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Synthesis and Antimicrobial Evaluation of Newtetrazolyl-*N*-substituted Maleimideand Phthalimide Derivatives

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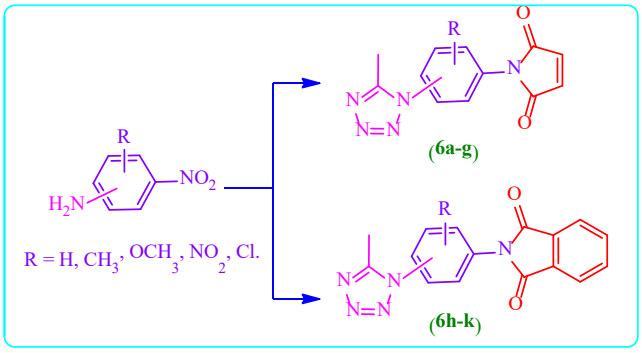
ABSTRACT

In the present study, a series of new tetrazolyl-N-substituted maleimide (6a-g) and phthalimide (6h-k) derivatives have been synthesized.The structures of newly synthesized compounds were confirmed by their IR,1H NMR and 13C NMR spectral data. All synthesized compounds were screened for their in vitroantimicrobial activities against both gram positive and gram negative bacterial pathogens. Among the screened compounds, 6b, 6c, 6e, 6f, 6g and 3k were shown good antimicrobial activities.



Keywords: Tetrazole, Maleimide, Phthalimide, Trifluroacetic acid, Antimicrobial activity.

INTRODUCTION

Antimicrobial resistance has become a severehazard tohuman health and themostchallenging issue to worldwide researchers [1]. According to theWorld Health Organization, everydaythousandsof peoples are dying due to microbialinfections [2]. There are several reasons for rise in microbial resistance. Themutationin genetic material, transfer of drug-resistant genes from onemicrobe to another, replication and spreading of survivor resistantstrains [3], improper use of antibiotics in viral infection,incorrect diagnosis referring broad spectrum antibiotic over a narrow spectrum antibiotic, notfinishing complete course, overuse of antibiotics [4], unhygienicenvironment [5]are the few of them [6]. Broad-spectrum antibiotics have displayed to select for resistance mechanisms in non-target species that are readily transferred to pathogenic bacteria [7]. The use of broad-spectrum antibiotics can leads toundesirabledistractions to the microbiota, which has serious roles in various features of human biology [8]. The innovation of antimicrobial agents with aninnovative model of action is in urgent need for the clinical management of microbial resistance [9].

Maleic anhydride was prepared for the first time two centuries ago bythe catalytic oxidation of benzene using vanadium pentoxide

[10].Being a multifunctionalentity, it finds applications in nearly every field of both laboratory and industrialchemistry. It has been used as potential building block in organic synthesis. It is aversatile synthon wherein all the sites are amenable for a variety of reactions andpossesses exceptionally selective reactivity towards several nucleophiles. A vast array ofnucleophilic reactions undergone by maleicanhydrides confer a high synthetic potentialon them [11]. In the past century, several symmetrically and unsymmetrically substitutedmaleic anhydride derivatives have been prepared. They have been used extensively in the synthesis of a widearray of key intermediates employed in the heavy and fine chemical industries [12].

Maleimides are important class of organic compounds due to their pharmacological and chemical applications [13]. It isimportant nucleusin many bioactive molecules possessing various activities such as CNS depressant [14],antispasmodic [15],nerve conduction blocking [16], analgesic [17], antitumor [18],anti-convulsant [19],antibacterial [20], antifungal [21], and anti-tubercular [22].The *N*-substituted succinimides are important compounds of many drugs and drug moieties.In literature number of methodsare reported for the synthesis of maleimides by dehydration of water molecule from maleamic acidssuch as using of acetic anhydride and sodium acetate [23],molting method [24],maleic acid salt [25],phase transfer catalysis [26],trifluroacetic acid [27].One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having significance applications as therapeutic agents. We have reportedsome new tetrazole containing maleamic and phthaleamic acid derivatives as potential *β*-lactamase enzyme inhibitors [28].

In continuation with our efforts towards the synthesis of new bioactive heterocyclic compounds having antimicrobial activities [29], herewith,we are reporting the synthesis of new tetrazolyl-*N*-substituted maleimide and phthalimide derivatives (6a-k) and their antimicrobial screening against both Gram positive and Gram negative pathogens.

EXPERIEMENTAL SECTION

Materials and methods

All the chemicals used were of laboratory-grade. The melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-300 and 400 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a Bruker DRX-75 and 100 MHz NMR in $CDCl_3$. The chemical shifts are in (ppm). The coupling constants (*J*) are reported in hertz (Hz).

General procedure for the synthesis of tetrazolyl-N-substituted maleimide (6a-g) andphthalimide derivatives (6h-k)

The maleamic (5a-g) or phthaleamic acids (5h-k) (10 mmol) was taken in 50 ml round bottom flaskcontaining acetonitrile (20 ml). The catalytic amount of trifluroacetic acid was added in it. The reaction mixture was reflux at 65-700C temperature for appropriate time (Table 1). The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled at room temperature. The solvent was evaporated under reduced pressure. The crude product was extracted by ethyl acetate. The organic layer was washed with water and brine solution. The organic layer was dried over anhydrous sodium sulphate. Then, the solvent ethyl acetate was evaporated under reduced pressure. The crude product obtained was crystalized from ethanol to furnish the corresponding tetrazolyl-N-substituted maleimide (6a-g) and phthalimide derivatives (6h-k)with 62-76 % yields.

1-(3-Methyl-4-(5-methyl-1*H*-tetrazol-1-yl)phenyl)-1*H*-pyrrole-2,5-dione (6a): Yield: 73%; M. P.: 110-112°C; IR (Neat) ν=3065, 2942, 1710, 1619, 1587, 1490, 1441, 1395, 1256, 1134, 1037, 885 cm-1; 1H NMR (400 MHz, CDCl3) δ=1.90 (s, 3H), 2.44 (s, 3H), 6.97 (s, 2H), 7.48 (d, J=8 Hz, 1H), 7.62 (dd, J=4 & 8 Hz, 1H), 7.76 (d, J=8 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ=11.50, 16.29, 118.67, 121.37, 122.90, 129.75, 133.15, 134.39, 140.20,158.72, 163.64.90; Anal. calcd. for C13H11N5O2: C, 57.99; H, 4.12; N, 26.01; Found: C, 57.98; H, 4.11; N, 26.03.

1-(3-Methoxy-4-(5-methyl-1H-tetrazol-1-yl)phenyl)-1H-pyrrole-2,5-dione (6b): Yield: 76%; M. P.: 129-131 °C; IR (Neat) *ν*=3115, 2938, 2855, 1711, 1607, 1590, 1479, 1454, 1405, 1260, 1040, 866, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*=2.39 (s, 3H), 3.76 (s, 3H), 6.92 (s, 2H), 7.38 (d, *J*=4 Hz, 1H), 7.42 (dd, *J*=4 & 8 Hz, 1H), 7.56 (d, *J*=8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*=11.37, 56.42, 105.12, 110.28, 113.91, 131.92, 133.75, 135.92, 154.35, 159.13, 162.27; Anal. calcd. for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55; Found: C, 54.71; H, 3.90; N, 24.57.

1-(5-Methyl-2-(5-methyl-1*H*-tetrazol-1-yl)phenyl)-1*H*-pyrrole-2,5-dione (6c):Yield: 65%; M. P.: 150-152 oC; IR (Neat) ν=3039, 2962, 1711, 1607, 1593, 1491, 1439, 1380, 1251, 1147, 1033, 930, 880 cm-1; 1H NMR (400 MHz, CDCl3) δ=1.90 (s, 3H), 2.43 (s, 3H), 6.95 (s, 2H), 7.52 (d, J=8 Hz, 1H), 7.78 (dd, J=4 & 8 Hz, 1H), 7.82 (d, J=8 Hz, 1H); Anal. calcd. for C13H11N5O2: C, 57.99; H, 4.12; N, 26.01; Found: C, 57.97; H, 4.11; N, 26.03.

1-(4-(5-Methyl-1H-tetrazol-1-yl) phenyl)-1H-pyrrole-2,5-dione (6d): Yield: 74%; M. P.: 170-172 oC; IR (Neat) ν=3140, 3007, 2980, 1715, 1610, 1577, 1488, 1449, 1402, 1280, 1110, 1039, 855, 743 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.56 (s, 3H), 6.80 (s, 2H), 7.46 (d, J=8 Hz, 2H), 7.92 (d, J=8 Hz, 2H); Anal. calcd. for C12H9N5O2: C, 56.47; H, 3.55; N, 27.44; Found: C, 56.49; H, 3.54; N, 27.42.

1-(4-Methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)-1H-pyrrole-2,5-dione (6e): Yield: 69%; M. P.: 138-140 oC; IR (Neat) ν=3055, 2944, 2876, 1719, 1627, 1571, 1510, 1460, 1376, 1245, 965, 880, 789 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.10 (s, 3H), 2.49 (s, 3H), 6.97 (s, 2H), 7.46 (d, J=8 Hz, 1H), 7.64 (dd, J=4 & 8 Hz, 1H), 7.70 (d, J=4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ=11.88, 17.74, 122.89, 124.54, 129.85, 132.65, 139.31, 145.13, 152.53, 155.37, 167.98; Anal. calcd. for C13H11N5O2: C, 57.99; H, 4.12; N, 26.01; Found: C, 58.02; H, 4.09; N, 25.99.

1-(4-(5-Methyl-1H-tetrazol-1-yl)-3-nitrophenyl)-1H-pyrrole-2,5-dione (6f): Yield: 72%; M. P.: 122-124 oC; IR (Neat) ν=3049, 2943, 1714, 1610, 1589, 1494, 1405, 1376, 1123, 1019, 847, 732 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.64 (s, 3H), 6.93 (s, 2H), 7.59 (d, J=8 Hz, 1H), 7.68 (m, 2H); Anal. Calcdfor C12H8N6O4: C, 48.01; H, 2.69; N, 27.99; Found: C, 48.04; H, 2.67; N, 27.97.

1-(3-Chloro-4-(5-methyl-1H-tetrazol-1-yl)phenyl)-1H-pyrrole-2,5-dione (6g): Yield: 74%; M. P.: 120-122 oC; IR (Neat) ν=3064, 2944, 1712, 1615, 1581, 1488, 1390, 1247, 1119, 1034, 873 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.65 (s, 3H), 6.93 (s, 2H), 7.53 (d, J=8 Hz, 1H), 7.59 (m, 2H), 7.69 (d, J=4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ=11.65, 110.32, 118.20, 124.34, 130.12, 134.67, 145.71, 151.47, 153.17, 166.16; Anal. Calcdfor C12H8ClN5O2: C, 49.75; H, 2.78; Cl, 12.24; N, 24.18;; Found: C, 49.73; H, 2.79; Cl, 12.25; N, 24.15.

2-(3-Methoxy-4-(5-methyl-1H-tetrazol-1-yl)phenyl)isoindoline-1,3-dione (6h): Yield: 73%; M. P.: 163-165 oC; IR (Neat) ν=3112, 3045, 2956, 1714, 1622, 1580, 1476, 1388, 1244, 1127, 989, 835 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.46 (s, 3H), 3.88 (s, 3H), 7.24 (m, 1H), 7.33 (d, J=8 Hz, 2H), 7.51 (d, J=8 Hz, 1H), 7.86 (d, J=8 Hz, 2H), 8.01 (d, J=4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ=29.84, 56.44, 110.75, 115.42, 121.66, 124.23, 128.52, 158.79, 135.05, 138.91, 154.12, 156.90, 166.51; Anal. calcd. for C17H13N5O3: C, 60.89; H, 3.91; N, 20.89; Found: C, 60.91; H, 3.92; N, 20.86.

2-(4-(5-Methyl-1H-tetrazol-1-yl)phenyl)isoindoline-1,3-dione (6i): Yield: 65%; M. P.: 191-193 oC; IR (Neat) ν=3057, 2942, 1708, 1620, 1584, 1498, 1459, 1367, 1291, 1077, 840, 776 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.69 (s, 3H), 7.64 (m, 2H), 7.78 (m, 2H), 7.85 (m, 2H), 8.01 (m, 2H); 13C NMR (100 MHz, CDCl3) δ=29.85, 56.44, 122.92, 124.25, 126.49, 127.68, 133.43, 135.02, 143.65, 153.86, 169.01; Anal. calcd. for C16H11N5O2: C, 62.95; H, 3.63; N, 22.94; Found: C, 62.92; H, 3.65; N, 22.92.

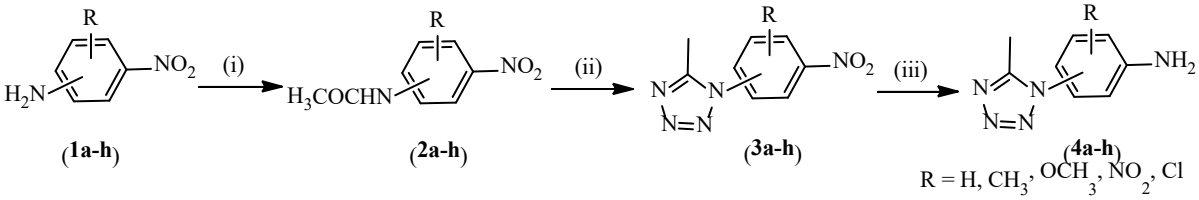
2-(3-Methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)isoindoline-1,3-dione (6j): Yield: 75%; M. P.: 154-156 oC; IR (Neat) ν=3060, 2938, 1713, 1625, 1598, 1479, 1464, 1387, 1244, 1121, 1041, 890 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.14 (s, 3H), 2.50 (s, 3H), 7.36 (d, J=8 Hz, 1H), 7.57 (m, 2H), 7.85 (m, 2H), 8.00 (m, 2H); Anal. calcd. for C17H13N5O2: C, 63.94; H, 4.10; N, 21.93; Found: C, 63.90; H, 4.12; N, 21.96.

2-(4-Methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)isoindoline-1,3-dione (6k): Yield: 62%; M. P.: 144-146 oC; IR (Neat) ν=3120, 3043, 2922, 1711, 1614, 1586, 1510, 1463, 1391, 1220, 1156, 1041, 963, 876 cm-1; 1H NMR (400 MHz, CDCl3) δ=2.12 (s, 3H), 2.48 (s, 3H), 7.39 (d, J=8 Hz, 1H), 7.48 (m, 2H), 7.79 (m, 2H), 8.01 (m, 2H); Anal. calcd. for C17H13N5O2: C, 63.94; H, 4.10; N, 21.93; Found: C, 63.97; H, 4.08; N, 21.92.

RESULTS AND DISCUSSION

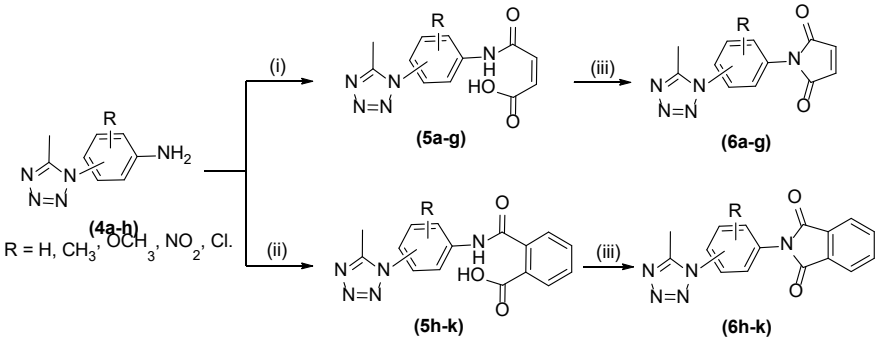
Chemistry

The synthetic sequence followed for the synthesis of tetrazolyl-*N*-substituted maleimideand phthalimide derivatives (6a-k) is as shown in Schemes 1 and 2. In the first, we have synthesized 1, 5-disubstituted tetrazole containing amines (4a-h) [30].



Scheme 1: Reaction Conditions: (i) Ac2O, Pyridine, DCM, rt; (ii) NaN3, TiCl4, CH3CN, rt;(iii) NaBH4, Ni(OAc)2.4H2O, CH3CN + H2O (3:1), rt

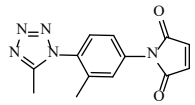
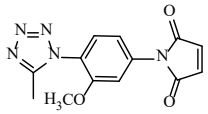
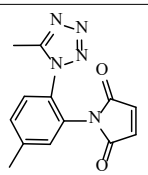
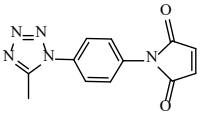
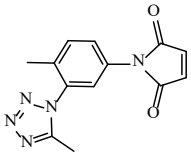
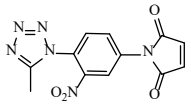
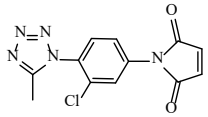
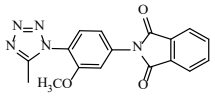
In the second step, the synthesized 1, 5-disubstituted tetrazole containing amines (4a-h) and maleic anhydride and phthalic anhydride were stirred in DCM at room temperature for 8h to furnish the corresponding maleamic (5a-g) and phthaleamic acids (5h-k), respectively [31]. The trifluroacetic acid catalyseddehydrative cyclization of maleamic (5a-g) and phthaleamic acids (5h-k) in acetonitrile furnished the corresponding tetrazolyl-N-substituted maleimide (6a-g) and phthalimide derivatives (6h-k), respectively (Scheme 2).

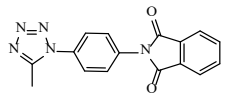
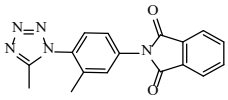
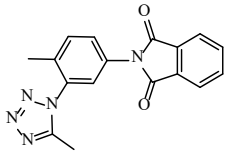


Scheme 2: Reaction Conditions: (i) Maleic anhydride, DCM, rt; (ii) Phthalic anhydride, DCM, rt; (iii) TFA, CH3CN, 65-70°C

The structures of synthesized compounds were confirmed by 1H NMR and 13C NMR spectral technique. The yields and physical data of all the derivatives are summarized in Table 1.

Table 1: Structures of synthesized compounds

Entry	Products (6a-k)	Time (h)	M.P. (°C)	Yield (%)
6a		2	110-112	73
6b		4	129-131	76
6c		5	150-152	65
6d		6	170-172	74
6e		3.5	138-140	69
6f		4.5	122-124	72
6g		5.5	120-122	74
6h		2.5	163-165	73

6i		5	191-193	65
6j		4	154-156	75
6k		3	144-146	62

Antimicrobial activity

The *in vitro* antimicrobial activity of all synthesized compounds was evaluated by using agar well diffusion method [32]. The both Gram positive pathogens *Staphylococcus aureus* ATCC 6538*, Micrococcus luteus*ATCC 9341, *Bacillus subtilis*ATCC 6633 and Gram negative pathogens *Escherichia coli* ATCC8739*, Salmonella typhi*ATCC9207*, Shigellaboydii*ATCC 12034*, Enterobacteraerogenes*ATCC13048*, Pseudomonas aeruginosa* ATCC9027, *Salmonella abony*NCTC6017 has been used for antimicrobial screening. The antifungal activity of synthesized compounds was determined against *Aspergillusniger*ATCC 16404*, Saccharomyces cerevisiae*ATCC 9763, *Candida albicans*ATCC10231 fungal pathogens. Tetracycline and fluconazole were used as antibacterial and antifungal standard reference compounds, respectively. The synthesized compounds (**6a-k**) were dissolved in DMSO at a concentration of 1mg/ml. Each bacterium and fungi was inoculated into sterile Nutrient broth medium and kept at 37°C for 24 h for developing inoculums, and then this broth was used for the study. Using sterile saline, the bacterial suspension was diluted to adjust the turbidity to the 0.5 McFarland standards. 200µL diluted suspension of each pathogen was inoculated on sterile Mueller Hinton agar plates. Wells were punched in the agar medium. Using Micropipette, 100µl of the each compound solution was put in a separate well. 100µl of DMSO solution without any compound was also placed in a well to check its activity against the pathogenic culture. All Petri dishes were incubated for 24 h at 37°C. A clear zone around the well was considered as positive results. After complete incubation, the antimicrobial activity of the synthesized compounds (**6a-k**) was measured. The zones were measured and recorded by using scale in millimetre (mm). The compounds **6b**, **6c**, **6e**, **6f,6g** and **6k** have shown good antibacterial and antifungal activities (Table 2).

Table 2: Results of antimicrobial assay of synthesized compounds against potent pathogens

Compounds → Pathogens ↓	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**	**6j**	**6k**	**Standard**
S. aureus	--	18	24	--	12	12	18	--	--	--	10	33
M. luteus	--	20	22	--	12	16	16	--	--	--	24	32
B. subtilis	--	18	22	--	06	05	13	--	--	--	06	34
E. coli	--	14	09	--	10	06	12	--	--	--	05	29
S. typhi	--	10	11	07	07	08	08	--	--	--	--	27
S. boydii	--	18	26	06	10	12	16	--	--	--	08	30
E. aerogenes	--	06	06	--	--	04	06	--	--	--	05	29
P. aeruginosa	--	19	22	--	11	06	25	--	--	--	12	33
S. abony	--		13	--	12	10	11	--	--	--	--	30
A. niger	--	12	15	--	--	16	12	--	--	--	--	30
S. cerevisiae	--	28	30	--	--	16	16	--	--	--	20	32
C. albicans	--	25	28	08	--	12	20	--	--	--	12	32
Note: (--)=Not active												

Minimal inhibitory concentration (MIC)

The Minimum inhibitory concentration (MIC) is the lowest concentration of a specific compound that inhibits the visible growth of a specific microorganism after overnight incubation. The compounds with less MIC values are more potent in killing pathogens. In this research study, the MIC was determined for the most potent selected antimicrobial compounds. The MIC was deduced by following the method and guidelines of Clinical and Laboratory Standard Institute (CLSI). From this study, it would not be erroneous to say that 6b, 6c,6e,6f, 6g and6k compounds are good candidates for inhibiting the potent pathogens and could serve as potent drug in near future. All experiments were performed in triplicates and results are expressed as mean ± SD in µg/ml (Table 3).

Table 3: MIC values of most potent compounds

Compounds → Pathogens ↓	**6b**	**6c**	**6e**	**6f**	**6g**	**6k**	**Standard**
B. subtilis	160	120	90	115	140	90	15 (Tetracycline)
E. aerogenes	100	80	65	75	200	270	25(Tetracycline)
C. albicans	120	95	120	110	180	210	20(Fluconazole)

CONCLUSION

In summary, a series of new tetrazolyl -*N*-substituted maleimide and phthalimide derivatives have been synthesized and evaluated for their *in vitro* antimicrobial activities. The six compounds, 6b, 6c, 6e, 6f, 6g and 6k have shown excellent antimicrobial activities. It would not be specious to say that these newly synthesized compounds are good candidates for inhibiting the potent antibacterial and antifungal pathogens. We hope that on structural modifications, it will leads to a potent antimicrobial agents.

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