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Synthesis, Characterization and Antimicrobial Activity of Mercapto oxadiazole Analogs

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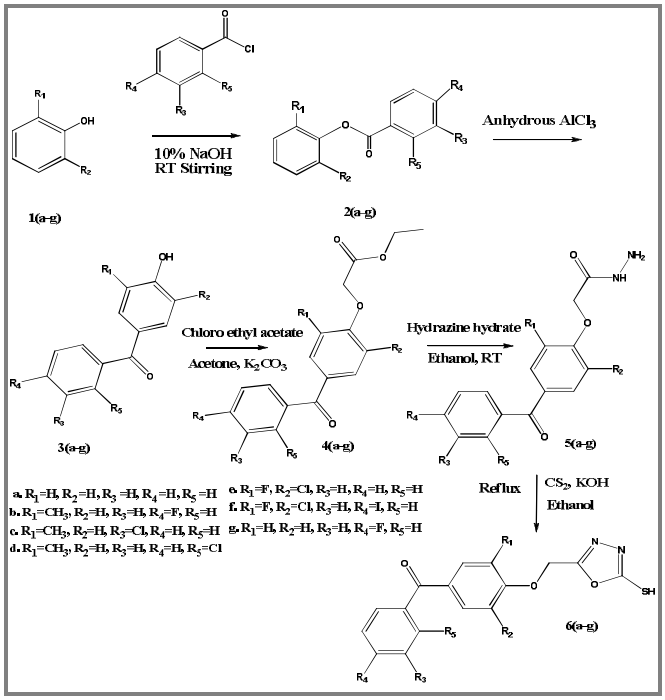
ABSTRACT

In the present study, we synthesized analogs of oxadiazolebenzophenone which vary in the number and position of the methyl and halogen groups on the benzophenone moiety, which were then evaluated for their anti-bacterial and antifungal activities.

Graphical Abstract



Synthesis of Mercapto oxadiazole Analogs

Keywords: Benzophenone, Antibacterial, Fries Rearrangement, Oxadiazole.

INTRODUCTION

Heterocyclic compounds comprising nitrogen have been considered as a basis of prospective interest in natural products and they are regularly used in create novel therapeutic compounds for therapeutic uses. Oxadiazole is a five component heterocyclic ring which is a versatile lead compound for designing effective bioactive markers [1]. The existence of heterocyclic structures in in specific varieties of compounds is increasing their pharmacological impact. Cai-Jun Chen *et al*., reported synthesis and antifungal activity of 1, 3, 4-oxadiazole derivatives [2]. All the newly synthesized compounds were evaluated for their *in vitro* antifungal activity. Among the series following compound exhibited good antifungal activity [3]. A series of new 2-amino 1, 3, 4-oxadiazoles were synthesized followed by condensation with various substituted aldehydes to yield their Schiff bases. The synthesized compounds were evaluated for their antimicrobial activity against two Gram positive bacteria two Gram negative bacteria and two fungal species yeast strains. All the synthesized compounds showed good antimicrobial activity [4].

Bhat *et al*., reported the preparation of 5-(2,4-dichloro-5-fluorophenyl)-2-substituted-1,3,4-oxadiazole, and tested for their antimicrobial activity against *E. coli*, *S. aureus* and *Klebsiella pneumonia* by serial dilution method using nitrofurazone as standard drug for comparison of activity. Among the tested compounds most of the compounds were active comparable with that of standard. The activity may be due to presence of 2, 4-dichloro-5-fluorophenyl and 4-chloroaryloxymethyl group [5]. 1-Cyclohexyl-3-carbethoxy-2-methyl-5-(5-mercapto-4,5-dihydro-1,3,4-oxadiazol-2-yl) methoxy indole was synthesized and evaluated for their antimicrobial activity against *E. coli, Aspergillus niger* and *Candida albicans*. The results show moderate antibacterial activity and high order of activity against fungal strains [6]. El-Sayed reported the newly synthesized compounds, which were evaluated for their HIV inhibitory activity as reverse transcriptase inhibitors by using microtiter anti-HIV assays with CEM-SS cells or fresh human peripheral blood mononuclear cells. Compound 12 showed the highest activity with an IC_{50} value of 1.44 μM [7]. Mamatha et al synthesized oxadiazole analogs and assessed for antiTB, antidiabetic, antibacterial and antifungal activities. A new compound containing both morpholine and oxadiazole groups, 4-{2-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-ethyl}-morpholine, was obtained by reaction of 1,3,4 oxadiazole-2-thiol with 4-(2-chloroethyl) morpholine hydrochloride [8].

MATERIALS AND METHODS

Chemistry: The chemicals were procured from Sigma Aldrich Chemical Co. Ltd, Mumbai. TLC was performed on aluminium-backed silica plates and visualized by UV-light. Melting points were measured by the open capillary method and were uncorrected. FT-IR spectra were determined on Perkin Elmer spectrophotometer version 10.03.09 instrument over the range of 600 to 4000 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz in deuterated chloroform and the chemical shifts were recorded in ppm downfield using TMS as the internal standard. Mass spectra were obtained with a VG70-70H spectrophotometer and the elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. The results of elemental analyses were within ±0.4% of the theoretical values. Synthesis of Benzophenone-mercaptooxadiazole derivatives, the protocol for the synthesis of hydroxybenzophenone analogues and benzophenone-mercaptooxadiazole derivatives are given below

General procedure for the synthesis of substituted hydroxybenzophenone analogues (3a-g): The starting benzoates were synthesized by the reaction of substituted phenols with substituted benzoyl chlorides in 10 % sodium hydroxide solution. The reaction mixture was stirred for 3-4 h at 0-5°C and was monitored by thin layer chromatography (TLC) using 8:2 (n-hexane:ethyl acetate) solvent mixture. Further, hydroxybenzophenone **3a-g** was synthesized by Fries rearrangement. Substituted benzoates and anhydrous aluminium chloride (0.002 mol) were homogenized and the mixture was heated upto 150-170°C without solvent for 2-3 h. Then the reaction mixture was cooled to 0°C and

quenched with 6N hydrochloric acid in ice cold water. The reaction mixture was stirred for about 2-3 h. The solid was filtered and recrystallized with ethanol. Compound 3a is taken as a representative example to explain characterization data.

Synthesis of hydroxybenzophenone (3a): Yield 85%; M.P: 133-135°C FT-IR (KBr, cm^{-1}): 1640 (C=O), 3518 (OH); ^{1}H NMR ($CDCl_3$): 6.76-7.86 (m, 9H, Ar-H), 12.2 (bs,1H, OH); ^{13}C-NMR ($CDCl_3$): δ 116.1, 129.08, 131.1, 132.6,132.9, 133.5, 139.1, 163.13, 195.1; LC-MS *m/z* 199 (M+1). Elemental Analysis: Calcd. for $C_{13}H_{10}O_2$: C, 79.22; H, 5.70%. Found: C, 78.88; H, 5.69%.

General protocol for the synthesis of (4-benzoyl phenoxy)-acetic acid ester analogues (4a-g): To a mixture of substituted hydroxy benzophenones 3a-g (0.05 mol) and chloro ethyl acetate (0.075 mol) in dry acetone (40 mL), anhydrous potassium carbonate (0.075 mol) was added and were refluxed for 8-10 h. The reaction mixture was cooled and solvent removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate, and extracted with ether (3×30 mL). The ether layer was washed with 10% sodium hydroxide solution (3×30 mL) followed by water (3×30 mL) and then dried over anhydrous sodium sulphate and evaporated to afford compounds 4a-g. Compound 4a is taken as a representative example to explain characterization data.

Synthesis of (4-benzoyl phenoxy)-acetic acid ester (4a): Yield: 93%. M.P.: 52-54°C. IR (KBr) νmax (cm^{-1}): 1672 (C=O), 1719 (ester, C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, 3H, CH_3 of ester), 4.21 (q, 2H, CH_2 of ester), 5.01 (s, 2H, OCH_2), 6.81-7.85 (m, 9H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 14.5, 61.15, 65.8, 115.3, 129.08,131.8, 132.1,133.3, 133.9, 139.4, 161.7, 169.8, 194.6; LC-MS *m/z* 285 (M+1). Elemental Analysis: Cal. for $C_{17}H_{16}O_4$ (212): C, 72.22; H, 5.70. Found: C, 72.20; H, 6.16%.

General protocol for the synthesis of (4-benzoyl phenoxy)-acetic acid hydrazide derivatives (5a-g): To the solution of ester analogs4a-g (0.05 mol) in ethanol (20 mL), hydrazine hydrate (0.06 mol) was added and the reaction mixture was stirred at room temperature for 5 h. Reaction completion was monitored by thin layer chromatography using hexane:ethylacetate (3:1) solvent mixture and the reaction mixture was allowed to stand overnight. The white crystals 5a-g formed were filtered, washed and after drying recrystallized from ethanol. Compound 5a is taken as a representative example to explain characterization data.

Synthesis of (4-benzoyl phenoxy)-acetic acid hydrazide(5a): Yield 92%; M.P.:115-117°C; FT-IR (KBr, cm^{-1}): 3318 (NH_2), 3230 (NH), 1675 (amide, C=O), 3240–3350 (NH-NH); 1642 (C=O); ^{1}H NMR ($CDCl_3$): δ 3.86 (d, 2H, NH_2), 5.09 (s, 2H, OCH_2), 8.46 (t, 1H, NH), 6.81-7.85 (m, 9H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 65.9, 116.3, 129.78, 131.6, 132.3, 133.6, 133.9, 132.4, 161.7, 169.8, 194.9; LC-MS *m/z* 271 (M+1). Elemental Analysis: Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.89; H, 5.52; N, 10.96. Found: C, 66.78; H, 5.56; N, 10.08 %.

General procedure for the synthesis of (4-benzoyl phenoxy)-[1,3,4]oxadiazole-2-thiol derivatives 6a-g): A mixture of hydrazide analogs 5a-g (3 mmol), carbon disulfide (3 mL) and potassium hydroxide (6 mmol) in ethanol (60 mL) was refluxed till evolution of hydrogen sulfide was ceased. Afterwards the reaction mixture was cooled to room temperature. The solvent was removed at reduced pressure, poured to cold water and acidified with dil.HCl solution to precipitate [1, 3, 4] oxadiazole-2-thiol derivatives by bringing the pH between 3 and 4. The precipitate thus separated out was allowed to stand overnight, filtered, washed, dried and recrystallized from acetone. Compound 6a is taken as a representative example to explain characterization data.

Synthesis of [4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}(phenyl)methanone] (6a): Yield 84%; mp 120-122°C; FT-IR (KBr, cm^{-1}): 0(C=N), 2542 (SH), 1144 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 5.05 (s, 2H, OCH_2), 7.35 (d, 2H, Ar-H), 7.44 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.78 (d, 2H, Ar-H), 10.72 (s, 1H, SH);)^{13}C-NMR ($CDCl_3$): δ 15.5, 71.99, 114.2, 128.8, 130.6, 130.8, 131.6, 132.6, 138.9, 160.1,

162.9, 163.5; LC-MS m/z 313 (M+1). Elemental Analysis: Calcd. for $C_{16}H_{12}N_2O_3S$: C, 61.54; H, 3.97; N, 8.97; S, 10.27. Found: C, 61.50; H, 3.92; N, 8.95; S, 10.25%.

Synthesis of 4-fluorophenyl[4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}-3-methyl phenyl] methanone (6b): Yield 88%; M.P:128-126°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2547 (SH), 1144 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 5.08 (s, 2H, OCH_2), 7.31 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H), 7.35-7.69 (d, 3H, Ar-H), 2.16 (s, 3H, CH_3), 10.72 (s, 1H, SH).^{13}C-NMR ($CDCl_3$): δ 15.78, 71.99, 114.2, 128.8, 130.6, 130.8, 131.6, 132.6, 138.9, 160.1, 162.9, 163.5; LC-MS m/z 345 $(M+1)^+$. Elemental Analysis:Calcd. for $C_{17}H_{13}FN_2O_3S$: C, 59.29; H, 3.81; N, 8.13; S, 9.31%. Found: C, 59.27; H, 3.81; N, 8.15; S, 9.31%.

Synthesis of [4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}-3-methylphenyl]phenyl methanone. (6c): Yield 84%; M.P:115-117°C; FT-IR (KBr, cm^{-1}): 1609 (C=N), 2547 (SH), 1154 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 5.08 (s, 2H, OCH_2), 7.31 (d, 2H, Ar-H), 7.54 (t, 1H, Ar-H), 7.75 (d, 2H, Ar-H), 7.35-7.69 (d, 3H, Ar-H), 2.16 (s, 3H, CH_3), 10.72 (s, 1H, SH) ; ^{13}C-NMR ($CDCl_3$): δ 15.1, 71.5, 113.5, 115.8, 124.1, 128.8, 131.2, 131.0, 133.1, 134.1, 159.2, 161.8, 163.5, 165.54, 192.3; LC-MS m/z 327 $(M+1)^+$. Elemental Analysis:Calcd. for $C_{17}H_{14}N_2O_3S$: C, 62.58; H, 4.45; N, 8.52; S, 9.84% Found: C, 62.59; H, 4.43; N, 8.58; S, 9.87%.

Synthesis of 2-chlorophenyl [4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}-3-methyl phenyl] methanone (6d): Yield 81%; M.P: 101-103°C; FT-IR (KBr, cm^{-1}): 1605 (C=N), 2542 (SH), 1145 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 5.13 (s, 2H, OCH_2), 7.22 (d, 2H, Ar-H), 7.79 (d, 2H, Ar-H), 7.54-7.85 (d, 3H, Ar-H), 2.13 (s, 3H, CH_3), 10.81 (s, 1H, SH).^{13}C-NMR ($CDCl_3$): δ 14.8, 70.7, 111.8, 114.7, 123.8, 128.4, 130.9, 132.3, 134.8, 138.4, 160.2, 161.9, 162.5, 165.54, 197.3; LC-MS m/z 361 $(M+1)^+$, 363 $(M+3)^+$. Elemental Analysis:Calcd. for $C_{17}H_{13}ClN_2O_3S$: C, , 59.59; H, 3.63; N, 7.76; S, 8.89%. Found: C, 59.57; H, 3.61; N, 7.75; S, 8.81%.

Synthesis of 3-chloro-5-fluoro[4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}phenyl] phenyl methanone (6e): Yield 80%; M.P:114-116°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^{1}H NMR ($CDCl_3$):5.13 (s, 2H, OCH_2), 7.22 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.54-7.85 (d, 3H, Ar-H), 10.81 (s, 1H, SH).^{13}C-NMR ($CDCl_3$): δ 70.6, 112.8, 124.8, 127.8, 127.4, 127.7, 128.7, 130.2, 131.9, 132.8, 134.5, 138.4, 161.2, 162.9, 163.2, 197.3; LC-MS m/z 365 $(M+1)^+$, 367 $(M+3)^+$.Elemental Analysis:Calcd. for $C_{16}H_{10}ClFN_2O_3S$: C, 52.68; H, 2.75; N, 7.68; S, 7.04% Found: C, 62.29; H, 5.70; N, 8.28; S, 7.07%.

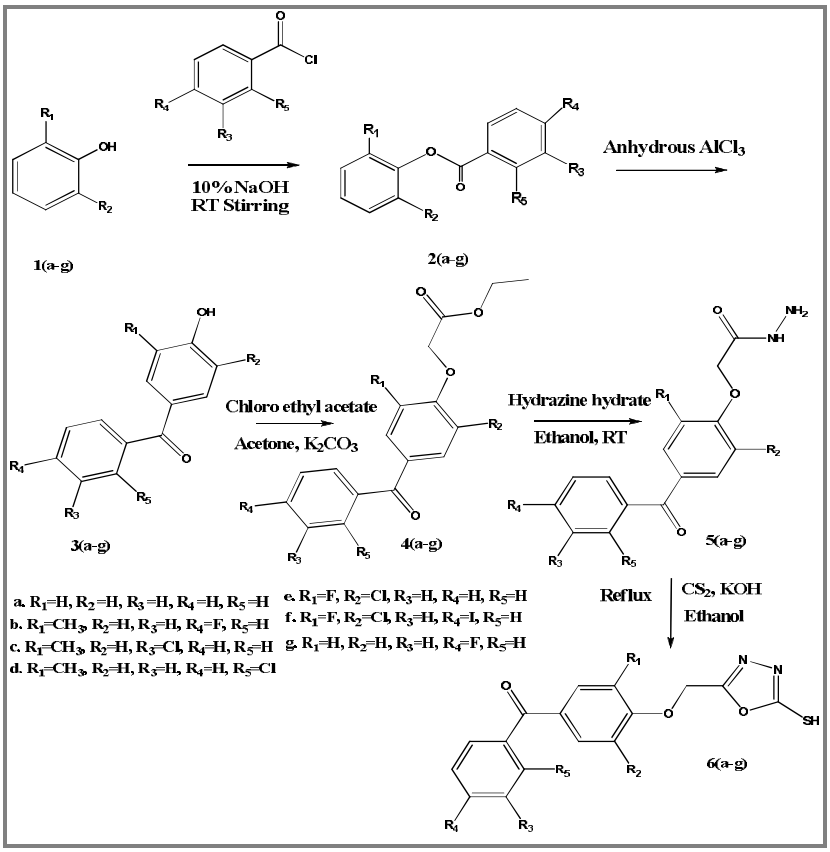
Synthesis of 3-chloro-5-fluoro[4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}phenyl] 4-iodo phenyl methanone (6f): Yield 80%; M.P:117-120^{0}C; FT-IR (KBr, cm^{-1}): 1610 (C=N), 2550 (SH), 1162 (C-O-C); ^{1}H NMR ($CDCl_3$): 5.23 (s, 2H, OCH_2), 7.55 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.54-7.64 (d, 2H, Ar-H), 10.41 (s, 1H, SH).^{13}C-NMR ($CDCl_3$): δ 72.6, 115.8, 122.2, 125.4, 126.2, 126.4, 128.2, 131.3, 131.2, 132.6, 134.2, 138.2, 160.1, 162.4, 162.2, 192.1; LC-MS m/z 490 $(M+1)^+$, 492 $(M+3)^+$.Elemental Analysis:Calcd. for $C_{16}H_9ClFIN_2O_3S$: C, 39.15; H, 1.85; N, 5.68; S, 6.56% Found: C, 39.16; H, 1.84; N, 5.65; S, 6.55%.

Synthesis of 5-fluorophenyl[4-{(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy}phenyl]methanone. (6g): Yield 79%; M.P:97-99°C; FT-IR (KBr, cm^{-1}): 1619 (C=N), 2555 (SH), 1165 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 5.17 (s, 2H, OCH_2), 7.35 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 7.54 (d, 2H, Ar-H), 7.69 (m, H, Ar-H), 10.41 (s, 1H, SH). ^{13}C-NMR ($CDCl_3$): δ 71.2, 98.3, 114.8, 123.9, 126.8, 131.9, 135.9, 137.5, 137.9, 153.4, 153.6, 160.2, 163.6, 194.3; LC-MS m/z 331 $(M+1)^+$.Elemental Analysis: Calcd. for $C_{16}H_{11}FN_2O_3S$: C, 58.18; H, 3.44; N, 8.49; S, 9.74% Found: C, 58.19; H, 3.45; N, 8.49; S, 9.72%.

Antimicrobial assay: Microbial cultures used in the research were obtained from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh, India. *Staphylococcus aureus* (MTCC 7443), *Escherichia coli* (MTCC-40), *Candida albicans* (MTCC-183)

and *Aspergillus niger* (MTCC-1344) cultures were used. Stock cultures of bacteria were maintained on nutrient agar (HI media, Mumbai) slants at 4°C with periodical sub culturing. The antimicrobial activities of compounds were screened by disc diffusion method by Makut *et al* [9]. The 500 µg solutions of the title compounds were taken on the pre-allotted discs after swabbing of test cultures on agar plates. 100 µL of 24 h cultures of test microorganisms in broth was used for the seeding. Streptomycin (500 µg solution) and Fluconazole (500 µg mL^{-1} solution) were used as positive controls for bacteria and fungi respectively, while the discs with only the solvent (200 µL $disc^{-1}$) was used as negative hour and fungal Petri plates for 5 days at 30°C. The diameters of the inhibition zones (in mm) were measured out after the incubation [10, 11] control. The plates were pre-incubated for 1 h at 4°C. The bacterial Petri plates were incubated at 37°C for 24 h.

Determination of minimum inhibitory concentration: The compounds with the activity at 500 µg mL^{-1}, were further examined at lower concentrations to know their Minimum Inhibitory Concentration against the microbial strain. Here half fold dilution method was used to prepare the test samples over the range of 250 µg mL^{-1}, 125µg mL^{-1}, 62.5 µg mL^{-1} to 0.9 µg mL^{-1} and their activity is measured by disc diffusion method. The lower concentration of the compound to exhibit the antimicrobial activity is noted [12].



Scheme 1. Synthesis of Mercapto oxadiazole Analogs.

RESULTS AND DISCUSSION

The synthetic protocol of the title compounds **6a–n** is outlined in the Scheme 1. Initially, the benzoylated products **2a–g** was prepared by the benzoylation of substituted phenols **1a–g** with substituted benzoyl chlorides. In the presence of anhydrous aluminium chloride, the compounds **2a-g** have undergone Fries rearrangement, to afford hydroxyl benzophenones **3a–g**, which were established by the disappearance of the carbonyl stretching band of the ester group and appearance of the -OH

stretching band in IR spectra (figure 1) and also, the appearance of broad singlet for -OH proton and decrease in one aromatic proton in ^{1}HNMR spectra (figure 2). The compounds, benzoyl phenoxy acetic acid ethyl esters, **4a-g** were obtained by refluxing substituted 3**a-g** with ethyl chloro acetate and were evidenced by the loss of -OH stretching and emergence of carbonyl stretching band for the ester group in the IR absorption spectra. The ^{1}H NMR confirmed the disappearance of broad singlet for -OH group and an appearance of triplet and quartet for -CH_3 and -CH_2 protons respectively. Upon treating the compounds **4a-g** with hydrazine hydrate, phenoxy-acetic acid hydrazide analogues **5a-g** were obtained, which were confirmed by the appearance of -NH_2 stretching band of amide in the IR spectrum. The appearance of the peaks for -NH_2 and -NH protons and concealing of triplet and quartet peaks for -CH_3 and -CH_2 protons respectively in ^{1}HNMR, confirmed the formation of the product. Upon cyclization of acid hydrazide analogues **5a-g** with carbon disulfide in the presence of KOH, claimed the corresponding 1, 3, 4-oxadiazol-2- thiol **6a-g**, which clearly evident with the absence of carbonyl and -NH_2 stretching bands in the IR spectra. The presence of -SH proton and the absence of -NH_2 and -NH protons of amide in the NMR spectrum also confirmed the product.

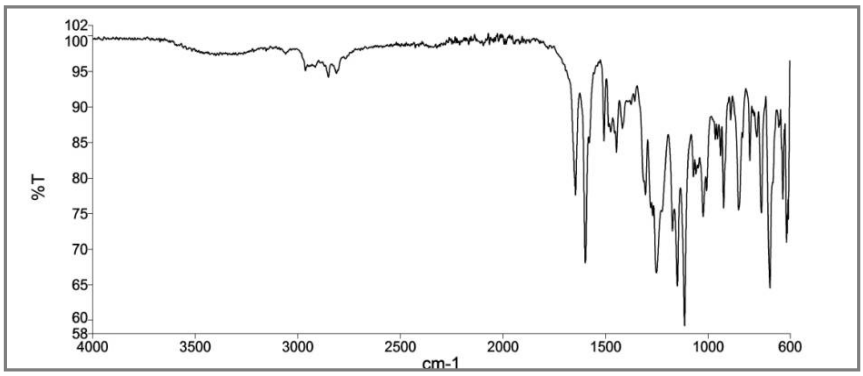
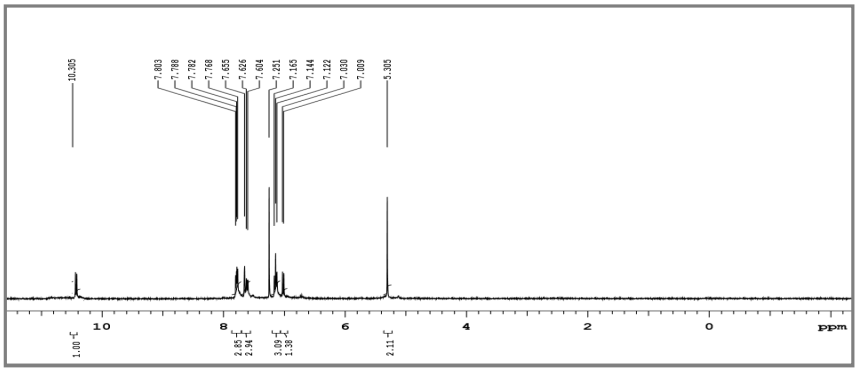


Figure 1. FT-IR of compound 6b.



Proton NMR of compound 6g.

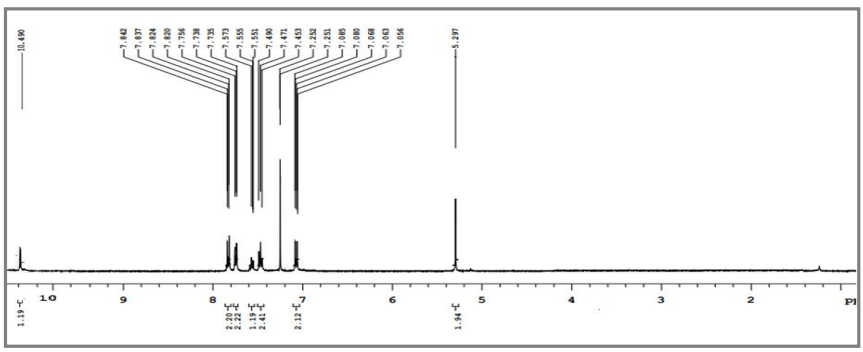
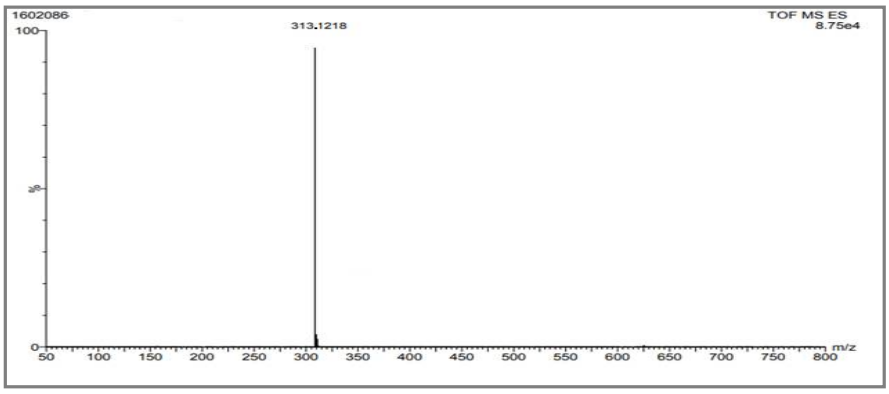


Figure 2. Proton NMR of compound 6e.



Mass spectrum of 6a

Antimicrobial Activity: The synthesized compounds were screened for *Candida albicans, Aspergillus niger, Escherichia coli* and *Staphylococcus aureus* by disc diffusion method to know the potency of the compounds to act as antimicrobial agents. The activity was measured in diameters of the zone of inhibition (Table 1). Synthesized compounds showed the excellent activity for the *Escherichia coli* and moderate activities against other tested microorganisms. Among all the synthesized compounds, benzophenone analogs **6a, 6c, 6g** and **6e** had disclosed promising activity against both bacteria and fungi in the series. Compounds **6c** and **6e** have chlorine moiety. Synthesized oxadiazole analog **6c** with chlorine revealed highest antibacterial activity against *Staphylococcus aureus and E.coli* with MIC at 31.25 µg mL^{-1}, which was comparable with standard streptomycin (Figure 3).

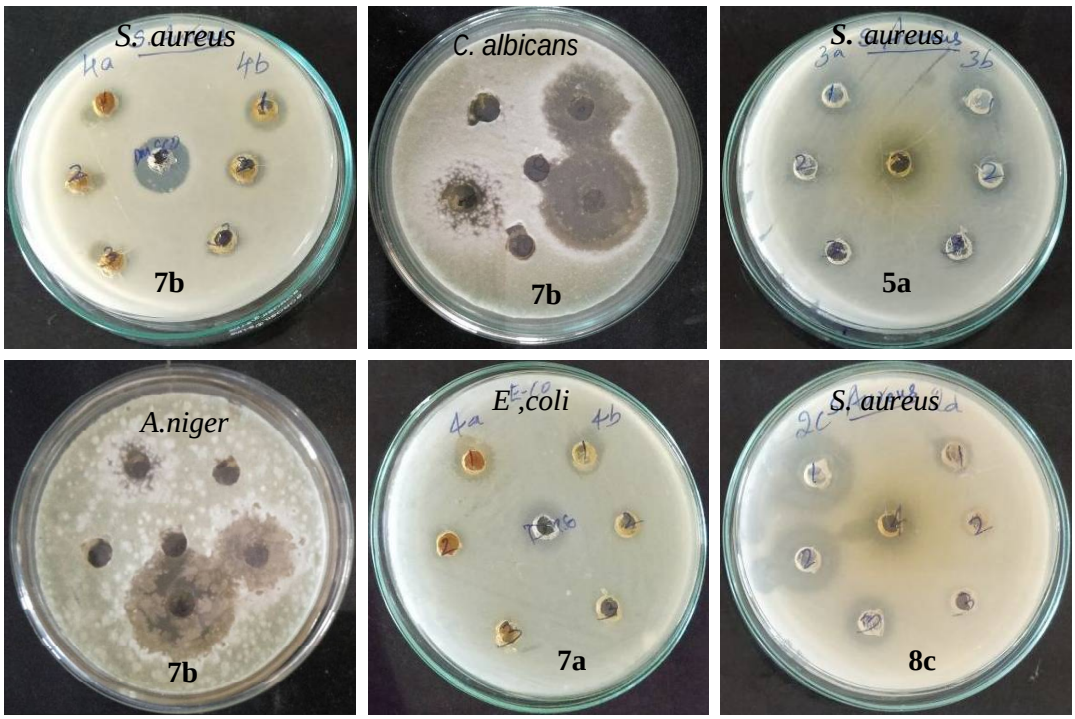


Figure 3. Antimicrobial activity of synthesized compounds.

With respect to antifungal activity, most of the benzophenone tagged oxadiazole compounds **6a, 6g** and **6c** showed good activity. Synthesized oxadiazoleanalogs **6a** and **6c** revealed highest antifungal activity against *Candida albicans and Aspergillus niger* with MIC at 31.25 µg mL^{-1}, which were comparable with standard fluconazole in figure 3. *SAR* suggests that, compounds with chlorine group

revealed the superior activity, in other words, compounds containing electron-withdrawing group on benzophenone showed the superior activity.

Table 1. Antimicrobial activity of the synthesized compounds at 250 µg mL^{-1}

Entry	Zone of inhibition (mm)			
	Escherichia coli	*Staphylococcus aureus*	*Candida albicans*	*Aspergillus niger*
6a	18	19	26	27
6b	12	12*	11	13
6c	24**	23	26**	27
6d	20	11	16	14
6e	18	17*	19	17
6f	17	13	11*	12
6g	18**	19	18	18
Std	29	34	35	31

ANOVA analysis followed by Tukey's test, significance levels. *p 0.05; **p 0.01; compared with the respective Standard Streptomycin (500 µg solution) and Fluconazole (500 µg mL^{-1} solution) were used as positive controls for bacteria and fungi respectively

Statistical analysis: The values of Antimicrobial activity are expressed as mean ± standard deviation. The inhibition zone was measured from the antimicrobial activity of compound and analyzed using one-way analysis of variance (ANOVA) followed by Tukey's test at $p < 0.05$. The software Origin Pro 9.0 was employed for the statistical analysis.

APPLICATION

Synthesized compounds showed the excellent activity for the *Escherichia coli* and moderate activities against other tested microorganisms. Among all the synthesized compounds, benzophenone analogs **6a, 6c, 6g** and **6e** had disclosed promising activity against both bacteria and fungi in the series. Compounds **6c** and **6e** have chlorine moiety. Synthesized oxadiazole analog **6c** with chlorine revealed highest antibacterial activity against *Staphylococcus aureus and E.coli* with MIC at 31.25 µg mL^{-1}, which were comparable with standard streptomycin. Also suggests that compounds with chlorine group revealed the superior activity, in other words, compounds containing electron-withdrawing group on benzophenone showed the superior activity.

CONCLUSION

In the present study, we synthesized analogs of oxadiazolebenzophenonewhich vary in the number and position of the methyl and halogen groups on the benzophenone moiety, which were then evaluated for their anti bacterial and antifungal activities. The compound **6c** is the potent anti bacterial and antifungal agents.

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