REVIEW OF RESEARCH
ISSN: 2249-894X
IMPACT FACTOR : 5.7631(UIF)
VOLUME - 11 | ISSUE - 7 | APRIL - 2022

DESIGN, SYNTHESIS, AND ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF NOVEL S AND N CONTAINING SUBSTITUTED CHALCONE DERIVATIVES

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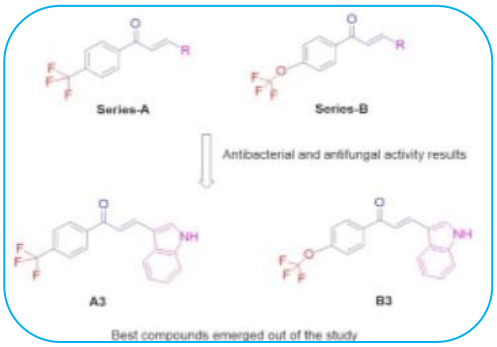
ABSTRACT:



Drug resistance, hypersensitivity, and systemic toxicity have hampered the clinical efficacy of many antibiotics, despite their widespread availability. Based on the above information, in this investigation, we designed, synthesised, and assessed our findings.S and N containing bromo substituted chalcones have better antibacterial and antifungal properties.The substances in question wereidentified and tested for their antibacterial efficacy against five strains of bacteria using spectroscopic techniques Gram-positive and Gram-negative pathogens of fungal and bacterial strains, respectively. In this experiment, compound(E)-3-(4-bromophenyl)-1-(2,4-dimethylthiazol-5-yl) prop-2-en-1-one (3) was more effective than the other substances tested group. Compound 3 with an attached bromine atom is one of the best active chalcones and also olefinic carbon has been found to be the most effective antibacterial agent compared to other carbon compounds.

KEY WORDS: *hypersensitivity, and systemic toxicity, bacterial strains.*

1.1 INTRODUCTION

Chalconeis a general designation for substances that contain the 1, 3-diphenyl-2-propen-1-one structure and are members of the flavonoid family [1-3]. They are open chain flavonoids with two aromatic rings connected by a three carbon,-unsaturated carbonyl system. Chalcones are abundant in nature, ranging from ferns to higher plants [4], with many of them polyhydroxylated in the aryl rings. In plants, the enzyme chalcone isomerase catalyses the conversion of chalcones to the equivalent (2S)-flavanones. Chalcones and flavanones have a close structural and biogenetic link, which explains why they frequently co-occur as natural products. The existence of a double bond in conjugation with carbonyl functionality is thought to be responsible for chalcones' biological activity, while the absence of this functionality renders them inactiveo [5-6]. They are known to exist in both cis- and trans-forms and can be easily cyclized to generate flavanones via Michael addition. Chalcones can be obtained by the acid or base catalyzed aldol condensation of acetophenones with aromatic aldehydes. Chalcones, which resulted in a variety of biological and pharmacological activities [7-9]. Antimicrobial, anti-inflammatory, analgesic, cytotoxic, antitumor, antimalarial, antitubercular, antiviral, anti-HIV, antiulcerative, antileishmanial, antioxidant, antiprotozoal, antihistaminic, antifedent, immunomodulatory, anticonvulsant, antihyperglycemic, antihyperlipidemic, and antiplatelet activities have been reported

for compounds with chalcone as the back As a result of their link with a wide range of biological functions, chalcones continue to garner a lot of scientific attention.

2. MATERIALS AND METHODS

All chemicals and solvents used were of Annular grade. The melting points were taken in open capillaries in an electrical apparatus and are uncorrected. IR spectra were recorded on AVATAR-330 FT-IR spectrometer (Thermo Nicolet range 4000-400 cm^{-1}) as KBr pellets. ^{1}H NMR spectra were recorded on a BRUKER AVANCE III 400 MHz NMR spectrometer operating at 400.13 MHz.^{13}C NMR spectra were recorded on a BRUKER AVANCE III 400 MHz NMR spectrometer operating at 100.61 MHz.

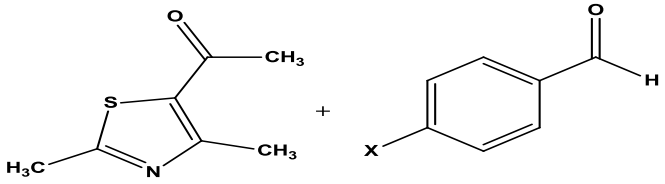
2.1 Determination of antibacterial and antifungal activity by Disc-Diffusion method

Nutrient agar plates were prepared under sterile conditions and incubated overnight to detect contamination. About 0.2 mL of working stock culture was transferred into separate nutrient agar plates and spreaded thoroughly using a glass spreader. Whatman No. 1 discs (6 mm in diameter) were impregnated with the test compounds dissolved in DMSO (200 µg/mL) for about half an hour. Commercially available drug disc (Ciprofloxacin 10 µg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating the disc of same size with DMSO solvent. The discs were placed on the inoculated agar plates and incubated at 37 ± 1 °C for about 18-24 h. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism [10-11].

Fungi were grown on Sabouraud's dextrose agar (SDA) medium, and testing was done on Sabouraud's dextrose broth (SDB) media. The sub-culture and viable count were performed in the same manner as in antibacterial research, with the exception of the temperature, which should be kept at 28 1 °C for approximately 72 hours. Similarly, for the disc diffusion approach, the petridishes were incubated for 72 hours at 28 1 °C. The antifungal investigations employed the same concentrations of the test drug, solvent (DMSO), and Amphotericin B (standard) as previously generated.

2.1.1 Synthesis of (E)-3-(4-aryl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one (1-3)

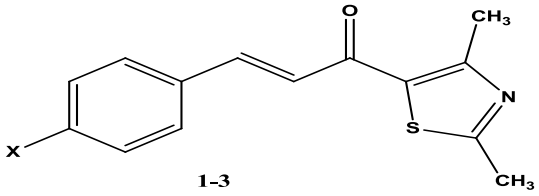
A mixture of appropriate 1-(2,4-dimethylthiazol-5-yl)ethanone (2 mmol), 4-Substituted benzaldedye (2 mmol) and sodium hydroxide were stirred at about (0-5)ºC for 3h. The reaction mixture was neutralized with dilute HCl and kept in the refrigerator overnight. The product was filtered and washed with cold water. The solid that separated was filtered, dried and the crude chalcone was recrystallized from ethanol. Synthetic routes of compounds are given in **Scheme 1**.



X=F, Cl, Br

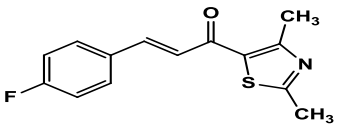
Ethanol

NaOH



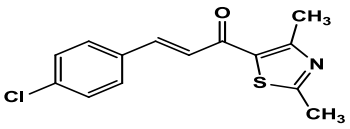
1-3

	X
1	F
2	Cl
3	Br



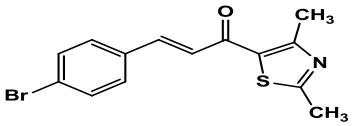
(*E*)-1-(2,4-dimethylthiazol-5-yl)-3-(4-fluorophenyl)prop-2-en-1-one

Compound 1



(*E*)-3-(4-chlorophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one

Compound 2



(*E*)-3-(4-bromophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one

Compound 3

3. Result and discussion

3.1 Analytical and spectral data of (E)-3-(4-fluorophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one(1)

MF: $C_{14}H_{12}FNO$ Sm.p (°C): 113-114 Yield (%): 73 Elemental analysis: (%) C, 65.43; H, 5.12; N, 5.09; O, 5.81; F, 6.90; S, 11.65 (65.01) (5.09) (4.12) IR (KBr, cm^{-1}): 2922 (υAr-CH), 2858 (υali-CH), 1654 (υC=O), 1604 (υC=N), 1473 (υC=C), 1103-902 (aromatic C-H in-plane bending vibration), 72 (υC-S), 677-460(aromatic C-H out of plane bending vibration). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm):): 7.21-7.94 (m, Ar-H); 2.43 (-CH-); 2.39 (-CH-); 1.56 (t, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 187.70 (C=O), 167.01 C=N, 118.77-163.42 (Ar-C), 19.07,19.21 (CH_3).

3.2 Analytical and spectral data of (E)-3-(4-Chlorophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one(2)

MF: $C_{14}H_{12}ClNOS$ m.p (°C): 132-133 Yield (%): 82 Elemental analysis: (%) C61.74; H, 4.84; N, 4.80; O, 5.48; Cl, 12.15; ; S, 10.3 (60.02) (4.09) (4.01)IR (KBr, cm-1): 3064, 2929 (υAr-CH), 2841 (υali-CH), 1653 (υC=O), 1504 (υC=N), 1450 (υC=C), 1114, 1018 (aromatic C-H in-plane bending vibration), 736 (υC-S), 815 (υC-Cl), 661-445(aromatic C-H out of plane bending vibration); 1H NMR (400 MHz,

CDCl3, δ, ppm):): 6.92-7.93 (m, Ar-H); 2.85 (-CH-); 2.43 (-CH-); 1.63 (CH3). 13C NMR (100 MHz, CDCl3, δ, ppm): 190.06 (C=O), 167.71 (C=N), 114.43-161.62 (Ar-C), 21.63,17.80 (CH3).

3.3 Analytical and spectral data of (E)-3-(4-bromophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one (3)

MF: $C_{14}H_{12}BrNOS$ m.p (°C): 183-184 Yield (%): 71 Elemental analysis: (%) C,53.38; H, 4.20; N, 4.17; O, 4.76; Br, 23.76; ; S, 9.54 (52.64) (4.13) (3.09) IR (KBr, cm-1): 2929 (υAr-CH), 2860 (υali-CH), 1627(υC=O), 151 (υC=N), 1456 (υC=C), 1122-891 (aromatic C-H in-plane bending vibration), 756 (υC-S), 686-468(aromatic C-H out of plane bending vibration). 1H NMR (400 MHz, CDCl3, δ, ppm):): 7.94-7.29 (m, Ar-H); 2.58 (-CH-); 2.44 (-CH-); 1.57 (CH3). 13C NMR (100 MHz, CDCl3, δ, ppm): 189.71 (C=O), 165.64 (C=N), 122.60-143.80 (Ar-C), 21.66,21.02 (CH3).

4. ANTIBACTERIAL ACTIVITY

As shown in Table 1, (fig **1a-e**), the in vitro antibacterial activities of compound **1-3** was evaluated against a series of Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Streptococcus pyogenes and compared with the standard drug ciprofloaxin.

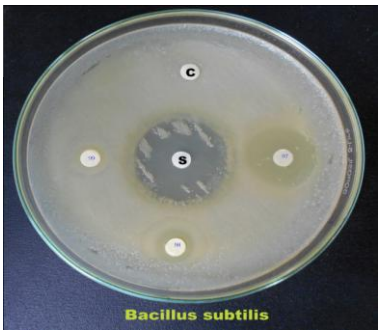
Table 1: Zone of inhibition of 1-3 against *B. subtilis, S. aureus, E. coli, P. aeruginosa, and S. pyogenes*

Compound/Standard	*B. subtilis*	*S.aureus*	*E. coli*	*P.aeruginosa*	*S. pyogenes*
Compound 1	21	19	11	14	18
Compound 2	17	16	15	14	20
Compound 3	16	13	15	13	11
ciprofloxacin	29	32	32	33	32

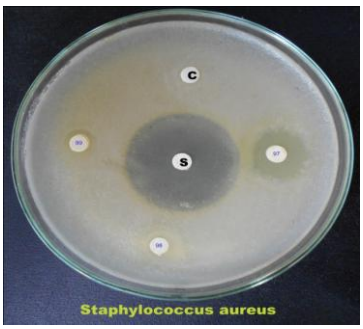
The susceptibility of bacterial strains compound **1-3** was evaluated by measuring the zones of inhibition. The drug and the derivative 1 showed inhibition diameters range 11-21mm. Derivative **1** was found to be most active against Bacillus subtilis, Staphylococcus aureus aeruginosa and displayed mild to moderate activity against Pseudomonas aeruginosa, Streptococcus pyogenes. Escherichia coli exhibited poor activity aganist our synthesised compound **1.** Comparison of antibacterial activity data with standard drug suggested that **1** exhibited comparable activity against Bacillus subtilis.

The drug and the derivative 2 showed inhibition diameters range 14-20 mm. Addition of Chloro group at fluoro position of compound **1** (compound **2**) exhibited good activity against Streptococcus pyogenes. From **Table 1** inform compound **2** showed moderate activities against Bacillus subtilis & Staphylococcus aureus. The results suggest that the antibacterial activity is markedly decreases by chloro than fluoro group in phenyl ring[12-13].

a



b



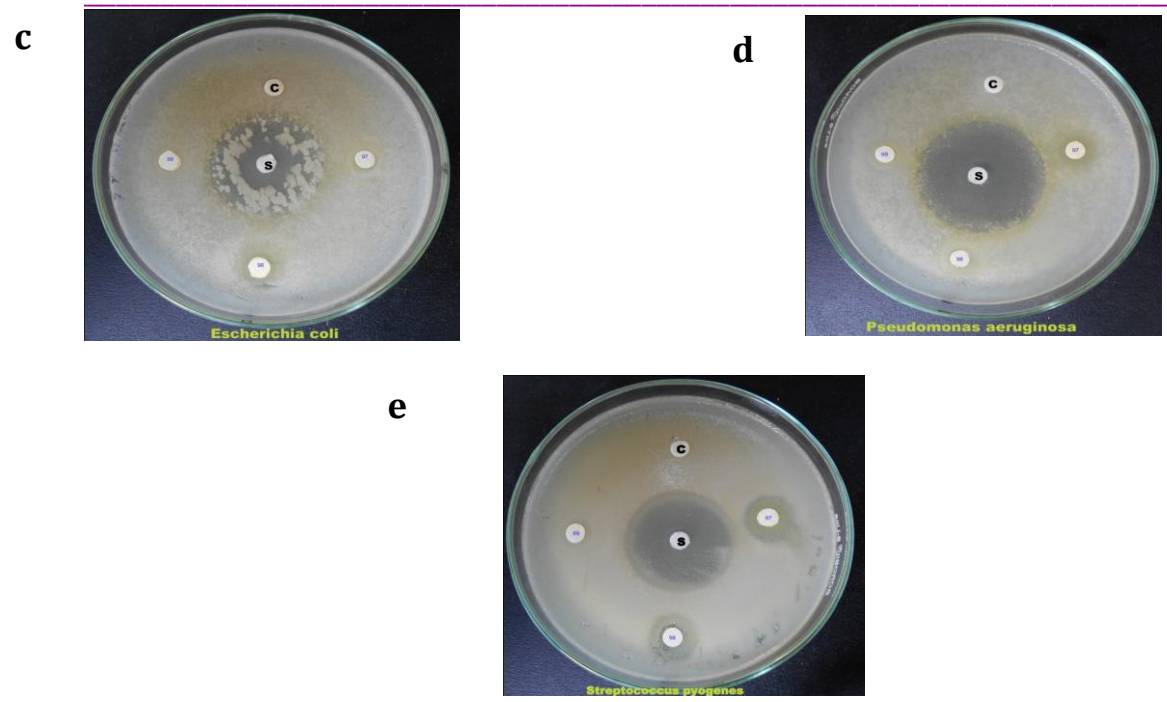


Fig 1 (a-e) Zone of inhibition of 1-3 against *B. subtilis, S. aureus, E. coli, P. aeruginosa, and S. pyogenes*

Further addition of bromo group at fluoro group of compound**1** (compound **3**) exhibited remarkable changes in all the tested bactrial strains. The drug and the derivative 3 showed inhibition diameters range 14-20 mm.

From **Table 1**, it is clearly seen that compound **3** showed 1.3 grater values against Escherichia coli than the compound **3** and among five bacterial strains Bacillus subtilis more inhibited by compound **3** (16mm).The compound **3** alsopossesses moderate activity against Escherichia coli (15 mm). The results suggest that the antibacterial activities are markedly influenced by bromo group in phenyl ring[14].

5. ANTIFUNGAL ACTIVITY

Compound **1-3** was screened against Aspergillus flavus, Aspergillus niger, Fusarium oxysporum, Penicillimchryogenum and Trigodermaveride. The results compared with standard drug Amphotericin-B. The results tabulated in **Table 2a-e**. The compound **1** showed good activity to poor activity against selected fungal strains. Compound **1** showed excellent activity against Trigodermaveride (14mm), while compound **1** showed good activity against Aspergillus niger (12mm). Fungal strains namely Aspergillus flavus Fusarium oxysporum and Penicillimchryogenum exhibited moderate activity with Zone of inhibition ranging from 08-06mm.

Table 2: Zone of inhibition of 1-3 against *A. flavus, A. niger, F.oxysporum, P.chryogenum and T. veride*

	Zone of inhibition (mm)				
Compound/Standard	***A.flavus***	***A. niger***	***F. oxysporum***	***P.chryogenum***	***T. veride***
Compound 1	08	12	06	06	14
Compound 2	12	16	15	08	09
Compound 3	18	20	22	18	24
Amphotericin-B	28	26	24	22	28

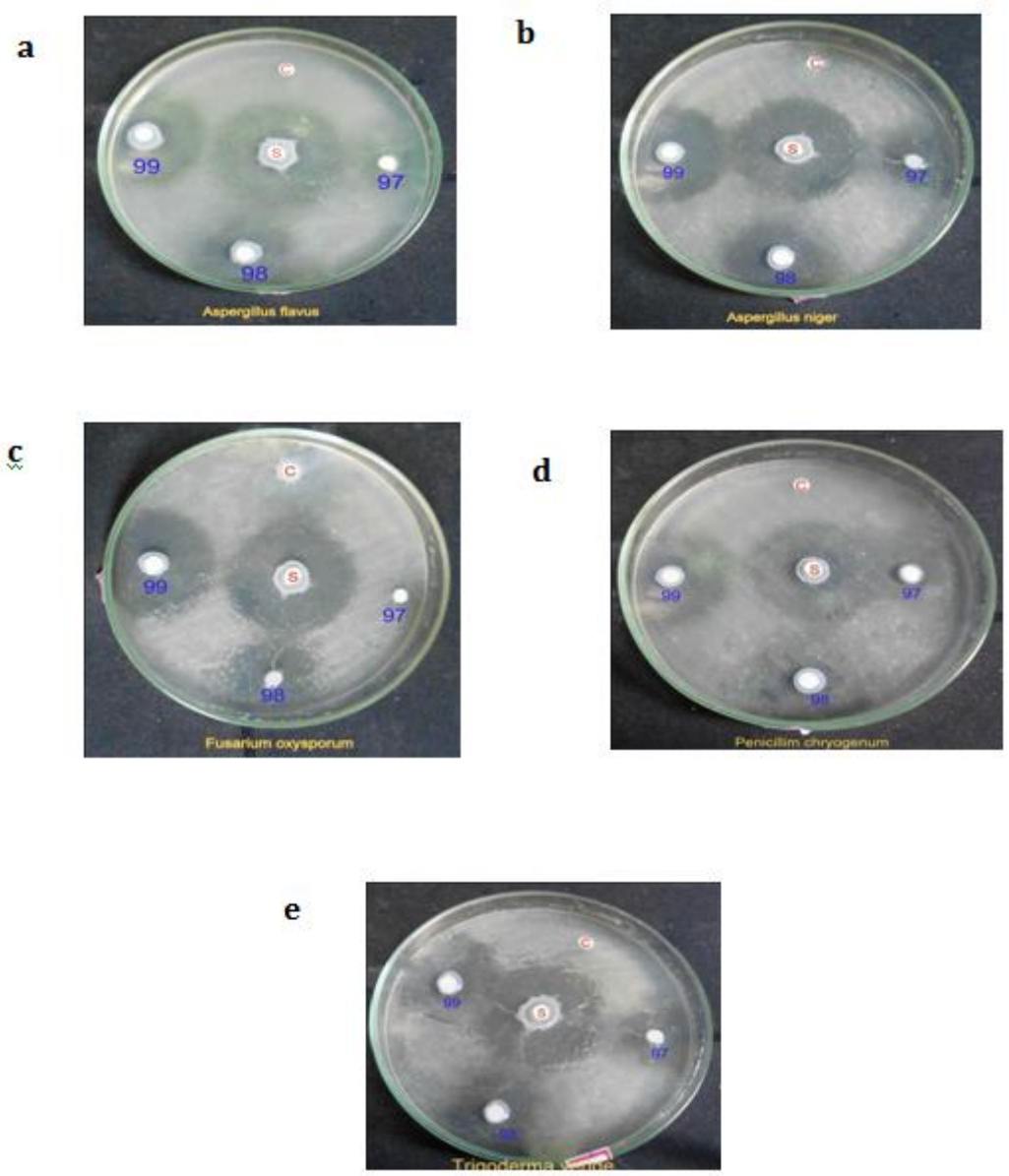


Fig 2 (a-e): Zone of inhibition of 1-3 against *A. flavus, A. niger, F.oxysporum, P.chryogenum and T. veride*

Incorporation of Chloro group at fluoro position of compound 1 (compound 2) group increase fungal activity against most of fungal strains. Compound 2 showed excellent activity against Trigodermaveride (19 mm), while compound 2 showed good activity against Aspergillus niger (16 mm) and Fusarium oxysporum (15mm). Even though compound 2, showed poor activity against Penicillimchryogenum.

Introduce of bromo group at fluoro group of compound**1** (compound **3**) exhibited remarkable changes in all the tested fungal strains. From Table 10, it is clearly seen that compound **3** showed activity in the range 18-24 mm. T. Veride, & A. niger showed moderate activity and A.flavus exhibited poor activity against compound **3.** Compound **3** showed excellent activity against Trigodermaveride (24mm), Fusarium oxysporum (22 mm) and Aspergillus niger (20 mm), while compound **3** showed good activity against Aspergillus flavus (12mm). Fungal strains namely Aspergillus flavus Fusarium oxysporum (18 mm) and Penicillimchryogenum (18 mm). Comparing of compound **3** to othersynthesised compounds **1** and **2** incorporation of bromo group reasonably increases inhibition

activity against most if the fungal strains.

6. CONCLUSION

The appearances C=O and C=C bands at FT-IR spectra were preliminary evidence for the formation of respective chalcone. ^{1}H and ^{13}C NMR spectral date gives conformation regarding preparation of (E)-3-(4-chlorophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one . Compound 3 physical analytical data showed in Table 3, Appearances of C=O and C=C bands in FT-IR spectra were preliminary evidence for the formation of respective chalcone. ^{1}H and ^{13}C NMR spectral date gives conformation regarding preparation of (E)-3-(4-bromophenyl)-1-(2,4-dimethylthiazol-5-yl)prop-2-en-1-one. Antimicrobial analysis results shows that the compound **1** was screened for their antimicrobial activity against bacterial strains viz., *B. subtilis, E. coli, P. aeruginosa, S. aureus &. pyogenes* and fungal strains viz., *A. flavus, A. niger, P. chryogenum, T. veride& F. Oxysporum.* Ciprofloxacin and Amphotericin B were used as standard drugs for bacterial and fungal strains, respectively. The *in vitro* antimicrobial activities of compound **1** showed good activity against B. subtilis and T. veride in bacterial and fungal strains, respectively. The compound **2** was screened for their antimicrobial activity against bacterial strains viz., *B. subtilis, E. coli, P. aeruginosa, S. aureus &. pyogenes* and fungal strains viz., *A. flavus, A. niger, P. chryogenum, T. veride& F. Oxysporum.* Ciprofloxacin and Amphotericin B were used as standard drugs for bacterial and fungal strains, respectively. From the results of antimicrobial analyses of compound **2** showed good activity against S. pyogenes and A. niger in bacterial and fungal strains, respectively. From the results of antimicrobial analyses of compound **3** showed good activity against *B. subtilis* and T. veride in bacterial and fungal strains, respectively.

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