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Synthesis and Evaluation of in vitro Antimicrobial Activity of Novel 2-[2-(Aroyl)aroyloxy]methyl-1,3,4-Oxadiazoles[1]

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Abstract—Synthetic pathway of the ten novel 2-[2-(aroyl)aroyloxy]methyl-1,3,4-oxadiazoles as new potential antimicrobial agents is illustrated. Intramolecular cyclization of 2-(2-aroylaryloxy) aceto hydrazides to 2-[2-(aroyl)aroyloxy]methyl-1,3,4-oxadiazoles was achieved with triethyl orthoformate in good yields. The compounds were characterized by IR, ^{1}H NMR, mass spectra and by means of CHN analysis. The target compounds were tested for their in vitro antimicrobial activity against representative strains by disc diffusion method and micro dilution methods. Several compounds showed antimicrobial activity comparable with or higher than the standard drugs.

Keywords: benzophenones, 1,3,4-oxadiazoles, antimicrobial activity, MIC

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INTRODUCTION

The problem of increasing antimicrobial resistance among bacterial and fungal pathogens is of growing concern to physicians, microbiologists, research scientists and professionals of the pharmaceutical industry [1, 2]. Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased [3]. In general, microorganisms have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents [4]. This is a cause for concern, because a number of patients have suppressed immunity, and due to new bacterial and fungal strains, which are multi-resistant [5]. Consequently, new infections can occur resulting in high mortality [6, 7] Therefore, action must be taken to counter this problem. For example, measures such as the controlled use of antibiotic, development of research to a better understanding of the genetic mechanisms of resistance and to continue studies to develop new drugs, either synthetic such as sulfonamides nitrofuranes, penicillins, cephalosporins, tetracycline's macrolides, and oxazolidinones [8, 9], or natural. The ultimate goal is to offer appropriate and efficient antimicrobial drugs to the patient.

The inhibitors of microorganism growth under standardized conditions may be utilized in demonstrating the therapeutic efficacy of drugs. Any subtle change in the drug molecule, which may not be detected by chemical methods can be revealed by a change in the antimicrobial activity and hence microbiological assays are very useful for resolving doubts regarding possible changes in the potency of drugs and their preparation. The microbial assay is based upon the compulsion of inhibition of growth of microorganisms by marked concentration of the synthetic or natural compounds to be examined with that produced by the known concentration of a standard drug having a known activity [10].

Compounds containing benzophenone [11, 12] and 1,3,4-oxadiazole moieties [13, 14] find a unique place in medicinal chemistry. 1,3,4-Oxadiazole is associated with potent pharmacological activity due to the presence of toxophoric –N=C–O– linkage. Considerable evidences have been gathered to reveal the efficiency of 1,3,4–oxadiazole including antimicrobial activity [15]. The synthesis of oxadiazoles continues to attract interest, due to its interesting structural implications of the biological systems. In view of these observations and our continued interest in the synthesis of biologically active heterocyclic compounds [16], it was worthwhile to synthesize integrated 1,3,4–oxadiazole moiety to a benzophenone framework.

RESULTS AND DISCUSSION

The reaction sequence for the title compounds is outlined in scheme. Compounds (**1a–j**) to (**3a–j**) have been prepared as previously reported by our group [16–18]. Compounds (**3a–j**) with triethyl orthofor-

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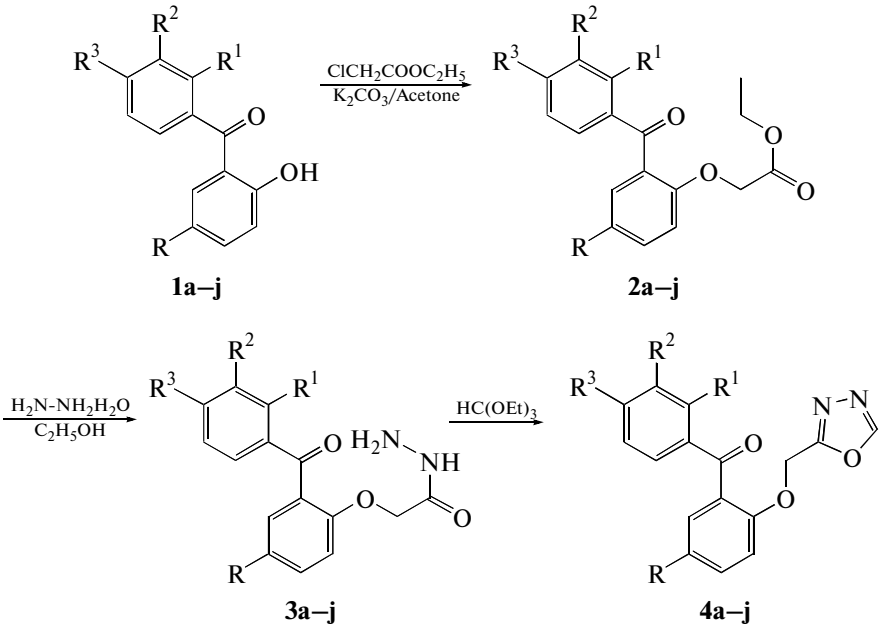
mate underwent intramolecular cyclization, to yield substituted 2-[2-aroylaroyloxymethyl]-1,3,4-oxadiazoles (**4a–j**). The antimicrobial activities of synthesized compounds were screened against eight bacteria and four fungi using in vitro disc diffusion method. The results revealed that most of the synthesized compounds exhibited antimicrobial activities against *Staphylococcus aureus*, *St. aureus* (MRSA), *Enterobacter aerogenes*, *Micrococcus luteus*, *Klebsiella pneumonia*, *Salmonella typhimurium*, *S. paratyphi-B*, *Proteus vulgaris*, *Candida albicans*, *Botyritis cinerea*, *Malassesia pachydermatis*, and *C. krusei* organisms. The results are summarized in Table 1 and 2. Compounds (**4a**), (**4d**), (**4g**), (**4h**), and (**4j**) showed good activity more than standard drug against *S. aureus*. Compound **4a** with methyl and chloro groups at the para position in phenyl ring and the meta position in benzoyl ring, respectively showed good activity against both Gram-positive and Gram-negative bacteria among all synthesized compounds compared with the standard. Among the compounds (**4g–j**) in which chloro group is substituted in the phenyl ring compounds (**4g**), (**4h**) and (**4j**) show good activity against *S. aureus*. Compound (**4a**) showed significant antifungal activity against *B. cinerea* and *C. krusei*. In contrast, compounds (**4b**) and (**4i**) with bromo and (**4c**) with methoxy groups exhibited lowest activity and this can be attributed to the bulkiness of bromo and methoxy groups which might render the molecule to penetrate through the cell wall. The MIC values of active compounds (**4a**), (**4d–h**) and (**4j**) against bacteria and fungi are given in Table 3 and 4 respectively.



a: R = CH_3, $R^1 = R^3 = H$, $R^2 = Cl$
b: R = CH_3, $R^1 = Br$, $R^2 = R^3 = H$
c: R = CH_3, $R^1 = R^2 = H$, $R^3 = OCH_3$
d: R = CH_3, $R^1 = R^2 = R^3 = H$
e: R = CH_3, $R^1 = R^2 = H$, $R^3 = Cl$
f: $R = R^3 = CH_3$, $R^1 = R^2 = H$
g: $R = R^2 = Cl$, $R^1 = R^3 = H$
h: R = Cl, $R^1 = R^2 = R^3 = H$
i: R = Cl, $R^1 = Br$, $R^2 = R^3 = H$
j: R = Cl, $R^1 = R^2 = H$, $R^3 = CH_3$

Scheme 1. Synthesis of 2[2-(aroyl)aroyloxy]methyl-1,3,4-oxadiazoles.

Significant MIC values were observed against Gram-positive and Gram-negative bacteria. Compounds (**4a**), (**4e**), (**4g**), (**4h**) and (**4j**) showed good activity against *S. aureus*. In comparison to compound (**4d**), the presence of chloro group in the benzoyl ring in compounds (**4a**) and (**4e**) increased the potency against *S. aureus* by one fold. Interestingly the presence of chloro group in the phenyl ring in compounds

Table 1. In vitro antibacterial activity of compounds (**4a–j**)

Compounds	Zone of inhibition in mm							
	gram-positive bacteria				gram-negative bacteria			
	S. aureus	*S. aureus* (MRSA)	*E. aerogenes*	*M. luteus*	*K. pneumonia*	*S. typhimurium*	*S. paratyphi-B*	*P. vulgaris*
(4a)	19	17	22	23	25	26	29	27
(4b)	10	9	9	10	11	10	9	9
(4c)	11	9	9	10	9	10	7	11
(4d)	18	9	11	14	14	16	10	11
(4e)	16	13	14	14	14	13	12	10
(4f)	15	11	15	13	11	17	9	12
(4g)	23	14	13	19	13	20	11	16
(4h)	21	13	17	18	11	20	9	13
(4i)	12	10	10	11	10	12	7	9
(4j)	23	15	18	16	14	23	9	17
Streptomycin	17	22	24	26	22	25	19	24

(**4g**), (**4h**) and (**4j**) increased the potency against *S. aureus* by two fold. In comparison to compound **4d** in **4a** the potency is increased by two fold against bacteria *S. paratyphi-B*, three fold by *S. aureus* (MRSA) and *S. typhimurium*, four fold by *M. luteus* and *K pneumonia* and fivefold by *E. aerogenes*. Besides, the potency of compound (**4a**) is increased by two fold against fungi *B. cinerea*, three fold by *C. krusei* and four fold by *C. albicans* compared to compound (**4d**). In general, compound (**4a**) showed better activity than standard drugs for most of the tested bacteria and fungi.

EXPERIMENTAL

Chemicals were purchased from Aldrich Chemical Co. TLC was performed on aluminum-backed silica plated with visualization by UV-light. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded in Nujol on FT-IR Shimadzu 8300 spectrometer and ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were obtained with a VG70-70H mass spectrometer and the elemental analysis (C, H, and N) was performed on Elementar Vario EL III elemental analyzer.

Table 2. In vitro antifungal activity of compounds **4a–j**

Compounds	Zone of inhibition in mm			
	C. albicans	*B. cinerea*	*M. pachydermatis*	*C. krusei*
(4a)	19	16	20	22
(4b)	9	11	10	12
(4c)	9	7	10	8
(4d)	11	10	12	14
(4e)	9	10	13	14
(4f)	15	11	13	12
(4g)	11	9	12	10
(4h)	11	12	11	13
(4i)	10	9	10	7
(4j)	13	12	11	15
Ketoconazole	22	10	26	16

The synthesis of the hitherto unreported title compounds is as outlined in scheme in 65–73.5% yield. Hydroxy benzophenones (**1a–j**) on reaction with ethyl chloroacetate affords ethyl (2-aroylaryloxy)acetates (**2a–j**) in excellent yield, which on treatment with hydrazine hydrate yields corresponding 2-(2-aroylaryloxy)acetohydrazides (**3a–j**) [16–18]. Intramolecular cyclization of (**3a–j**) with triethyl orthoformate resulted substituted 2-[2-aroylaroyloxymethyl]-1,3,4-oxadiazoles (**4a–j**).

Synthesis of 2-[2-(3-chlorobenzoyl)-4-methylphenoxy]methyl-1,3,4-oxadiazole (4a): A suspension of compound (**3a**) (0.52 g, 1.6 mmol) in triethyl orthoformate (10 mL) was refluxed until (**3a**) disappeared. A solid was separated on cooling, which was filtered off, dried and recrystallized from ethanol to afford compound (**4a**). Compounds (**4b–h**) were synthesized analogously starting with derivatives (**3b–h**), respectively.

(**4^a**): Yield 72%. Mp 116–118°C; IR (Nujol): 1648 (C=N), 1665 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 2.3 (3 H, s, CH_3), 4.55 (2 H, s, CH_2), 6.85–7.7 (7 H, m, Ar-H), 9.4 (1 H, s, oxadiazole-H). MS: *m/z* 328.5 (M^+, 78), 301.5 (49.5), 299.5 (52.5), 285.5 (36.5), 139.5

Table 3. MIC (μg/mL) of compounds **4a–j** against tested bacteria

Compounds	Minimum inhibitory concentration (μg/mL)							
	gram-positive bacteria				gram-negative bacteria			
	S. aureus	*S. aureus* (MRSA)	*E. aerogenes*	*M. luteus*	*K. pneumonia*	*S. typhimurium*	*S. paratyphi-B*	*P. vulgaris*
(4a)	31.25	62.5	15.62	15.62	15.62	15.62	125	<15.62
(4d)	62.5	500	500	250	250	125	500	500
(4e)	31.25	125	125	63.5	63.5	250	125	250
(4f)	250	500	250	250	500	62.5	500	500
(4g)	15.62	250	250	32.5	250	31.25	500	62.5
(4h)	15.62	250	62.5	62.5	550	31.25	500	125
(4j)	15.62	125	62.5	125	250	15.62	500	125
Streptomycin	6.25	>100	25	6.25	6.25	30	ni	6.25
Ciprofloxacin	<0.78	>100	<0.78	>100	<0.78	>100	6.25	<0.78

ni = no inhibition.

(100), 111.5 (13.5). Anal. calcd. for $C_{17}H_{13}ClN_2O_3$ (328.5): C, 62.11; H, 3.99; Cl, 10.78; N, 8.52. Found: C, 62.09; H, 3.95; Cl, 10.75; N, 8.50%.

2-[2-(2-Bromobenzoyl)-4-methylphenoxy]methyl-1,3,4-oxadiazole (4b). Yield 73%. Mp 131–133°C; IR (Nujol): 1655 (C=N), 1674 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.3 (3 H, s, CH_3), 4.51 (2 H s, CH_2), 6.8–7.75 (7 H, m, Ar-H), 9.3 (1 H, s, oxadiazole-H); MS: *m/z* 373 (M^+, 77), 345 (49), 346 (53), 330 (37), 184 (100), 157 (13). Anal. calcd. for $C_{17}H_{13}BrN_2O_3$ (373): C, 54.69; H, 3.48; Br, 21.44, N, 7.50. Found: C, 54.67; H, 3.45; Br, 21.84, N, 7.30%.

2-[2-(4-Methoxybenzoyl)-4-methylphenoxy]methyl-1,3,4-oxadiazole (4c). Yield 73%. Mp 135–138°C; IR (Nujol): 1650 (C=N), 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.25 (3 H s, CH_3), 3.8 (3 H, s, OCH_3), 4.5 (2 H, s, CH_2), 6.9–7.8 (7 H, m, Ar-H), 9.35 (1 H, s, oxadiazole-H); MS: *m/z* 324 (M^+, 77.5), 297 (49.5), 295 (54), 281 (38), 135 (100), 107 (14). Anal. calcd. for $C_{18}H_{16}N_2O_4$ (324): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.63; H, 4.92; N, 8.61%.

2-(2-Benzoyl-4-methylphenoxy)methyl-1,3,4-oxadiazole (4d). Yield 73.5%. Mp 112–114°C; IR (Nujol): 1653 (C=N), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.28 (3 H, s, CH_3), 4.52 (2 H, s, CH_2), 6.85–7.8 (8 H, m, Ar-H), 9.3 (1 H, s, oxadiazole-H); MS: *m/z* 294 (M^+, 76), 267 (47), 265 (52), 251 (35), 105 (100), 77 (12). Anal. calcd. for $C_{17}H_{14}N_2O_3$ (294): C, 69.38; H, 4.79; N, 9.52. Found: C, 69.31; H, 4.72; N, 9.48%.

2-[2(4-Chlorobenzoyl)-4-methylphenoxy]methyl-1,3,4-oxadiazole (4e). Yield 71%. Mp 118–120°C; IR (Nujol): 1655 (C=N), 1673 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.25 (3 H, s, CH_3), 4.53 (2 H, s, CH_2), 6.8–7.8 (7 H, m, Ar-H), 9.36 (1 H, s, oxadiazole-H); MS: *m/z* 328.5 (M^+, 76.5), 301.5 (46.5), 299.5 (50.5), 285.5 (35.5), 139.5 (100), 111.5 (12.5). Anal. calcd. for $C_{17}H_{13}ClN_2O_3$(328.5): C, 62.11; H, 3.99; Cl, 10.78; N, 8.52. Found: C, 62.06; H, 3.91; Cl, 10.72; N, 8.51%.

2-[2(4-Methylbenzoyl)-4-methylphenoxy]methyl-1,3,4-oxadiazole (4f). Yield 72%. Mp 120–122°C; IR (Nujol): 1650 (C=N), 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.32 (6 H, s, $2CH_3$), 4.55 (2 H, s, CH_2), 6.85–7.7 (7 H, m, Ar-H), 9.4 (1 H, s, oxadiazole-H);

Table 4. MIC (μg/mL) of compounds **4a–j** against tested fungi

Compounds	Minimum inhibitory concentration (μg/mL)			
	C. albicans	*B. cinerea*	*M. pachydermatis*	*C. krusei*
(4a)	31.5	125	250	31.5
(4d)	500	500	250	250
(4e)	250	250	125	125
(4f)	125	500	250	125
(4g)	500	500	250	250
(4h)	500	250	500	250
(4j)	250	250	500	250
Fluconazole	>100	ni	12.5	12.5
Ketoconazole	25	25	15	15

ni = no inhibition.

MS: *m/z* 308 (M^+, 78), 280 (50), 281 (53), 265 (38), 119 (100), 92 (14). Anal. calcd. for $C_{18}H_{16}N_2O_3$ (308): C, 70.12; H, 5.19; N, 9.09. Found: C, 70.15; H, 5.15; N, 9.07%.

2-[2(3-Chlorobenzoyl)-4-chlorophenoxy]methyl-1,3,4-oxadiazole (4g). Yield 68%. Mp 124–126°C; IR (Nujol): 1635 (C=N), 1655 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.55 (2 H, s, CH_2), 6.85–7.7 (7 H, m, Ar-H), 9.4 (1 H, s, oxadiazole-H); MS: *m/z* 349 (M^+, 78.5), 322 (50), 320 (53), 306 (38), 139.5 (100), 111.5 (14). Anal. calcd. for $C_{16}H_{10}Cl_2N_2O_3$ (349): C, 55.04; H, 2.89; Cl, 20.31; N, 8.02. Found: C, 55.01; H, 2.85; Cl, 20.28; N, 8.05%.

2-(2-Benzoyl-4-chlorophenoxy)methyl-1,3,4-oxadiazole (4h). Yield 70%. Mp 126–128°C; IR (Nujol): 1640 (C=N), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.55 (2 H, s, CH_2), 6.8–7.7 (7 H, m, Ar-H), 9.2 (1 H, s, oxadiazole-H); MS: *m/z* 314.5 (M^+, 79), 287.5 (51), 285.5 (54), 271.5 (39), 105 (100), 77 (15). Anal. calcd. for $C_{16}H_{11}ClN_2O_3$ (314.5): C, 61.06; H, 3.52; Cl, 11.26; N, 8.90. Found: C, 61.02; H, 3.56; Cl, 11.21; N, 8.96%.

2-[2(2-Bromobenzoyl)-4-chlorophenoxy]methyl-1,3,4-oxadiazole (4i). Yield 65%. Mp 100–102°C; IR (Nujol): 1655 (C=N), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.5 (2 H, s, CH_2), 6.9-7.65 (7 H, m, Ar-H), 9.1 (1 H, s, oxadiazole-H); MS: *m/z* 393.5 (M^+, 77), 366.5 (50), 364.5 (53), 350.5 (38), 184 (100), 157 (16). Anal. calcd. for $C_{16}H_{10}BrClN_2O_3$ (393.5): C, 48.82; H, 2.56; Br, 20.30; Cl, 9.01; N, 7.12. Found: C, 48.72; H, 2.48; Br, 20.39; Cl, 9.11; N, 7.06%.

2-[2(4-Methylbenzoyl)-4-chlorophenoxy]methyl-1,3,4-oxadiazole (4j). Yield 65%. Mp 138–140°C; IR (Nujol): 1630 (C=N), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.2 (3 H, s, CH_3), 4.6 (2 H, s, CH_2), 6.9–7.6 (7 H, m, Ar-H), 9.2 (1 H, s, oxadiazole-H); MS: *m/z* 328.5 (M^+, 75), 301.5 (47), 299.5 (51), 285.5 (35), 119 (100), 92 (12). Anal. calcd. for $C_{17}H_{13}ClN_2O_3$ (328.5): C, 62.11; H, 3.99; Cl, 10.78; N, 8.52. Found: C, 62.05; H, 3.88; Cl, 10.68; N, 8.47%.

Materials and methods for the antimicrobial activity: Streptomycin and ciprofloxacin (Sigma) were used as positive controls against bacteria. Fluconazole and ketoconazole (Himedia, Mumbai) were used as positive controls against fungi.

The following Gram-positive bacteria were used for the experiments; *S. aureus (MTCC 7443), S. aureus (MRSA) (MTCC 84), E. aerogenes (MTCC 111), M. luteus (MTCC 1538)*. The Gram-negative bacteria included, *K. pneumonia (MTCC 109), S. typhimurium (MTCC 2488), S. paratyphi-B (MTCC 733), P. vulgaris (MTCC 321). In addition, fungi C. albicans (MTCC 227), B. cinerea (MTCC 2880), M. pachydermatis, C. krusei (MTCC 231)* were also used for the experiments. All cultures were obtained from the Department of Microbiology, Manasagangotri, Mysore.

Bacterial inoculums were prepared by growing cells in Mueller Hinton Broth (MHA) (Himedia) for 24 h at 37°C. These cell suspensions were diluted with sterile MHB to provide initial cell counts of about 10^4 CFU/ml. The filamentous fungi were grown on sabouraud dextrose agar (SDA) slants at 28°C for 10 days and the spores were collected using sterile doubled distilled water and homogenized.

Antibacterial activity was carried out using a disc diffusion method [20]. Petri plates were prepared with 20 mL of sterile Mueller Hinton Agar (MHA) (Himedia, Mumbai). The test cultures were swabbed on the top of the solidified media and allowed to dry for 10 min. The tests were conducted at 1000 μg/disc. The loaded discs were placed on the surface of the medium and left for 30 min at room temperature for compound diffusion. Negative control was prepared using respective solvent. Streptomycin (10 μg/disc) was used as positive control. The plates were incubated for 24 h at 37°C for bacteria and 48 h at 27°C for fungi. Zone of inhibition was recorded in millimeters and the experiment was repeated twice.

Minimum inhibitory concentration (MIC) studies of synthesized compounds were performed according to the standard reference method for bacteria [21] and filamentous fungi. Required concentrations (1000 μg/mL, 500 μg/mL, 250 μg/mL, 125 μg/mL, 62.5 μg/mL, 31.25 μg/mL and 15.62 μg/mL) of the compound was dissolved in DMSO (2%), and diluted to give serial two-fold dilutions that were added to each medium in 96 well plates. An inoculum of 100 mL from each well was inoculated. The anti-fungal agents ketoconazole, fluconazole for fungi and streptomycin, ciprofloxacin for bacteria were included in the assays as positive controls. For fungi, the plates were incubated for 48–72 h at 28°C and for bacteria the plates were incubated for 24 h at 37°C. The MIC for fungi was defined as the lowest extract concentration, showing no visible fungal growth after incubation time. 5 mL of tested broth was placed on the sterile MHA plates for bacteria and incubated at respective temperatures. The MIC for bacteria was determined as the lowest concentration of the compound inhibiting the visual growth of the test cultures on the agar plate.

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