Article

Design, Ultrasonic-assisted Synthesis and Evaluation *In vitro* Antimicrobial Activity of Bis-isoxazole Derivatives Bearing Chloro-pyridinyl Group

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An ultrasonic-assisted synthesis of bis-isoxazole derivatives was developed. Eight 3-(6-chloropyridin-3-yl)-5-{[(3-arylisoxazol-5-yl)methoxy]methyl}isoxazoles were synthesized by 1,3-dipolar cycloaddition reaction between substituted isoxazolyl alkyne compounds and 6-chloro-*N*-hydroxynicotinimidoyl chloride. The structures of the synthesized compounds were confirmed by HRMS, FTIR, ^{1}H and ^{13}C NMR spectroscopy. Wherein, the antifungal and antibacterial activities of target compounds were tested. The synthesized compounds **6**a and **6**h exhibited better antifungal activity in comparison with the standard drug itraconazole. The minimum inhibitory concentrations(MICs) of both compound **6**a and compound **6**h were both 4 μg/mL against Candida albicans ATCC 10231.

Keywords Ultrasonic-assisted; Bis-isoxazole; 1,3-Dipolar cycloaddition; Antimicrobial activity

1 Introduction

At present, the fast-growing antimicrobial resistance of many bacteria is becoming one of the worldwide health threats[1]. Especially, invasive fungal infections also cause severe infection combining with multiple diseases[2,3]. It is reported that *Candida albicans*(*C. albicans*) could cause not only severe mucosal infections, but also fatal invasive infections[4—6]. Therefore, it is necessary to develop some new antifungal drugs.

It is well known that isoxazole derivatives exhibit diverse biological activities and pharmacological properties, such as anti-inflammatory[7—9], antibacterial[10,11], antihyperglycemic[12], analgesic[13], and antifungal activities[14], and are active ingredients in many natural products and synthetic drugs[15,16]. The drugs, for example, flucloxacillin and cloxacillin bearing an isoxazole unit in the molecule(Fig.1) have been applied to clinical treatment. In our previous study, it was found that pyridin-3-yl substituted bis-isoxazole ether [3-(2-chlorophenyl/2-methoxyphenyl)-5-({[3-(pyridin-3-yl)isoxazol-5-yl]methoxy}-methyl)isoxazole](Fig.2) revealed good antifungal activities[17].

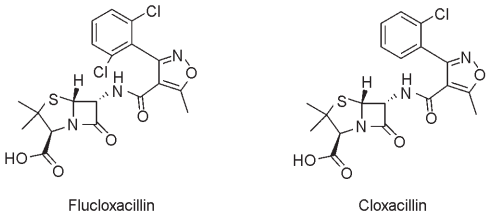

Fig. 1 Structures of flucloxacillin and cloxacillin

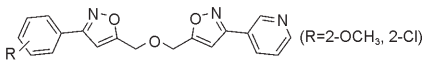

Fig.2 Substituted 3-phenyl-5-({[3-(pyridin-3-yl)isoxazol-5-yl]-methoxy}methyl)isoxazole

Those findings encourage us to design and synthesize novel isoxazole derivatives and evaluate their antimicrobial activities. The primary study reported that the main methods for synthesizing isoxazole compounds included 1,3-dipolar cycloaddition reaction, cyclo-isomerization reaction, condensation reaction, and so on. Among them, 1,3-dipolar cycloaddition reaction between nitrile oxides and alkynes[18] is one of the most efficient and convenient methods for synthesizing isoxazole derivatives[19,20], because raw materials with different functional groups are readily accessible, and the product yields are high[21,22].

Ultrasonic-assisted organic synthesis is an emerging synthesis method, which has the advantages like short reaction time, higher yield and easier manipulation[23,24]. However, the ultrasonic-assisted synthesis of bis-isoxazole compounds hasn't been reported. On the other hand, it is reported that the molecules with an electron-withdrawing group on benzene ring may enhance the antibacterial activity[25—27]. Considering all above factors, in our present work, chloropyridinyl was introduced to synthesize the novel bis-isoxazole compounds *via* 1,3-dipolar cycloaddition under ultrasonic radiation condition. We expect that the designed compounds possessed favorable antimicrobial activity. The structures of the synthesized products were confirmed by HRMS, ^{1}H and ^{13}C NMR, and FTIR spectroscopy. Further, the antifungal and antibacterial activities of target compounds were tested against *C. albicans* (ATCC 1023), *P. aeruginosa*(ATCC 27853),

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E. coli(ATCC 25922), *Staphylococcus aureus*(*S. aureus* ATCC 25923, *S. aureus* ATCC 3933) and *S. epidermidis*(ATCC 12228).

2 Experimental

2.1 Materials and Methods

All analytical-grade substituted benzaldehydes were purchased from Aladdin Reagent Co. and Shanghai Darui Reagent Co.(China). Other solvents and reagents were provided by Beijing Chemical Plant(China). All chemicals were directly used without further purification. A KQ2200E ultrasonic reactor(100 W, Kunshan Ultrasonic Instrument Co., Ltd., China) with a thermometer was used to synthesize the target product. An XT-4 melting point apparatus(Beijing Teke Instrument Co., Ltd., China) was used to determine the melting point of pro-duct and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AVANCE-500 or 600 NMR spectrometer (Bruker, Germany) in DMSO-d_6 and with tetramethy-silane(TMS) as an internal standard. An Agilent 1290-micr-OTOF Q II spectrometer(Agilent Technologies Co., Ltd., USA) was used to measure the HRMS spectra of the products. An IRAffinity-1 instrument(Shimadzu, Japan) was utilized to collect the IR spectroscopic data in the range of 500—4000 cm^{-1}.

2.2 General Procedure for Synthesis of 3-Aryl-5-[(prop-2-yn-1-yloxy)methyl]isoxazoles(5)

According to literature[17,28], 3-aryl-5-[(prop-2-yn-1-yloxy)-methyl]isoxazoles were synthesized from substituted benzaldehydes.

Firstly, a solution of substituted benzaldehyde(**1**, 20 mmol) and 50 mL of ethanol was added in a 100 mL three-necked flask. The solution of dissolved 30 mmol of hydroxylamine hydrochloride in 20 mL of distilled water was adjusted to pH=8—9 by NaOH(6 mol/L), then was poured into a three-necked flask, and refluxed for 2—4 h. The reaction process was monitored by means of thin layer chromatography(TLC). After the reaction completed, the reaction slurry was cooled in ice water until the solid was completely precipitated. The sediment was filtered, then washed by water and dried to provide substituted benzaldehyde oxime(**2**) in yields of 87%—96%.

And then, substituted benzaldehyde oxime(**2**, 10 mmol) was dissolved in 20 mL of *N*,*N*-dimethylformamide(DMF) in a 100 mL three-necked flask. *N*-Chlorosuccinimide(NCS, 11 mmol) was added to the above reaction solution under ice bath condition. The reaction was radiated under ultrasound for 15—30 min and monitored by TLC. After the reaction was over, propargyl alcohol(15 mmol) and triethylamine(10 mmol) were slowly poured into the flask, followed by ultrasonic reaction for 15—30 min. After the reaction completed, the reaction mixture was cooled in ice water and filtered to obtain a solid crude product, which was purified by means of column chromatography(silica gel, 200—300 mesh, eluent petroleum ether/ethyl acetate, volume ratio 4/1) to furnish(3-arylisoxazol-5-yl)methanol(**4**) in yields of 56%—90%. (3-Arylisoxazol-5-yl)methanol(**4**, 2 mmol) was dissolved in 20 mL of anhydrous tetrahydrofuran(THF) in a 100 mL three-necked flask. NaH (6 mmol) and propargyl bromide(3 mmol) were added to the above reaction solution under ice-water bath condition. The reaction was radiated by ultrasound for 30—50 min and monitored by TLC. After the reaction finished, the slurry reaction mixture was filtered, and the filtrate was concentrated under reduced pressure by a rotary evaporator to furnish the crude product. Sequentially, it was purified by means of column chromatography(silica gel, 200—300 mesh, eluent petroleum ether/ethyl acetate, 4/1) to furnish 3-aryl-5-[(prop-2-yn-1-yloxy)methyl]isoxazole(**5**) in yields of 70%—90%.

2.3 General Procedure for Synthesis of 6-Chloro-*N*-hydroxynicotinimidoyl Chloride(E)

Firstly, 2-chloro-5-(chloromethyl)pyridine(A, 50 mmol) was dissolved in 50 mL of ethanol in a three-necked flask(250 mL). Na_2CO_3(100 mmol) was dissolved in distilled water(60 mL). Cetyltrimethylammonium bromide(2.5 mmol) and sodium carbonate solution was added to the above reaction solution. The mixture was stirred at reflux temperature for about 2 h and the reaction was monitored by TLC. After the reaction completed, the mixture was cooled to room temperature and filtered. The filtrate was extracted with ethyl acetate. The organic phase was dried using anhydrous sodium sulfate as a desiccant and concentrated under reduced pressure using a rotary evaporator to furnish the crude product, which was purified by means of column chromatography(silica gel, 200—300 mesh, eluent petroleum ether/ethyl acetate, 1/1) to furnish(6-chloropyridin-3-yl)methanol(B) in a yield of 87%.

Next, (6-chloropyridin-3-yl)methanol(B, 40 mmol) was dissolved in 50 mL of benzene in a three-necked flask(250 mL). $NaHCO_3$(80 mmol) was dissolved in distilled water and poured into the reaction solution. 2,2,6,6-Tetramethylpiperidine-nitrogen-oxide(TEMPO, 4 mmol) and I_2(40 mmol) were added sequentially. The mixture was stirred at room temperature for 10—15 h and the reaction was monitored by TLC. After the reaction was over, the remaining I_2 was removed by reacting with $Na_2S_2O_3$. The mixture was extracted with ethyl acetate, and the organic phase was dried using anhydrous sodium sulfate as a desiccant and evaporated under reduced pressure using a rotary evaporator to furnish the crude product, which was purified by means of column chromatography(silica gel, 200—300 mesh, eluent petroleum

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ether/ethyl acetate, 6/1) to furnish 6-chloronicotinaldehyde(C) in a yield of 80%.

Then, 6-chloronicotinaldehyde(C, 30 mmol) was dissolved in 50 mL of ethanol in a three-necked flack(100 mL). Hydroxylamine hydrochloride(33 mmol) was dissolved in 20 mL of distilled water, and the solution was adjusted to pH=8—9 with NaOH solution(6 mol/L). The mixture was added to a three-necked flask and refluxed for 2 h. The reaction process was monitored by TLC. After the reaction was over, the reaction solution was poured into ice water to precipitate solid, which was filtered to offer 6-chloronicotinaldehyde oxime(D) in a yield of 87%.

Finally, 6-chloro-*N*-hydroxynicotinimidoyl chloride(E, 19.4 mmol) was synthesized between 6-chloronicotinaldehyde oxime(D, 20 mmol) and NCS(30 mmol) in a yield of 97% by a similar procedure from substituted benzaldehyde(**1**) to *N*-hydroxybenzimidoyl chloride(**3**) referring to the literature[17]. Yield 85%. IR(KBr, $\tilde{\nu}$/cm^{-1}): 3232, 3132, 3066, 3008, 2812, 2723, 2152, 1697, 1651, 1620, 1558, 1492, 1458, 1361, 1292, 1257, 1114, 1014, 941, 844, 748, 729. ^{1}H NMR(600 MHz, DMSO), δ: 12.83(s, 1H, C═N—OH), 8.78(d, J=2.6 Hz, 1H, pyridyl), 8.19(dd, J=8.4, 2.6 Hz, 1H, pyridyl), 7.65(d, J=8.4 Hz, 1H, pyridyl). ^{13}C NMR (151 MHz, DMSO), δ: 152.05, 147.85, 137.99, 132.70, 128.80, 124.90. HR-MS, m/z calcd. for $C_6H_4Cl_2N_2O[M+H]^+$: 190.9779; found: 190.9783.

2.4 General Procedure for Synthesis of 3-(6-Chloropyridin-3-yl)-5-{[(3-arylisoxazol-5-yl)meth-oxy]-methyl}isoxazoles(6)

3-Aryl-5-[(prop-2-yn-1-yloxy)methyl]isoxazole(**5**, 5.0 mmol) and 6-chloro-*N*-hydroxynicotinimidoyl chloride(E) were dissolved in 20 mL of anhydrous THF in a three-necked flask(100 mL). Under ultrasonic wave radiation, zinc powder(7.5 mmol) and triethylamine(1.8 mL) were added to the above mixture under ice bath condition for 30 min, and then the temperature was set to 50 °C. The reaction was monitered by TLC. Zinc powder was removed by filtration, and the filtrate was extracted with ethyl acetate after the reaction was over. The organic phase was dried using anhydrous sodium sulfate as a desiccant and evaporated under reduced pressure using a rotary evaporator to furnish the crude product, which was purified by means of column chromatography(silica gel, 200—300 mesh, eluent petroleum ether/ethyl acetate, 2/1) to furnish the product 3-(6-chloropyridin-3-yl)-5-{[(3-arylisoxazol-5-yl)methoxy]methyl} isoxazole(**6**) in yields of 56%—73%.

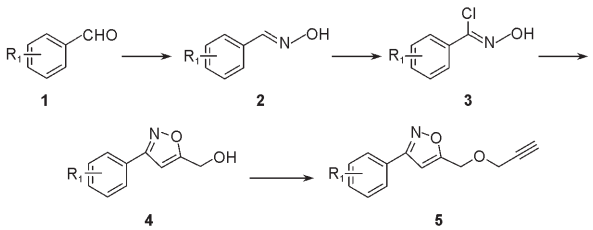
2.5 Biological Activity Analysis

The *in vitro* antibacterial activity was tested by the antimicrobial susceptibility test method of Clinical and Laboratory Standards Institute(CLSI)[29]. Bacteria strains were cultured in a Mueller-Hinton broth for 6—8 h at 37 °C. Meantime, yeast strains were incubated in a yeast extract peptone dextrose medium for 24 h at 35 °C. The bacteria inoculum concentration ranged from 2×10^8 CFU/mL to 4×10^8 CFU/mL(about twice of the final inoculum concentration), while the yeast ranged from 1.0×10^3 CFU/mL to 5.0×10^3 CFU/mL(twice about the final inoculum concentration). Compounds **6**a—**6**h(5.12 mg) were respectively dissolved in 1 mL of dimethylsulfoxide(DMSO). The test was carried out in a sterile 96-well plate, into each well of which was added 100 μL of prepared inoculum according to the literature[25,30]. Here, ciprofloxacin and itraconazole were respectively chosen as positive controls against bacteria and fungi. The minimum inhibitory concentration(MIC) was defined as the lowest concentration, which inhibits the visible growth of a microbe.

3 Results and Discussion

In the previous work, substituted 3-phenyl-5-({[3-(pyridin-3-yl)isoxazol-5-yl]methoxy}methyl)isoxazoles were found to possess good antifungal activities[17]. As continuation of our work, considering the pharmaceutical activity of pyridyl and the effect of electron-withdrawing group(—Cl) on pharmacophore, the synthesis of new bis-isoxazole compounds bearing chloropyridinyl was explored using 6-chloro-*N*-hydroxynicotinimidoyl chloride and the corresponding terminal alkynes as raw materials by 1,3-dipolar cycloaddition.

Herein, the intermediate products 3-aryl-5-[(prop-2-yn-1-yloxy)methyl]isoxazoles(**5**) were prepared in yields of 70%—90% according to the literature[17]. The synthesis route of compound **5** is shown in Scheme 1. 6-Chloro-*N*-hydroxynicotinimidoyl chloride(E) was synthesized starting with 2-chloro-5-(chloromethyl)pyridine(A). Compound A was firstly hydrolyzed to (6-chloropyridin-3-yl) methanol(B), and then was selectively oxidized to 6-chloronicotinaldehyde(C) by I_2. Further, the nucleophilic addition reaction of compound C with hydroxylamine hydrochloride produced compound D. Finally, 6-chloro-*N*-hydroxy-nicotinimidoyl chloride(E) was synthesized by *N*-chlorosuc-cinimide chlorination of 6-chloro-



R_1=2-OCH_3; 4-Cl; 4-Br; 4-NO_2; H; 4-CH_3; 4-OCH_3; 2-Cl

Scheme 1 Synthesis of 3-aryl-5-[(prop-2-yn-1-yloxy)methyl] isoxazoles

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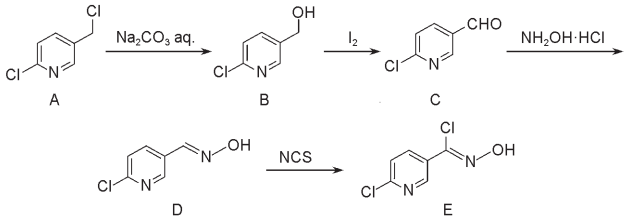
nicotinaldehyde oxime(D). The synthesis route of compound E is shown in Scheme 2. The yields and melting points of the obtained corresponding products are listed in Table 1.



Scheme 2 Synthesis of 6-chloro-*N*-hydroxynicotinimidoyl chloride

Table 1 Yields and melting points of compounds B—E

Entry	Compound	Yield*(%)	Melting point/°C
1	B	87	45—47
2	C	80	77—79
3	D	87	182—183
4	E	97	144—146

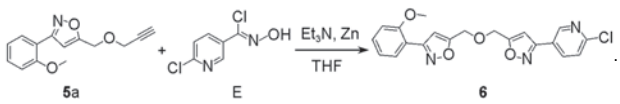
* Isolated product yields.

As shown in Table 1, compounds B—E were respectively obtained in 87%, 80%, 87% and 97% yields *via* nucleophilic substitution, oxidation, nucleophilic addition and elimination, and nucleophilic substitution reactions in order. Subsequently, the synthesis of new bis-isoxazoles was explored by employing 3-(2-methoxyphenyl)-5-[(prop-2-yn-1-yloxy)methyl]isoxazole (**5**a) and 6-chloro-*N*- hydroxynicotinimidoyl chloride(E) under conventional, ultrasonic and microwave heating conditions. The results are summarized in Table 2. As shown in Table 2, the target product 3-(6-chloro-3-pyridine)-5-({[3-(2-methoxyphenyl)isoxazol-5-yl]methoxy}methyl)isoxazole(**6**a) was successfully obtained in yields of 74%(conventional heating), 73%(ultrasonic heating) and 40%(microwave heating), respectively. Herein, three heating modes were all gradually heated to 50 °C in the water bath. The yield of target product obtained by the ultrasonic heating was similar to that of the conventional heating method in the three heating methods. Both of them were over 70%, but the reaction time required by ultrasonic heating was significantly shorter than that of the conventional heating. However, compared with ultrasonic heating at the same reaction time, the obtained yield by microwave heating was lower. This might be attributed to the reflection of Zn powder to microwave, which is unfavorable to the reaction. Therefore, ultrasonic heating method was chosen for synthesizing the target compounds.

Table 2 Selection of heating methods[a]

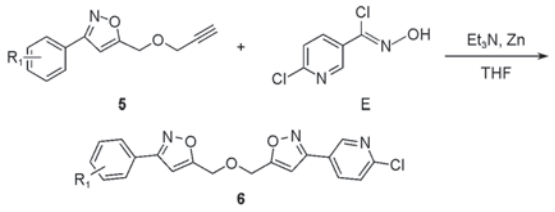
Entry	Heating method	Time/h	Yield[b](%)
1	Conventional	5	74
2	Ultrasonic	1	73
3	Microwave	1	40

a.



b. Isolated product yields.

In accordance with the reaction conditions for the synthesis of compound **6**a, other seven bis-isoxazole derivatives were explored using different substituted 3-aryl-5-[(prop-2-yn-1-yloxy)methyl]isoxazole and 6-chloro-*N*-hydroxynicotinimidoyl chloride(E) as raw materials. The synthesis route of 3-(6-chloropyridin-3-yl)-5-{[(3-arylisoxazol-5-yl)methoxy]methyl}isoxazoles(**6**) is shown in Scheme 3. The experimental results are shown in Table 3.



Scheme 3 Synthesis of isoxazoles from alkynes and nitrile oxide

Table 3 Synthesis of bis-isoxazole derivatives under ultrasonic radiation

Entry	R_1	Compound	Yield*(%)	Melting point/°C
1	2-OCH_3	**6**a	73	106—108
2	4-Cl	**6**b	60	127—130
3	4-Br	**6**c	59	138—140
4	4-NO_2	**6**d	56	164—166
5	H	**6**e	63	112—114
6	4-CH_3	**6**f	68	132—134
7	4-OCH_3	**6**g	71	131—132
8	2-Cl	**6**h	61	116—118

* Isolated product yields.

It was observed that 1,3-dipolar cycloaddition of chlorinated oxime and isoxazole alkynes was readily carried out (Table 3). Eight different substituted 3-(6-chloropyridin-3-yl)-5-{[(3-phenylisoxazol-5-yl)methoxy]methyl}isoxazoles were successfully synthesized in yields of 56%—73% under ultrasonic heating condition. It is worth noting that the other isomer was not found by measurement of high resolution mass spectrometry, which is consistent with the results in the literature[17]. It suggested that the regioselectivity of 1,3-dipolar cycloaddition reaction was closely related to the selection of substrates and catalyst. The possible reaction mechanism is depicted in Scheme 4. Compound E loses HCl to produce nitrile oxide tautomers **1**′ and **2**′ under alkaline environment. Furthermore, 1,3-dipolar structure nitrile oxide **2**′ underwent 1,3-dipolar cycloaddition reaction with terminal alkynes **5** to obtain the target product **6**.

Isoxazole and pyridine were important and effective drug cores[31—38]. It was hypothesized to possess favorable antibacterial activity when isoxazole ring and pyridine ring were unified into a molecule. Ciprofloxacin and itraconazole

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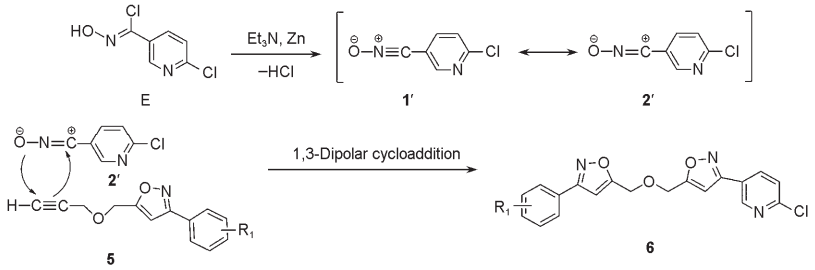

Scheme 4 Mechanism to synthesized isoxazoles from alkynes and nitrile oxide

were drugs for treating different bacterial and fungal infections, and had therapeutic effect on human and animal in clinical therapy. Herein, the synthesized compounds **6**a—**6**h were screened for the *in vitro* antifungal activities against fungi *C. albicans* ATCC 10231, and antibacterial activities against *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *S. aureus* ATCC 25923, ATCC 3933 and *S. epidermidis* ATCC 12228, respectively. Ciprofloxacin and itraconazole were chosen as positive controls. The antifungal and antibacterial activities of bis-isoxazole derivatives were evaluated based on the antimicrobial susceptibility test recommended by the American Institute of Clinical and Laboratory Standards (CLSI)[29]. The MICs of the synthesized compounds are shown in Table 4. As shown in Table 4, eight bis-isoxazole derivatives synthesized had no significant effect on the bacteria(*E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 25923, ATCC 3933 and *S. epidermidis* ATCC 12228), but compounds **6**a and **6**h had better antifungal effects against *C. albicans* ATCC 10231. The MICs of both compound **6**a and compound **6**h were 4 μg/mL. According to the relationship between chemical structure and drug property, the introduction of halogen and other substituents can increase the lipophilicity, thereby improving the pharmacological activity of the drug molecule[25]. In our previous study, compound 3-(2-methoxyphenyl)-5-[(3-pyridylisoxazole-5-methoxy)methyl]isoxazole and 3-(2-chlorophenyl)-5-[(3-pyridylisoxazole-5-methoxy)methyl]isoxazole(MICs were 1 and 4 μg/mL, respectively) have good antifungal activity[17]. In order to increase their antimicrobial activity, the electron-withdrawing group(—Cl) was introduced at the 2-position of pyridine ring on the premise that the substituents on the phenyl ring remained unchanged(the *ortho*-position of substituted benzene ring was either 2-OCH_3 or 2-Cl) (compounds **6**a and **6**h). However, the results showed that the antifungal activity of the drug molecule constructed was not increased(the MICs of compounds **6**a and **6**h both were 4 μg/mL), which might be due to the introduction of chlorine atom to pyridine ring, which had little effect on the antimicrobial activity of the entire drug molecule.

Table 4 Antimicrobial activities of bis-isoxazole derivatives

Entry	Compound	MIC/(μg·mL^{-1})					
		E.coli ATCC 25922	*P. aeruginosa* ATCC 27853	*S. aureus* ATCC 25923	*S. aureus* ATCC 3933	*S. epidermidis* ATCC 12228	*C. albicans* ATCC 10231
1	**6**a	>64	>64	>64	>64	>64	4
2	**6**b	>64	>64	>64	>64	>64	>64
3	**6**c	>64	>64	>64	>64	>64	>64
4	**6**d	>64	>64	>64	>64	>64	>64
5	**6**e	>64	>64	>64	>64	>64	>64
6	**6**f	>64	>64	>64	>64	>64	>64
7	**6**g	>64	>64	>64	>64	>64	>64
8	**6**h	>64	>64	>64	>64	>64	4
9	Ciprofloxacin	0.125	0.125	0.25	0.125	0.25	/
10	Itraconazole	/	/	/	/	/	0.5

4 Conclusions

A facile method for synthesizing 3-(6-chloropyridin-3-yl)-5-{[(3-arylisoxazol-5-yl)methoxy]methyl}isoxazoles under ultrasonic radiation was presented. Ultrasonic radiation can significantly shorten the reaction time compared with conventional heating. Also, eight desired products were obtained with yields of 56%—73%. Herein, the antifungal and antibacterial activities of bis-isoxazole derivatives were evaluated. The obtained target products did not have obvious antibacterial activities to the tested bacteria. However, compound 3-(6-chloropyridin-3-yl)-5-({[3-(2-methoxyphenyl)-isoxazol-5-yl]methoxy}methyl)isoxazole(**6**a) and 3-(2-chlorophenyl)-5-({[3-(6-chloropyridin-3-yl)isoxazol-5-yl]methoxy}-methyl)isoxazole(**6**h) had favorable antifungal activity to *C. albicans* ATCC 10231. Their MICs were both 4 μg/mL.

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Conflicts of Interest

The authors declare no conflicts of interest.

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