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Synthesis and antimicrobial activity of some new Mannich base derivatives

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ABSTRACT

A series of new mannich base derivatives 4-(furan-2-yl(2-(furan-2-ylmethylene)hydrazinyl)methyl)morpholine (**1-6**) were synthesized and synthesized compounds (**1-6**) were confirmed by IR, ¹H NMR, ¹³C NMR, Mass spectral, mass spectral fragmentation and elemental analysis. Synthesized compounds (**1-6**) were screened for antimicrobial activity. Structural activity relationship has been discussed in this paper.

Keywords: Mannich base derivatives, Antibacterial activity, antifungal activity, Structural activity relationship.

INTRODUCTION

Mannich reaction is one of the most important carbon-carbon bond formation reactions in organic synthesis[1–3] and very useful compounds as building blocks in the synthesis of pharmaceuticals and natural products[4,5]. With their advantages of atom-efficient transformations, readily available materials, and various products, multicomponent reactions (MCRs) have received significant research interest from chemical and medicinal communities[6,7]. As one of the mostly studied MCRs, discovered in 1912, Mannich reaction is an aminoalkylation reaction of aldehyde [8] , It is an important basic reaction in organic synthesis [9]. Mannich bases have several biological activities such as antimicrobial [10], cytotoxic[11], anticancer[12] and analgesic activity[13]. Morpholine derivative plays an important role in the treatment of several diseases. Heterocyclic ring systems having morpholine nucleus have aroused great interest in recent years due to their variety of biological activities such as possess antimicrobial [14], anti-inflammatory [15] and central nervous system [16]

activities. Aim of this work, synthesis new Mannich base derivatives and their antimicrobial activities.

EXPERIMENTAL SECTION

Melting points were recorded in open capillary tubes and were uncorrected. The IR spectra (KBr) were recorded on a Shimadzu 8201pc (4000-400 cm^{-1}). The ^1H NMR and ^{13}C NMR were recorded on Bruker DRX-400 MHz. Mass spectra (EI) were recorded on a Jeol JMS D-300 spectro meter operating at 70eV. The Elemental analysis (C, H, N and S) were recorded using an Elementer analyzer model (Varian EL III). The purity of the compounds was checked by thin layer chromatography (TLC).

General procedure for the preparation of compound (1-6)

A mixture of furfuraldehyde (0.1mol) morpholine (0.1mol) and (furan-2-ylmethylidene) hydrazine (0.1 mol) in ethanol, the reaction mixture was refluxed for 5h. The reaction mixture were cooled and poured in to ice-cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallised from absolute ethanol. Using above procedure was followed by all the remaining compounds **2-6**.

4-(furan-2-yl(2-(furan-2-ylmethylene)hydrazinyl)methyl)morpholine (1)

IR spectrum (KBr), ν , cm^{-1} : 3010(Ar-CH), 2921(NH), 1623(C=N), 830 (Ar-H), 648(-CH-); ^1H NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 8.11(1H, s, HC=N), 6.52 -7.82 (3H, dd, furyl), 7.21(1H, d, J=1.6 Hz, NH), 5.38(1H, d, J=1.4Hz, -CH-NH-), 6.43-7.68(3H, dd, furyl), 2.68(4H, d, CH₂-N-CH₂), 3.50(4H, d, CH₂-O-CH₂); ^{13}C NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 138.7(HC=N), 149.1(C-HC=N), 118.9, 114.3, 149.1(furyl), 78.2(CH), 157.8(C-CH), 106.7, 148.2, 112.8 (furyl ring), 45.0 (CH₂-N-CH₂), 67.9(CH₂-O-CH₂); EI-Ms:m/z(Relative intensity %): 275.12 (M^+ , 12%), 209.22, 143.62(100%), 131.67, 116.32, 101.27.

2-(furan-2-ylmethylene)hydrazinyl(phenyl)methyl)morpholine (2)

IR spectrum (KBr), ν , cm^{-1} : 3014 (Ar-CH), 2918(NH), 1620(C=N), 628(-CH-); ^1H NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 8.07(1H, s, HC=N), 7.53 -7.86 (4H, dd, furyl), 7.11(1H, d, J=1.4 Hz, NH), 5.32 (1H, d, J=1.3Hz, -CH-NH-), 7.26-7.48(5H, m, Ph), 2.60(4H, d, CH₂-N-CH₂), 3.55(4H, d, CH₂-O-CH₂); ^{13}C NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 137.1(HC=N), 147.5(C-HC=N), 112.0, 110.8, 148.1(furyl), 77.5(CH), 158.2(C-CH), 128.1-129.2(ph), 44.8(CH₂-N-CH₂), 67.1(CH₂-O-CH₂); EI-Ms: m/z (Relative intensity %): 285.47 (M^+ , 37%), 219.20, 207.36, 131.27, 116.37, 101.72.

4-((4-chlorophenyl)(2-(furan-2-ylmethylene)hydrazinyl)methyl)morpholine (3)

IR spectrum (KBr), ν , cm^{-1} : 3017(Ar-CH), 2915(NH), 1613(C=N), 842 (C-Cl), 661(-CH-); ^1H NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 8.14(1H, s, HC=N), 6.72-7.22(3H, dd, furyl), 7.13(1H, d, J=1.6Hz, NH), 5.41(1H, d, J=1.6 Hz, -CH-NH-), 7.34-7.52 (4H, dd, Ph), 2.62(4H, d, CH₂-N-CH₂), 3.43(4H, d, CH₂-O-CH₂); ^{13}C NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 135.9(HC=N), 146.8(C-HC=N), 110.2, 114.5, 142.8(furyl), 76.9(CH), 131.8(C-Cl), 154.5(C-CH), 128.2-128.9(ph), 46.2(CH₂-N-CH₂), 69.1(CH₂-O-CH₂); EI-Ms: m/z (relative intensity %): 319.52 (M^+ , 14%), 253.78, 241.71, 191.25, 177.24.

4-((2-(furan-2-ylmethylene)hydrazinyl)(morpholino)methyl)phenol (4)

IR spectrum (KBr), ν , cm^{-1} : 3026(Ar-CH), 2934(NH), 1452(Ph-OH), 1633(C=N), 611(-CH-); ^1H NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 11.96(1H, s, -OH), 8.13(1H, s, HC=N), 6.50-7.12(3H, dd, furyl), 7.17(1H, d, $J=1.7\text{Hz}$, NH), 5.31(1H, d, $J=1.7\text{Hz}$, -CH-NH-), 7.34-7.55(4H, dd, Ph), 2.69(4H, d, $\text{CH}_2\text{-N-CH}_2$), 3.58(4H, d, $\text{CH}_2\text{-O-CH}_2$); ^{13}C NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 158.8(C-OH), 137.2(HC=N), 147.9(C-HC=N), 117.5, 113.0, 148.2(furyl), 78.1(CH), 155.2(C-CH), 127.0-128.2(ph), 46.9($\text{CH}_2\text{-N-CH}_2$), 67.7($\text{CH}_2\text{-O-CH}_2$); EI-MS: m/z (relative intensity %): 307.67 (M^+ , 27%), 235.27, 223.27, 192.36, 177.37. 101.27.

4-((2-(furan-2-ylmethylene)hydrazinyl)(4-methoxyphenyl)methyl)morpholine (5)

IR spectrum (KBr), ν , cm^{-1} : 3064(Ar-CH), 2962(NH), 1609(C=N), 682(-CH-); ^1H NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 8.21(1H, s, HC=N), 6.49-7.10(3H, dd, furyl), 7.19(1H, d, $J=1.1\text{Hz}$, NH), 5.39(1H, d, $J=1.1\text{Hz}$, -CH-NH-), 7.31-7.54 (4H, dd, Ph), 2.71(4H, d, $\text{CH}_2\text{-N-CH}_2$), 3.67(4H, d, $\text{CH}_2\text{-O-CH}_2$); ^{13}C NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 138.2(HC=N), 147.6(C-HC=N), 118.7, 111.0, 142.3(furyl), 76.6(CH), 154.1(C-CH), 127.0-128.3(Ph), 46.5($\text{CH}_2\text{-N-CH}_2$), 69.1($\text{CH}_2\text{-O-CH}_2$); EI-MS: m/z (Relative intensity %): 315.72 (M^+ , 30%), 249.47, 237.41(100%), 207.38, 192.25, 177.24.

4-((2-(furan-2-ylmethylene)hydrazinyl)(morpholino)methyl)-N,N-dimethylaniline(6)

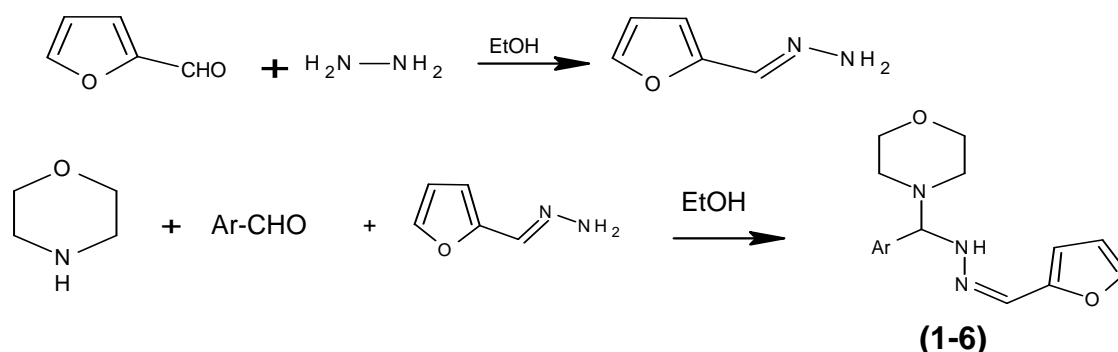
IR spectrum (KBr), ν , cm^{-1} : 3034(Ar-CH), 2932(NH), 1654(C=N), 619(-CH-); ^1H NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 8.17(1H, s, HC=N), 6.52-7.32(3H, dd, furyl), 7.16(1H, d, $J=1.6\text{Hz}$, NH), 5.40(1H, d, $J=1.6\text{Hz}$, -CH-NH-), 7.26-7.48(4H, dd, Ph), 2.68(4H, d, $\text{CH}_2\text{-N-CH}_2$), 3.50(4H, d, $\text{CH}_2\text{-O-CH}_2$), 1.82(6H, s, -N(CH_3) $_2$); ^{13}C NMR spectrum (400 MHz, DMSO- d_6), δ , ppm: 136.7(HC=N), 148.2(C-HC=N), 118.8, 112.8, 146.2(furyl), 77.8(CH), 153.8(C-CH), 127.8-128.0(ph), 45.8($\text{CH}_2\text{-N-CH}_2$), 40.5(Ph-N(CH_3) $_2$), 68.2($\text{CH}_2\text{-O-CH}_2$); EI-MS: m/z (Relative intensity %): 328.51 (M^+ , 22%), 262.42, 250.41(100%), 207.32, 192.25, 177.24, 77.14.

Biological evaluation***In vitro* Antibacterial screening**

The compounds (**1-6**) were evaluated for their *in vitro* antibacterial activity against *Escherichia coli* (MTCC-739), *Pseudomonas aeruginosa*(MTCC-2435), *Micrococcus Klebsiella pneumonia* (recultured), and *Staphylococcus aureus*(MTCC-96), by disc diffusion method[17] was performed using Mueller-Hinton agar(Hi-Media) medium. Each compound was tested at a concentration at 100 $\mu\text{g/mL}$ in DMSO. The zone of inhibition was measured after 24h incubation at 37°C.

***In vitro* antifungal screening**

The compounds(**1-6**) were evaluated for their *in vitro* antifungal activity such as *Aspergillus niger*, *Candia albicans*, *Microsporum audouinii* and *Cryptococcus neoformans* (recaptured) using an disc diffusion method [18] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 100 $\mu\text{g/mL}$ in DMSO. The zone of inhibition (mm) was measured incubated at 37°C.



Scheme 1. Synthesis route of compounds (1-6)

RESULTS AND DISCUSSION

The compounds (**1-6**) were synthesized by Mannich base method (scheme 1). Physicochemical data of the compounds (**1-6**) are given in Table 1. The formations of all the compounds were confirmed by recording the IR, ^1H NMR, ^{13}C NMR and elemental analyses. The IR spectrum of compound **1** shows an absorption bands at 2921 and 648 cm^{-1} corresponding to aromatic NH and -CH- groups respectively. The ^1H NMR spectra of compound **1** shows a signals at δ 8.11, 7.21 and 5.38 corresponding to C=NH, NH, and -CH- protons respectively. ^{13}C NMR spectrum of compound **1** shows peaks at δ 78.2 corresponding to -CH- carbons. Mass spectral (figure 3) of compound **1** shows the molecular ion peak at m/z 275.12 (M^+ , 12%), which is conformed the molecular mass of compound **1**. Mass spectral fragmentation is represented in figure 4.

Antibacterial activity

Compound **3** has highly active against *K.pneumoniae* and compound **4** has highly activity against *Staphylococcus aureus* whereas compound **5** has equipotent activity against *K.pneumoniae* compared with standard ciprofloxacin. The bacterial zones of inhibition values are summarized in Table 2. Diagram for activity variation of compounds **1-6** is represented in Figure 1.

Antifungal activity

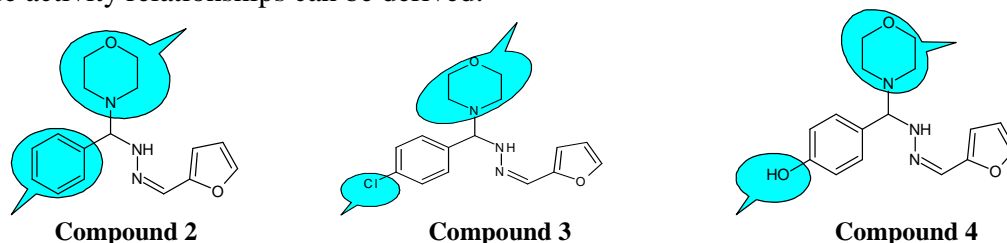
Compound **2** has highly activity against *C.albicans* where as compound **4** has equipotent activity against *Cryptococcus neoformans* compared with standard clotrimazole. The fungal zones of inhibition values are summarized in Table 3. Diagram for activity variation of compounds **1-6** is represented in Figure 2.

Table 1. Physicochemical data of compounds (1-6)

Com. No.	R ₁	Yield %	m.p $^{\circ}\text{C}$	M.F	M.W	Elemental Analysis Calculated(Found) %		
						C	H	N
1	Furyl	78	123	C ₁₄ H ₁₇ N ₃ O ₃	275.30	61.08(61.09)	6.22(6.20)	15.26(15.20)
2	-Ph	79	139	C ₁₆ H ₁₉ N ₃ O ₂	285.34	67.35(67.31)	6.71(6.70)	14.73(14.71)
3	-Ph-Cl	83	141	C ₁₆ H ₁₈ ClN ₃ O ₂	319.11	60.09(60.10)	5.67(5.60)	13.14(13.12)
4	-Ph-OH	80	156	C ₁₆ H ₁₉ N ₃ O ₃	301.34	63.77(63.75)	6.36(6.33)	13.94(13.92)
5	-Ph-OCH ₃	81	130	C ₁₇ H ₂₁ N ₃ O ₃	315.36	64.74(64.70)	6.71(6.70)	13.32(13.30)
6	-Ph-N(CH ₃) ₂	91	146	C ₁₈ H ₂₄ N ₄ O ₂	328.40	65.83(65.81)	7.37(7.34)	17.06(17.33)

Structural activity relationship

From the results of antimicrobial of the synthesized mannich base derivatives, the following structure activity relationships can be derived:



The compound (3) exhibit morboline and 4-Cl-Ph ring in mannich base derivative higher antibacterial activity against *K.pneumoniae* and compound (2) antifungal activity against *C.albicans* at concentration 100µg/mL. The compound (4) is exhibit morboline and 4-Cl-Ph ring in mannich base derivative higher antibacterial activity against *Staphylococcus aureus* and antifungal activity against *Cryptococcus neoformans* at concentration 100µg/mL.

Table 2. Antibacterial activity of compounds (1-6)

Compounds	<i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i>	<i>E. coli</i>	<i>Pseudomonas aeruginosa</i>
1	15	13	-	-
2	17	10	-	8
3	10	22	10	-
4	28	12	-	10
5	19	20	-	-
6	10	17	12	-
Ciprofloxacin	22	19	27	32

Zone of inhibition was measured at (mm) at concentration of 100µg/mL,
Ciprofloxacin is used as the standard

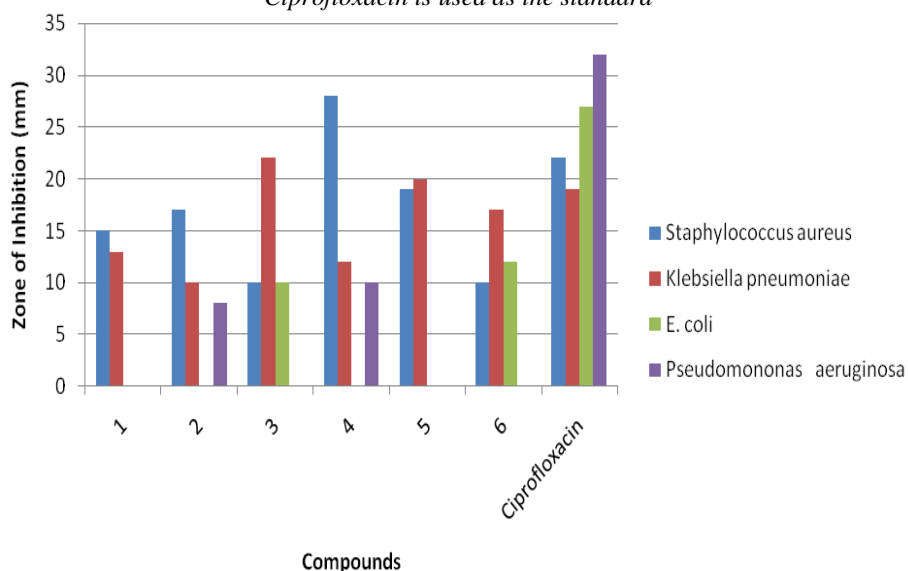
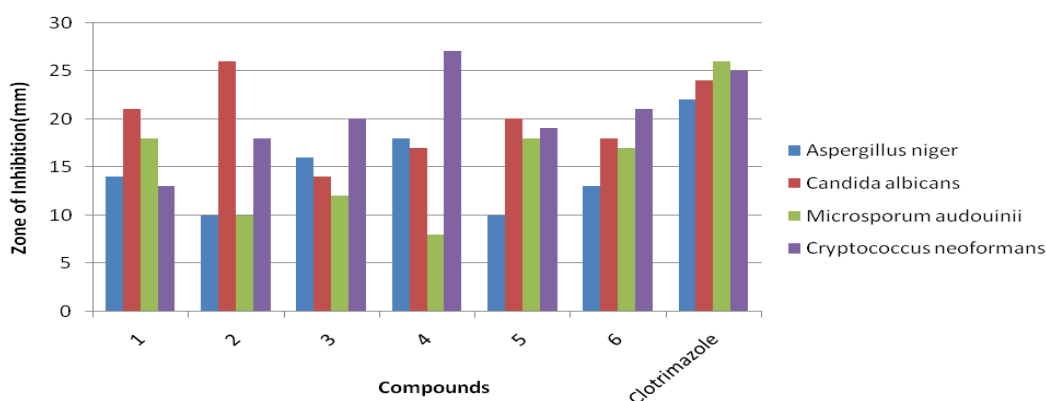
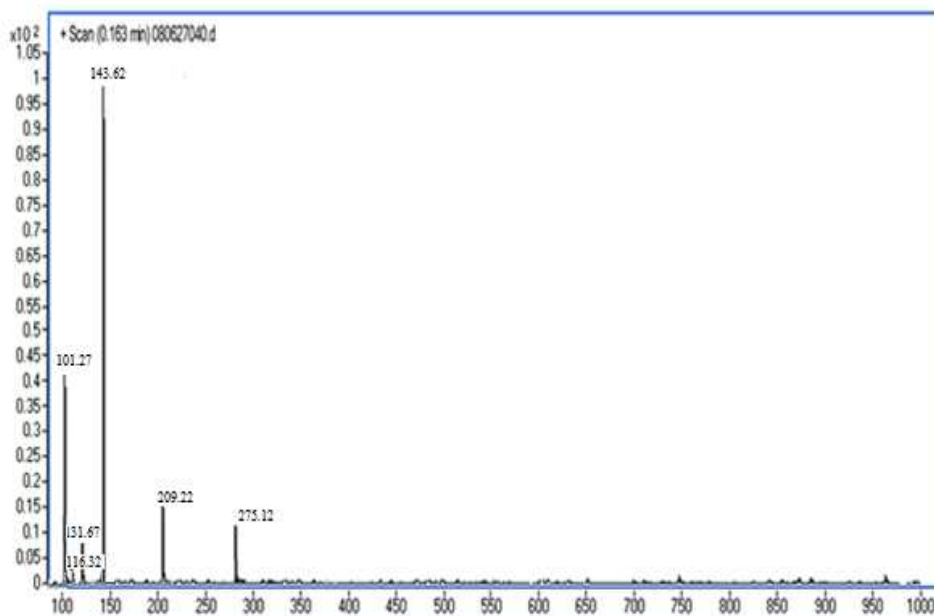


Figure 1. Antibacterial activity of compounds (1-6)

Table 3. Antifungal activities for compound (1-6)

Compounds	<i>Aspergillus niger</i>	<i>Candida albicans</i>	<i>Microsporium audouinii</i>	<i>Cryptococcus neoformans</i>
1	14	21	18	13
2	10	26	10	18
3	16	14	12	20
4	18	17	8	27
5	10	20	18	19
6	13	18	17	21
Clotrimazole	22	24	26	25

Zone of inhibition was measured at (mm) at concentration of 100 μ g/mL. Clotrimazole was used as a standard

**Figure 2. Antifungal activity of compounds (1-6)****Figure 3. Mass spectrum of compound (1)**

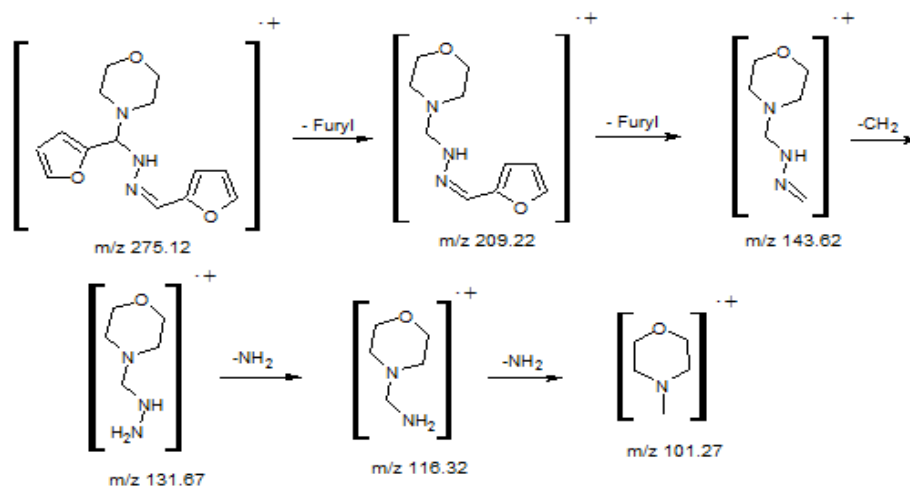


Figure 4. Mass fragmentation of the compound (1)

CONCLUSION

New series of Mannich base derivatives (**1-6**) were synthesized and screened for antimicrobial activity. The compound (**4**) has high antibacterial activity against *Staphylococcus aureus* compared with standard Ciprofloxacin and compound (**4**) has high antifungal activity against *Cryptococcus neoformans*. Therefore, this synthesized compound could be extended to analysis the various biological activities.

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