was obtained(Figure 1).Yield 62%; m.p. 180-182°C; λmax 341.5nm; IR (KBr): 3290-3373cm-1 (O-H), 2908cm-1 (C-H), 1622cm-1 (C=C, Ar), 1560cm-1 (N-H) ; 1H NMR (CDCl3) δ: 7.3(m,1H), 6.4-6.6 (m, 6H), 5.566(C-OH, Ar); Mass (m/z): 339.0

Synthesis of 3-(6-Methyl benzoxazoles-2-yl) phenol (compd. DS-4)

3-Hydroxy-benzaldehyde (1.28g, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol) was added to the mixture of corresponding Schiff base (1.26g, 0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-4was obtained.(Figure 1).Yield 65%; m.p. 158-160 °C; λmax 360nm; IR (KBr): 3297-3396cm-1 (O-H), 3030cm-1 (C-H, Ar), 2945cm1 (C-H, Aliphatic), 1627cm-1 (C=C, Ar), 1578cm-1 (N-H) 1079cm-1 (C-N, Aliphatic) ; 1H NMR (CDCl3) δ: 8.2-8.6 (m, 3H), 7.0-7.9 (m, 2H), 6.4-6.9 (m, 2H), 2.0-2.5 (s, 1H); Mass (m/z): 349.

Synthesis of 2-(4-Bromo-phenyl)-6-Methyl Benzoxazole (compd. DS-5)

4-Bromo-benzaldehyde (1.32g, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate(4.23g, 0.01mol)

was added to the mixture of corresponding Schiff base (1.31g, 0.01mol) in glacial acetic acid(12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-5 was obtained. (Figure1).Yield 60%; m.p. 148-149°C; λmax 326 nm; IR (KBr): 3508-3650cm-1 (O-H), 3024cm-1 (C-H, Ar), 2924cm-1 (C-H, Aliphatic), 1614cm-1 (C=C, Ar), 1550cm-1 (N-H), 1068cm-1 (C-N), 523-600cm-1 (C-Br); 1HNMR (CDCl3) δ: 8.0-8.1(m, 3H,), 7.1-7.6 (m, 2H), 2.5 (s, 1H); Mass (m/z): 439.0

Synthesis of 2-(4-chloro-phenyl)-6-Methyl Benzoxazole (compd. DS-6)

4-Chloro-benzaldehyde (1.38g, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol) was added to the mixture of corresponding Schiff base(1.18g, 0.01mol) in glacial acetic acid(12 ml) and after waiting an few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-6 was obtained. (Figure 1). Yield 62%; m.p. 152-154°C; λmax 309.5 nm; IR (KBr): 3253-3650cm-1 (O-H), 3030cm-1 (C-H, Ar), 2881cm-1 (C-H, Aliphatic), 1616cm-1 (C=C), 1044cm-1 (C-N, Aliphatic), 671cm-1 (C-Cl); 1H NMR (CDCl3) δ: 8.14-8.19 (m, 3H), 7.1-7.6 (m, 4H), 2.51 (s, 1H); Mass (m/z): 439.0

Synthesis of 2-(4-fluoro-phenyl)-6-Methyl Benzoxazole (compd. DS-7)

4-Fluoro-benzaldehyde (1.25ml ,0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol) was added to the mixture of corresponding Schiff base(1.21g, 0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was isolated by filtration and recrystalized from ethanol compound DS-7 was obtained (Figure 1).Yield 55%; m.p. 169-170 °C; λmax 296 nm; IR (KBr): 3286-3374cm-1 (O-H), 3029cm-1 (C-H, Ar), 2992cm-1 (C-H, Aliphatic), 1630cm-1 (C=C), 1573cm-1 (N-H), 1081cm-1 (C-N, Aliphatic), 1008-1173cm-1 (C-F); 1H NMR (CDCl3) δ: 8.14-8.19 (m, 2H) , 7.1-7.6 (m, 4H), 6.7-6.8 (s, 1H), 2.33 (s, 1H); Mass (m/z): 436.0

Synthesis of 2-(2-Methoxy phenyl)-6-Methyl-Benzoxazole (compd. DS-8)

Methoxy-benzaldehyde(1.45ml, 0.01 mol) was added to mixture of 5-methyl 2-amino phenol (1.22g, 0.01 mol) in ethanol (7.5 ml) and boiled for 5 min after the residue was removed by filtration the Schiff base was obtained from crystallization in ethanol then lead tetra acetate (4.23g, 0.01mol)was added to the mixture of corresponding Schiff base(1.32g, 0.01mol) in glacial acetic acid (12 ml) and after waiting a few minutes the crude product was Isolated by filtration and recrystalized from ethanol compound DS-8 was obtained (Figure 1).Yield 50%; m.p. 180-190; λmax 328.5 nm; IR (KBr): 3354cm-1 (O-H), 3035cm-1 (C-H, Ar), 2960cm-1 (C-H, Aliphatic), 1621cm-1 (C=C), 1574cm-1 (N-H), 1028cm-1 (C-N, Aliphatic); 1HNMR (CDCl3) δ: 8.5-9.8 (m, 2H),7.0-7.8 (m, 2H), 6.6-6.9(m, 2H), 3.6-3.8 (s, 1H),2.38 (s, 1H); Mass (m/z): 449.0

Microbiology

For the antibacterial and the antimycotic assays, the compounds were dissolved in absolute ethanol (0.8mg/ml). Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 400, 200, 100, 50, 25, 6.25, 3.12, 1.56, 0.78 µg/ml concentrations. The minimum inhibitory concentrations (MICs) were determined using the two-fold-serial dilution technique (10, 17, and 18). In order to ensure that the solvent per so had no effect no bacterial growth, a control test was also performed at the same dilutions as used in our experiments and found to be in inactive in culture medium.

All the compounds were tested for their in vitro growth inhibitory activity against different bacteria

and the yeast c albicans RSKK 628. THE bacterial strains used are staphylococcus aureus ATCC 6538 and Bacilus subtilis ATCC 6033 as Gram-positive and Escherichia coli ATCC 10536, and Ps. Aeruginosa RSKK 355 as Gram-negative bacteria. RSKK strains of the microorganisms used in this study were obtained from the culture collection of the dhanvantri research and analytical laboratory Kim, Surat, Gujrat.

Gentamicin,chloramphenicol and griseofulvin were used as control drugs. The observed data on the antimicrobial activity of the compounds and the control drugs are given in table 2.

Antibacterial Assay

The cultures were obtained in Mueller-Hinton broth (Difco) for all the bacteria after 24hrs of incubation at 37±10C. The testing was carried out in Mueller-Hinton broth at pH 7.4 and the two-fold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24h at 37±1°C, the last tube with no growth of microorganisms was recorded to represent MIC express in µg/ml (Table 2, 3, & 4).

Antimycotic Assay

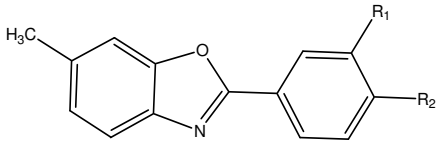
The yeast C, alb cans was maintained in Sabouraud dextrose broth (Difco) after incubation for 24h at 25±1°C. Testing was performed in Sabouraud dextrose broth at pH 7.4 and the two-fold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48h at 24h at 25±1°C, the last tube with no growth of yeast was recorded to represent MIC expressed in µg/ml (Table 2, 3, & 4).

RESULTS AND DISCUSSION

The benzoxazole derivatives were synthesized by the dehydrogenation of Schiff bases. The products were confirmed by chromatographic and spectral data. The melting point of all compounds was observed different from ingredients melting point which was conformed the synthesis of product. The purity of synthesized compounds was checked by observing single spot on TLC plate. All synthesized compounds was gave only signal spot. It means all synthesized compounds were obtained in pure form. The melting point and Rf value of all synthesized compounds are given in Table 1. The structure of synthesized compounds was determined by spectral analysis. The λmax of synthesized compounds was observed at range between 300-450nm. This range of λmax was showed the presence of α, β-unsaturated carbonyl moiety. The IR absorption band at 1600 cm-1 and 1400 cm-1 showed the presence of a conjugated carbonyl group (>C=O) and (C=C) respectively. The 1HNMR spectrum of compounds explained the presence of two doublets of vinylic protons (CH=CH) at δ 8.1-8.6 (1H, αH) & δ 7.1-7.8 (1H, αH). Mass spectroscopy helps to find the molecular weight of the synthesized compounds. The benzoxazole derivatives showed the molecular ion peak that equivalent to the molecular weight of proposed compound. Hence m/z value confirms the molecular weight of the respective synthesized compounds.

The benzoxazole derivatives contain amide and α, β- unsaturated carbonyl moiety which is responsible for anti microbel activity. The anti microbel activities of all synthesized compounds (DS-1-DS-8,) (table-2,3,& 4) were studied using cup-plate method and minimum inhibitory concentration. The zone of inhibition and minimum inhibitory concentration were calculated against the control drugs (chloramphenicol and gentamicin) anti-fungal activity of synthesized compounds were also done by calculating the zone of inhibition against the control drug (girsofloulavin) all synthesized compounds showed significant anti-microbial activity. The compound DS-2, DS-5 and DS-8 showed more activity due to CH3, -Cl, CH3OH groups and remaining compound DS-3, DS-4, showed moderate activity due to 4- OH and 3- OH groups DS-1, DS-6 and DS-7 showed lower activity due to C6H5CHO, Br and F groups. Hence the anti-microbial activity of the benzoxazole derivatives was increased when electron withdrawing groups present on the benzoxazole moiety.

Table 1. Melting point data of starting and synthesized compounds



S. No.	Compound	R_1	R_2	Appearance	Molecular formula	Yield (%)	Melting point (^{0}C)
1	5-Methyl-2-amino phenol.	-	-	Yellow	C_7H_9NO	-	126-128
2	DS-1	-	-	Yellowish crystalline	$C_{14}H_{11}NO$	78	162-164
3	DS-2	-	CH3	Silver crystalline	$C_{15}H_{13}NO$	82	175-177
4	DS-3	-	OH	-	$C_{14}H_{11}NO_2$	62	180-182
5	DS-4	OH	-	Yellow	$C_{14}H_{11}NO_2$	65	158-160
6	DS-5	-	Br	Yellow	$C_{14}H_{10}BrNO$	60	148-149
7	DS-6	-	Cl	Yellow	$C_{14}H_{10}ClNO$	62	152-154
8	DS-7	-	F	White	$C_{14}H_{10}FNO$	55	169-170
9	DS-8	=O	-	Silver	$C_{15}H13NO_2$	50	189-190

Table 2. Antimicrobial activity data (By cup plate method) of synthesized compounds

S.No.	Name of compounds	Mean Zone of inhibition (in mm)							
		Staphylococcus Aureus (G+ve)		E. Coli (G-ve)		Bacillus Subtilis (G.+ve)		P. Aeruginosa (G-ve)	
		50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
1	Gentamycin	20	22	-	-	18	21	-	-
2	Chloramphenicol	-	-	19	21	-	-	20	22
3	DS-1	14	16	16	18	12	10	12	15
4	DS-2	13	14	17	19	14	14	9	11
5	DS-3	16	18	14	16	12	12	11	12
6	DS-4	14	14	16	15	11	13	12	15
7	DS-5	9	11	14	15	10	16	9	11
8	DS-6	12	13	8	10	18	19	13	19
9	DS-7	13	15	10	12	9	12	11	12
10	DS-8	11	13	9	11	11	10	16	10

Table 3. Antimicrobial activity/Antifungal activity of synthesized compounds (by MIC method)

S. No.	Name of compounds	Staphylococcus Aureus (G+ve) (µg/ml)	Bacillus Subtilis (G.+ve) (µg/ml)	E. Coli (G-ve) (µg/ml)	P.Aeruginosa (G-ve) (µg/ml)	C. albicans (Fungus) (µg/ml)
1	Gentamicin	0.09	1.82	0.8	2.8	-
2	Chloramphenicol	0.06	0.82	0.6	1.4	-
3	Griseofulvin	-	-	-	-	59
4	DS-1	125	64.5	62	67	64.5
5	DS-2	64.5	32.5	78	82	32.7
6	DS-3	72.5	18.56	86	81	64.8
7	DS-4	145	64.5	65.2	86	32.5
8	DS-5	18.5	22.5	64.2	59	18.7
9	DS-6	32.5	32.5	79	72	39.34
10	DS-7	21.2	62.8	86.7	89	19.5
11	DS-8	148	70.5	89.5	71.5	35.5

Table 4. Antifungal activity data of synthesized compounds

S.No.	Name of Compounds	Mean zone of inhibition (in mm)	
		Candida Albicans	
		50 µg/ml	100 µg/ml
1	Griseofulvin	19	20
2	DS-1	10	12
3	DS-2	12	12
4	DS-3	15	17
5	DS-4	13	15
6	DS-5	09	10
7	DS-6	14	16
8	DS-7	15	13
9	DS-8	11	14

CONCLUSION

The antimicrobial activity of compounds (DS-1 – DS-8) was studied for their inhibitory effects and mean zone of inhibition in different nutrient broth medium with control drugs gentamicin, chloramphenicol and griseofulvin. These all synthesized compounds were shown antimicrobial and antifungal activity. Compounds DS-2, DS-4 and DS-8 showed moderate to good antimicrobial and antifungal activity.

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