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# Synthesis and Antimicrobial Evaluation of Novel 4-substituted Phenyl-(2-oxo-2*H*-chromen-3-yl) Prop-2-en-1-ylidene Pyrimidine Derivatives

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**ABSTRACT**

*In this study a series of novel 4-substituted phenyl-(2-oxo-2H-chromen-3-yl) prop-2-en-1-ylidene pyrimidine derivatives have been synthesised by refluxing substituted 3-acetyl coumarin with barbituric/thiobarbituric acid and variety of substituted benzaldehyde in presences of 10 mol% CAN in ethanol with constant stirring for about 4-5 h. All the newly synthesised compounds were characterised by FTIR, $^{1}H$ NMR, $^{13}C$ NMR and mass spectrometry analysis and were screened for in vitro antimicrobial and antioxidant activity study.*

**Keywords:** Coumarin derivatives; Barbiturates; Antimicrobial activity; Antioxidant activity

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## INTRODUCTION

Coumarins are the outstanding moiety of benzopyrones found in green plants both in free and combined state, having a broad spectrum of biological assests [1]. Wide therapeutic applications of coumarin derivatives are in anti-HIV, antitumor and photo chemotherapy [2]. Coumarins also exhibits dynamic anti-bacterial [3,4], anti-inflammatory [5], and anti-viral property [6]. Warfarin, acenocoumarol, carbochromen etc. and antibiotics such as novobiocin, clorobiocin, and coumermycin A1 consists of coumarin nucleus within their structure [7,8]. Various other fields of chemistry such as luminescence, laser technologies, and liquid crystalline materials possess wide applications of coumarin derivatives [9-13]. On the other hand Pyrimidines are the other group of pharmacological interest. Compounds with a pyrimidine ring system possess anticonvulsant, antimalarial, antimicrobial, and antitumor activities [14-18]. Drugs involving pyrimidine heterocycle moiety are helpful in the treatment of acute leukemia in children, hyperthyroidism and adult granulocytic leukemia [14]. They are also used in polymer and supramolecular chemistry [19-23]. Recently attention has been given to Conjugated molecules having a pyrimidine as the key unit and they have become prospective candidates for molecular wires [24,25] and light emitting devices [26]. Considering this, in our present research, we have synthesized 4-substituted phenyl-(2-oxo-2H-chromen-3-yl) prop-2-en-1-ylidene pyrimidine derivatives via one-pot three-component condensation reaction and screened for their biological evaluation.

## EXPERIMENTAL SECTION

### Materials and Methods

The reagents required were bought commercially from sigma aldrich. Electro thermal melting point apparatus with open capillary tubes were used to determine the melting point and are uncorrected. Analytical thin-layer chromatography was performed with E. Merck silica gel GF254 glass plates. Visualization of the developed chromatogram was performed by UV light (254 nm). Iodine vapor and 1:4 ratio Ethyl acetate and pet ether was used as a mobile phase. The FT-IR spectra in KBr pellets (100 mg) using Shimadzu FT-Infrared spectrophotometer were

taken. Bruker 400 MHz spectrometer in DMSO-$d_6$ was used for determination. $^1$HNMR and $^{13}$CNMR spectra and chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as internal standard. LC-MS were obtained using C-18 column on Shimadzu, LCMS 2010A, Japan. The zones of inhibition of antimicrobial activities are expressed as mean±SD of three replicates.

**Synthesis of Novel 4-Substituted Phenyl-(2-oxo-2H-chromen-3-yl) prop-2-en-1-ylidene Pyrimidine Derivatives**

To a mixture of substituted 3-acetyl coumarin (1), substituted benzaldehyde (2) and barbituric/thiobarbituric acid (3) in ethanol taken in a round bottom flask added 10 mol% of CAN and refluxed for about 5-6 h with constant stirring. The reaction was monitored by TLC. Reaction mixture was poured into the crushed ice and stirred for few minutes till the solid residue separated out, filtered, dried and recrystallized from ethanol.

**5-[(2E)-3(4-methylphenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]pyrimidine-2,4,6(1H,3H,5H) -trione (4a):**

Light yellow, yield 88% mp: 193−195 °C. IR (KBr, cm$^{-1}$): 1742 (C=O), 2962 (methyl C-H) 3197 (NH). $^1$H NMR (DMSO−$d_6$) δ (ppm): 2.49 (s, 3H, $CH_3$), 7.40−8.66 (m, 11H, Ar−H), 11.20, (s, 1H, NH), 11.34 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm):21.49 ($CH_3$), 116.20, 116.22, 117.90, 118.24, 124.49, 125.08, 128.99, 129.72, 129.85, 129.94, 130.89, 134.09, 134.64, 143.66, 147.20, 150.34, 154.70, 155.18, 158.57, 160.91, 161.74. LCMS: m/z [M$^+$]: 400.

**5-[(2E)-3-(4-methylphenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]-2-thioxodihydropyrimidine 4,6(1H,5H)-dione(4b):**

Light orange, yield 85% mp: 230−235 °C. IR (KBr, cm$^{-1}$): 1730 (C=O), 2943 (methyl C-H), 3210 (NH). $^1$H NMR (DMSO−$d_6$) δ (ppm): 2.68 (s, 3H, $CH_3$), 7.44−8.65 (m, 11H, Ar−H), 11.22, (s, 1H, NH), 11.36 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm):23.44 ($CH_3$), 115.18, 116.20, 117.88, 118.20, 123.45, 126.18, 128.89, 129.62, 129.85, 129.97, 131.87, 133.19, 134.54, 143.63, 147.27, 150.24, 154.87, 155.25, 158.51, 160.81, 161.63. LCMS: m/z [M$^+$]: 416.

**5-[(2E)-3-(4-chlorophenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]pyrimidine-2,4,6(1H,3H,5H)trione (4c):**

Yellow, yield 86% mp: 200−205°C. IR (KBr, cm$^{-1}$): 795 (C−Cl), 1745 (C=O), 3200 (NH). $^1$H NMR (DMSO−d6) δ (ppm): 7.400−8.661 (m, 11H, Ar−H), 11.26, (s, 1H, NH), 11.41 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm):116.22 117.89, 118.22, 124.45, 125.00, 128.97, 129.70, 129.84, 129.90, 130.86, 134.05, 134.60, 143.63, 147.18, 150.30, 154.68, 155.15, 158.55, 160.00, 161.64. LCMS: m/z [M$^+$] and [M$^+$+]: 420.83 and 422.90.

**5-[(2E)-3-(4-chlorophenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]-2-thioxodihydropyrimidine 4,6(1H,5H)-dione(4d):**

Yellow, yield 70% mp: 245−250°C. IR (KBr, cm$^{-1}$): 875 (C−Cl), 1760 (C=O), 3151 (NH). $^1$H NMR (DMSO−d6) δ (ppm): 7.46−8.76 (m, 11H, Ar−H), 11.16, (s, 1H, NH), 11.21 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm):116.18, 117.17, 118.19, 124.35, 125.22, 128.86, 129.63, 129.84, 129.93, 131.82, 134.23, 134.46, 142.63, 146.08, 151.31, 154.78, 155.12, 158.52, 160.34, and 161.64. LCMS: m/z [M$^+$] and [M$^+$+]: 436 and 438.

**5-[(2E)-3-(4-methoxyphenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]pyrimidine2,4,6(1H,3H,5H) -trione(4e):**

Yellow, yield 87% mp: 270−275°C. IR (KBr, cm$^{-1}$): 1307 (O-CH3) 1741 (C=O), 3030 (NH). $^1$H NMR (DMSO−$d_6$) δ (ppm): 3.88 (s, 3H, $OCH_3$), 7.42−8.60 (m, 11H, Ar−H), 11.25, (s, 1H, NH), 11.38 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm):29.73 ($OCH_3$), 116.15, 116.20, 117.93, 118.26, 124.52, 125.18, 128.89, 129.70, 129.81, 129.92, 130.83, 134.01, 134.60, 143.61, 147.25, 150.31, 154.75, 155.13, 158.52, 160.89, 161.73. LCMS: m/z [M$^+$]: 416.

**5-[(2E)-3-(4-methoxyphenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]-2-thioxodihydropyrimidine-4,6 (1H,5H)-dione(4f):**

Light red, yield 80% mp: 300−305°C. IR (KBr, cm$^{-1}$): 1310 (O-CH3), 1335 (C=S), 1751 (C=O), 3039 (NH). $^1$H NMR (DMSO−$d_6$) δ (ppm): 3.78 (s, 3H, $OCH_3$), 7.47−8.56 (m, 11H, Ar−H), 11.39, (s, 1H, NH), 11.42 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm):28.72 ($OCH_3$), 116.10, 116.20, 117.91, 118.20, 124.49, 125.16, 127.80, 128.70, 129.71, 129.84, 131.82, 133.05, 134.57, 143.54, 147.36, 149.31, 153.74, 154.11, 158.49, 160.85 161.69. LCMS: m/z [M$^+$]: 432.

**5-[(2E)-3-(4-hydroxyphenyl)-1-(2-oxo-2H-chromen-3-yl)prop-2-en-1-ylidene]-2-thioxodihydropyrimidine-4,6(1H,5H)-dione(4g):**
Light orange, yield 88% mp: 330−335°C. IR (KBr, $cm^{-1}$): 1305 (C=S), 1749 (C=O), 3039 (NH), 3290 (OH). 1H NMR (DMSO−$d_6$) δ (ppm): 7.74−8.76 (m, 11H, Ar−H), 11.27, (s, 1H, NH), 11.36 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm): 116.16, 116.23, 117.86, 119.12, 124.32, 125.70, 127.78, 128.39, 129.63, 129.74, 131.92, 133.32, 134.45, 143.65, 147.41, 149.29, 153.69, 154.01, 158.38, 160.81 161.58. LCMS: m/z [$M^+$]: 418.

**5-[(2E)-1-(5-bromo-2-oxo-2H-chromen-3-yl)-3-(4-hydroxyphenyl)prop-2-en-1-ylidene]-2thioxodihydropyrimidine -4,6(1H,5H)-dione (4h):**
Orange, yield 75% mp: 250−255°C. IR (KBr, $cm^{-1}$): 1330 (C=S), 1753 (C=O), 3028 (NH). 3269 (OH). $^1$H NMR (DMSO−$d_6$) δ (ppm): 7.47−8.56 (m, 11H, Ar−H), 11.33, (s, 1H, NH), 11.57 (s, 1H, NH). $^{13}$C NMR (DMSO−d6) δ (ppm): 116.11, 116.21, 117.90, 118.21, 124.40, 125.11, 127.81, 128.71, 129.70, 129.81, 131.80, 133.01, 134.50, 143.51, 147.30, 149.31, 153.70, 154.19, 158.41, 160.80 161.61. LCMS: m/z [$M^+$] and [$M^+$+]: 497 and 499.

**Antimicrobial Activity**
To carry out antimicrobial activity the following bacteria and fungi were used for the experiment, bacterial strains viz *K. pneumonia* ATCC 25923, *Escherichia coli* ATCC 25922, *S. typhimurium* ATCC 27853. All bacterial strains were maintained on nutrient agar medium at ±37°C. Fungal strains viz. *Aspergillus flavus* and *Candida albicans MTCC 227* were used in this study. These strains were obtained from IMTECH, Chandigarh, India. All microbial strains were maintained on potato dextrose agar (PDA) at ±25°C. Streptomycin and Fluconazole were used as standard drugs for antibacterial and antifungal activities respectively. After the incubation period, the minimum inhibition zone at which the microorganism growth was inhibited was measured in mm. The minimum inhibitory concentration were determined by using serial broth method and measured in mg/mL.

**Antioxidant Activity**
**Free radical scavenging activity by DPPH method:**
Free radical-scavenging capacities of synthesized compounds were determined according to previously reported procedure using the stable 2, 2-diphenyl-1-picryhydrazyl radical (DPPH) [27].

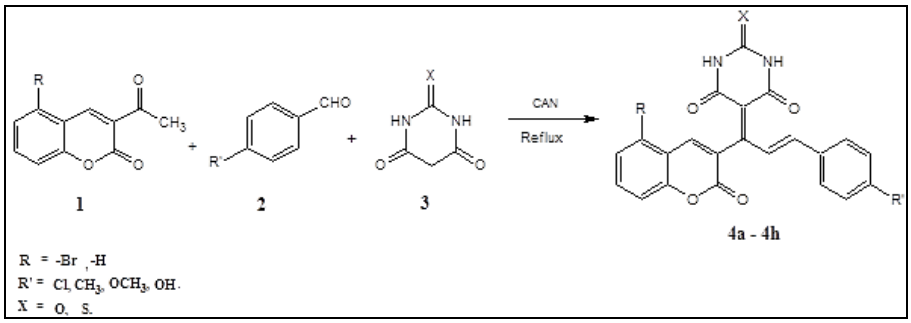
**Metal ion chelating assay:**
The ferrous ion chelating potency of synthesized organic compounds was investigated according to the method of Dinis et al. [28] with little modification, wherein the $Fe^{2+}$ chelating ability of synthesized compounds was monitored by absorbance of the ferrous iron ferrozine complex at 562 nm. In brief the test solution (2 ml) of different concentrations (25-100 µmol/L) in methanol was added to a solution of 2 mM $FeCl_2$ (0.05 ml), the reaction was initiated by adding 5 mM ferrozine (0.2 ml) and total volume was adjusted to 5 ml with methanol. Then, the mixture was shaken vigorously and left at room temperature for 10 min. Absorbance of the solution was measured spectrophotometrically at 562 nm. EDTA was used as a standard. The inhibition percentage of ferrozine-$Fe^{+2}$ complex formations was calculated using the formula:

$$\text{Metal chelating effect (\%)} = [(A_{control} - A_{sample})/A_{control}] \times 100$$

Where $A_{control}$ is the absorbance of control (control contains $FeCl_2$ ferrozine complex) and $A_{sample}$ is the absorbance of test compounds. EDTA is used as control. Test was performed and the results were averaged.

## RESULTS AND DISCUSSION

In the present study we reported that, the synthesis of 4-substituted phenyl-(2-oxo-2*H*-chromen-3-yl) prop-2-en-1-ylidene pyrimidine derivatives was achieved by the reaction of equimolar quantity of 3 acetyl coumarin, substituted benzaldehyde and barbituric and thiobarbituric acid in ethanol using CAN as catalyst at reflux temperature with constant stirring (Scheme 1).
The structure of the desired coumarin incorporated pyrimidine derivatives were confirmed by FTIR, $^1$H NMR, $^{13}$C NMR and LC-MS spectral data. The IR spectrum of a compound 4a showed a broad absorption band at a region 3197 $cm^{-1}$which corresponds to amine (NH) group and the band at 2962 $cm^{-1}$ corresponds to CH stretching vibration. In addition to these bands absorbed in the region at 1742 $cm^{-1}$ and 1671 $cm^{-1}$ corresponding to carbonyl group (C=O). The $^1$HNMR spectrum of compound 4a showed a singlet at δ 11.20 and 11.34 ppm is due amine protons (NH) The multiplet at δ 7.40−8.66 ppm corresponds to aromatic protons. The singlet at δ 2.49 is seen due to methyl protons (Table 1).




**Scheme 1: CAN as catalyst at reflux temperature with constant stirring**

**Table 1: Minimum inhibitory concentration**

| Compound | Concentration in mg/mL | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Stnd: A** | ***E.C*** | ***K.P*** | ***S.T*** | **Stnd: B** | ***A.F*** | ***C.A*** |
| 4a | 2.2 ± 0.4 | | | 1.8 ± 0.35 | 1.21 ± 0.4 | | 0.98 ± 0.21 |
| 4b | 2.47 ± 0.5 | 1.89 ± 0.7 | 2.12 ± 0.3 | 2.0 ± 0.25 | 1.46 ± 0.21 | 1.1 ± 0.23 | 1.21 ± 0.24 |
| 4c | 1.54 ± 0.3 | | 1.32 ± 0.2 | | 1.51 ± 0.32 | 1.12 ± 0.45 | |
| 4d | 1.7 ± 0.25 | 1.52 ± 0.31 | 1.6 ± 0.21 | 1.48 ± 0.12 | 1.34 ± 0.21 | 1.0 ± 0.24 | 0.87 ± 0.14 |
| 4e | 2.01 ± 0.41 | 1.70 ± 0.61 | 1.61 ± 0.32 | 1.55 ± 0.20 | 1.68 ± 0.64 | 1.42 ± 0.46 | 1.3 ± 0.31 |
| 4f | 1.87 ± 0.13 | | | 1.42 ± 0.3 | 1.48 ± 0.25 | | 1.17 ± 0.41- |
| 4g | 2.12 ± 0.51 | 1.84 ± 0.1 | 1.73 ± 0.20 | 1.48 ± 0.25 | 1.71 ± 0.61 | 1.5 ± 0.1 | |
| 4h | 1.65 ± 0.24 | 1.40 ± 0.3 | 1.35 ± 0.14 | | 1.62 ± 0.1 | | 1.23 ± 0.41 |

## *In Vitro* Antimicrobial Study

From the antibacterial activity results, all the samples displayed appreciable antibacterial activity against the tested pathogens at 25 and 50 mg/mL concentrations. The highest zone of inhibition was observed by compound 4d against *E.Coli*, followed by 4f against *K.Pneumonia* and by 4b against *S. typhimurium*. Moderate activity was exhibited by rest of the compounds. The results were depicted in the Table 2.

**Table 2: Antimicrobial results of the synthesised compounds 4-substituted phenyl-(2-oxo-2H-chromen-3-yl) prop-2-en-1-ylidene pyrimidine derivatives 4a-4h**

| **comp** | **EC** | | **KP** | | **ST** | | **AF** | | **CA** | |
|---|---|---|---|---|---|---|---|---|---|---|
| mg/mL | **25** | **50** | **25** | **50** | **25** | **50** | **25** | **50** | **25** | **50** |
| 4a | 2.4 ± 0.2 | 2.6 ± 0.2 | 2.5 ± 0.1 | 2.8 ± 0.1 | 3 ± 0.1 | 3.2 ± 0.1 | 1.4 ± 0.2 | 1.8 ± 0.2 | 1.5 ± 0.1 | 1.75 ± 0.1 |
| 4b | 2.6 ± 03 | 2.6 ± 0.3 | 2.8 ± 0.1 | 3.5 ± 0.1 | 3 ± 0.2 | 3.4 ± 0.2 | 1.1 ± 03 | 1.35 ± 0.3 | 1.42 ± 0.2 | 1.6 ± 0.1 |
| 4c | 2.4 ± 0.2 | 3 ± 0.2 | 3.1 ± 0.2 | 3.4 ± 0.2 | 2.8 ± 0.2 | 3 ± 0.2 | 1.2 ± 0.2 | 1.5 ± 0.2 | 1.6 ± 0.2 | 1.92 ± 0.2 |
| 4d | 2.7 ± 0.3 | 3.4 ± 0.3 | 3 ± 0.3 | 3.4 ± 0.3 | 2.5 ± 0.1 | 2.9 ± 0.1 | 1.3 ± 0.3 | 1.5 ± 0.3 | 1.2 ± 0.3 | 1.43 ± 0.3 |
| 4e | 2.3 ± 0.2 | 3 ± 0.2 | 2.7 ± 0.2 | 3.2 ± 0.2 | 2.3 ± 0.2 | 3 ± 0.2 | 1.12 ± 0.2 | 1.45 ± 0.2 | 1.5 ± 0.2 | 1.85 ± 0.2 |
| 4f | 2.1 ± 0.2 | 3.2 ± 0.2 | 3.2 ± 0.2 | 3 ± 0.2 | 2.8 ± 0.2 | 3. 2 ± 0.2 | 1.34 ± 0.2 | 1.56 ± 0.2 | 1.23 ± 0.2 | 1.6 ± 0.2 |
| 4g | 2.5 ± 0.1 | 3.5 ± 0.1 | 2.8 ± 0.1 | 3.5 ± 0.1 | 2.5 ± 0.1 | 3.1 ± 0.1 | 1.5 ± 0.1 | 1.69 ± 0.1 | 1.7 ± 0.1 | 2 ± 0.1 |
| 4h | 2.2 ± 0.2 | 3 ± 0.2 | 3.1 ± 0.3 | 3.5 ± 0.3 | 2.7 ± 0.2 | 3.3 ± 0.2 | 1.45 ± 0.2 | 1.82 ± 0.2 | 1.43 ± 0.3 | 1.75 ± 0.3 |
| Stnd:A | 2.7 ± 0.2 | 3.8 ± 0.2 | 3.4 ± 0.3 | 3.6 ± 0.3 | 3 ± 0.2 | 3.5 ± 0.2 | | | | |
| Stnd:B | | | | | | | 1.62 ± 0.2 | 2.01 ± 0.2 | 1.72 ± 0.3 | 2.12 ± 0.3 |

Antifungal screening, all compounds exhibited promising activity against the tested fungal pathogens at 25 and 50 mg/mL concentrations. Among the synthesized compounds, 4h showed significant activity against *A. flavus*, while compounds 4c and 4g against *Candida albicans*. The results were as shown in the Table 2. In addition, the synthesized compounds were subjected for the MIC and the results are displayed in Table 2. Among the eight compounds, compound 4d and 4g was found to be more effective against *E. coli* and compound 4b and 4g showed

significant activity against *K. pneumonia*. The compound 4a is effective against *S. typhimurium*. The MIC value of the antifungal activity of the compounds reveals that, compound 4e was found to be most effective against *A. flavus* and 4h is most effective against *C. albicans* pathogens compared to other compounds.

**Antioxidant Activity**

**Free radical scavenging activity by DPPH method:**

The activity results of the newly synthesized compounds are represented in Table 3. Among the tested compounds, the ones substituted with hydroxyl group 4h and 4h displayed potent DPPH free radical scavenging activity with 74 and 65 µg/mL percentage of inhibition when compared to standard BHT value 82 µg/mL. The presence of electron donating group (OH) is responsible for the blocking the DPPH free radical by donating electron pair.

**Table 3: DPPH activity**

| Sl. No | Sample code | % Inhibition |
|---|---|---|
| 1 | 4a | 46 |
| 2 | 4b | 55 |
| 3 | 4c | 59 |
| 4 | 4d | 61 |
| 5 | 4e | 43 |
| 6 | 4f | 57 |
| 7 | 4g | 65 |
| 8 | 4h | 74 |
| | **Standard(BHT)** | 82 |

**Iron chelating ability:**

The iron chelating study measures the ability of antioxidants to compete with ferrozine in chelating ferrous ion. [29] The ferrous ion-chelating activity of the newly synthesized compounds is represented in Table 4. The $Fe^{+2}$ chelating capacities varied significantly among different compounds. From the activity results, it revealed that among the tested compounds, compounds 4f displayed excellent chelating ability.

**Table 4: Metal ion chelating assay**

| Sl. No | Sample code | % Inhibition |
|---|---|---|
| 1 | 4a | 20 |
| 2 | 4b | 36 |
| 3 | 4c | 53 |
| 4 | 4d | 37 |
| 5 | 4e | 53 |
| 6 | 4f | 62 |
| 7 | 4g | 37 |
| 8 | 4h | 51 |
| | **EDTA** | 68 |

## CONCLUSION

In this report, novel 4-substituted phenyl-(2-oxo-2H-chromen-3-yl) prop-2-en-1-ylidene pyrimidine derivatives were prepared in one pot using three components with high yields and all the synthesized compounds were screened for their antimicrobial and antioxidant properties. The results showed that, most of the derivatives inhibited the growth with higher inhibition zones. It is concluded that all the compounds showed appreciable antimicrobial and antioxidant activity may be due to the structural orientation and the side chain moieties associated with the compounds and it can be used for effective antibiotic drug designing in the near future.

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