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Synthesis, characterization, and antimicrobial activity of novel heterocyclic compounds containing a ferrocene unit via Michael addition reaction

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Abstract A series of novel heterocyclic compounds containing a ferrocene unit were synthesized by reacting ferrocenylchalcone with pyrazolyl amine or triazolyl amine via Michael addition reaction. A novel synthetic route of ferrocenylchalcones was developed in which cinnamic acid and ferrocene were used as starting materials and phosphorus pentachloride was used as acylating agent. The structure of these newly synthesized compounds was confirmed by IR, elemental analysis, ^{1}H NMR, and ^{13}C NMR. The antibacterial activity and minimum inhibitory concentration (MIC) of all compounds were screened for *Escherichia coli*, *Saccharomyces aureus*, *Streptococcus*, *Actinomycete*, and *Saccharomyces cerevisiae* in vitro by filter paper disc diffusion method, and agar dilution method, respectively. The compounds **4a–c** exhibited moderate to excellent antibacterial activity in comparison to Ampicillin used as reference drug and MIC values between 1 and 64 μg/mL. Among these tested compounds, **4a**, **4b** show the best inhibitory activity.

Keywords Heterocyclic compounds · Ferrocenylchalcone · Pyrazolyl amine · Triazolyl amine · Synthesis · Michael addition reaction · Antimicrobial activity

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Introduction

Bioorganometallics was defined as the study of biomolecules or biologically active molecules that contain at least one carbon directly bound to a metal or metalloid by Gérard Jaouen in 1985 [1–5].

Ferrocene is known to exhibit a broad spectrum of biological activity and has become a useful organometallic compound in the field of pharmaceutical sciences due to its unique structure. Many ferrocenyl compounds display interesting cytotoxic, antitumur [5, 6], antimalarial [7, 8], anticancer, and antifungal HIV and DNA-cleaving activities [9–11]. On the other hand, the ferrocenylchalcone, an important intermediate in organic synthesis, and application more widely, is normally used for Michael addition reaction with amine compounds, which can introduce other groups having biological activity into the ferrocene group, such as producing pyrazole derivatives via reacting with hydrazine [12, 13], pyrimidine derivatives by treating with thiourea [14], and pyridine derivatives though reacting with nitrile [15], etc.

The Michael addition reaction plays an important role in organic synthesis reaction of building the carbon–sulfur bond and carbon–nitrogen bond [16–18]. The Michael addition of amine and ferrocenylchalcone usually requires a certain amount of strong base or Lewis acid as catalyst.

The pyrazole ring is a prominent structure found in numerous pharmaceutically active compounds. Pyrazoles have been implemented as antileukemic [18–22] antiproliferative [23, 24], antitumor agents [25–29], as insecticides [30], and as anti-inflammatory and antimicrobial agents [31–33]. On the other hand, the derivatives of 1,2,4-triazole possess a wide range of antimicrobial [34–36] and antitumor activities [34–37], and as potent tubulin polymerization inhibitors [38, 39]. The following 1,2,4-triazole derivatives are applied in medicine: alprazolam (tranquilizer), estazolam (hypnotic, sedative, tranquilizer), trapidil (hypotensive), trazodon (antidepressant, anxiolytic), and so on [34].

Recent studies have suggested that a combination of a ferrocenyl moiety with heterocyclic structures may increase their biological activities or create new medicinal properties [40]. Heterocyclic compounds containing ferrocenyl have been reported on less during recent years. For instance, Kumar et al. [41, 42] have synthesized 1,2,3-triazole tethered β-lactam–ferrocene and β-lactam–ferrocenylchalcone chimeric scaffolds and evaluated them for anti-tubercular activity. In view of above-mentioned facts, we envisioned the synthesis of novel heterocyclic compounds containing ferrocenyl and pyrazolyl or triazolyl derivatives that may have significant biological activities. Here, a series of novel compounds containing a ferrocenyl group were synthesized by using ferrocenylchalcone and 1-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*–pyrazol-4-amine, 5-methyl-1-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-pyrazol-4-amine, or 1-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-1,2,4-triazol-3-amine via Michael addition reaction in the presence of triethylamine.

Experimental

All the reagents described in this paper are commercially available, and all solvents were freshly distilled before use. The melting points were recorded on a X-4

microscopic melting point meter, apparatus and are uncorrected. Elemental analysis (C, H and N) was recorded on a Vario EL III. IR spectra were recorded on a VECTOR-22 instrument and using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on an ADVANCE III 400 MHz instrument and using $CDCl_3$ as solvent and $SiMe_4$ as an internal reference.

Procedure for synthesis of ferrocenylchalcone (**1**)

A mixture of 1.48 g (0.01 mol) cinnamic acid and 2.50 g (0.012 mol) phosphorus pentachloride in a drying three-neck flask (100 mL) was stirred at 20 °C for 2 h. Then, 4.8 mL (0.08 mol) carbon disulfide, 1.48 g (0.008 mol) ferrocene, and 1.33 g (0.01 mol) anhydrous aluminum chloride were added to the above stirred solution, and the reaction mixture was kept under stirring for 3 h at 45 °C. Carbon disulfide was removed by vacuum distillation and 5.5 mL water and sodium bicarbonate were added, respectivel,y so that no bubbles appeared. The solid obtained by filtration was washed well with 5 % hydrochloric acid, 5 % sodium hydroxide, and water to pH 7, finally obtaining a purple red solid. The solid was recrystallized from CH_3CH_2OH/H_2O ($v_{CH_3CH_2OH} : v_{H_2O}* = *1 \equiv 1$) with the addition of activated carbon, when 2.17 g red needle crystals were obtained. The yield was 85.8 %, m.p. 139–140 °C.

IR (KBr, υ_{max}/cm^{-1}): 3,114, 3,085, 3,055, 3,025, 1,648 ($\upsilon_{C=O}$), 1,611, 1,590 ($\upsilon_{C=C}$), 1,496, 1,451; ^{1}H NMR ($CDCl_3$, 400 M, TMS, δ: ppm): 4.25 (s, 5H, Fc–H), 4.63–4.94 (d, 4H, Fc–H),7.14–7.18 (d, 1H, =CH), 7.28–7.69 (m, 5H, Ar–H),7.81–7.83 (d, 1H, =CH); Anal. Calcd. for $C_{19}H_{16}FeO$: C, 72.18 %; H, 5.10 %; Found: C, 72.15 %; H, 5.12 %.

General procedure for synthesis of compounds (**3a–c**)

Two mmol amine (**2a–c**), 0.28 g (2.4 mmol) tetrahydro-2*H*-thiopyran-4-alcohol, 0.63 g (2.4 mmol) triphenylphosphine, 0.42 g (2.4 mmol) DEAD and 10 mL THF were added to a dry three-neck flask (50 mL), and the reaction mixture was stirred at room temperature overnight. It was then concentrated under reduced pressure and 0.66 g (12 mmol) iron powder and 20 mL 95 % ethanol were added to the stirred solution, and the reaction mixture was heated at 50 °C. Next, 0.5 mL concentrated hydrochloric acid was added dropwise, and the reaction mixture was heated to reflux for 4 h, cooled, and filtered. The solution from reduced pressure condensation was washed with 30 mL (1 M) hydrochloric acid and ethyl acetate (10 mL × 2), and the water phase was adjusted to pH > 9 with sodium hydroxide and extracted with ethyl acetate (10 mL × 2).The combined extract was dried and evaporated to dryness, to provide a yellow solid. The solid was recrystallized from CH_3CH_2OH/H_2O with the addition of activated carbon.

*1-(Tetrahydro-2H-thiopyran-4-yl)-1H-pyrazol-4-amine (**3a**)*

The product of **3a** was white powder 0.27 g, the yield was 91.6 %, m.p. 192–194 °C. ^{1}H NMR ($CDCl_3$, 400 M, TMS, δ: ppm): 1.60–1.74 (m, 2H, –CH–CH_2–), 1.93–1.96 (d, 2H, –CH–CH_2–), 2.79 (s, 2H, –NH_2), 3.85–3.95 (m, 1H, –CH–

); 4.26 (s, 4H, $–CH_2–S–CH_2–$), 6.56 (s, 1H, pyrazole-H), 6.65 (s, 1H, pyrazole-H);^{13}C NMR ($CDCl_3$, 100 M, TMS, δ: ppm):28.39, 32.26, 52.51, 111.54, 124.66, 146.88; Anal. Calcd. for $C_8H_{13}N_3S$: C, 52.43 %; H, 7.15 %; N, 22.93 %; Found: C, 52.40 %; H, 7.18 %; N, 22.89 %.

*5-Methyl-1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazol-4-amine (**3b**)*

The product of **3b** was white powder 0.26 g, the yield was 65.99 %, m.p. 93–95 °C. ^{1}H NMR ($CDCl_3$, 400 M, TMS, δ: ppm): 1.48 (s, 3H, $–CH_3$), 1.66–1.76 (m, 2H, $–CH–CH_2–$), 1.94–1.98 (d, 2H, $–CH–CH_2–$), 2.82 (s, 2H, $–NH_2$), 3.86–3.92 (m, 1H, –CH–); 4.267 (s, 4H, $–CH_2–S–CH_2–$), 6.67 (s, 1H, pyrazole-H); ^{13}C NMR ($CDCl_3$, 100 M, TMS, δ: ppm): 11.08, 28.38, 32.23, 52.51,114.26,146.89, 150.01; Anal. Calcd. for $C_9H_{15}N_3S$: C, 54.79 %; H, 7.66 %; N, 21.30 %; Found: C, 54.82 %; H, 7.64 %; N, 21.28 %.

*1-(Tetrahydro-2H-thiopyran-4-yl)-1H-1,2,4-triazol-3-amine (**3c**)*

The product of **3c** was white powder 0.17 g, the yield was 46.20 %, m.p. 105–106 °C. ^{1}H NMR ($CDCl_3$, 400 M, TMS,δ: ppm): 1.84–1.91 (m, 2H,$–CH–CH_2–$), 2.08–2.11 (d, 2H, $–CH–CH_2–$), 2.87 (s, 2H, $–NH_2$), 4.06–4.23 (m, 5H,–CH–,$–CH_2–S–CH_2–$ coupling superimpose), 7.70 (s, 1H, triazole-H); ^{13}C NMR ($CDCl_3$, 100 M, TMS, δ: ppm): 28.39, 31.77, 57.03, 139.95, 163.21; Anal. Calcd. for $C_7H_{12}N_4S$: C, 45.63 %; H, 6.56 %; N, 30.41 %; Found: C, 45.60 %; H, 6.52 %; N, 30.38 %.

General procedure for synthesis of compounds (**4a**–**c**)

A mixture of 1 mmol compound **3a**–**c**, 0.32 g (1 mmol) compound **1**, 10.01 g triethylamine and 10 mL ethanol in a drying three-neck flask (50 mL) was stirred at room temperature overnight. Then, the black solid was obtained by concentration under reduced pressure. The crude product was purified by column chromatography on silica gel eluted with (v_{methanol}:$v_{\text{dichloromethane}}$ = 1:10) to give the compound **4a**–**c** as needle crystals.

*1-Ferrocenyl-3-phenyl-3-((1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazol-4-yl)amino)propan-1-ketone (**4a**)*

The product of **4a** was yellow needle crystals (0.18 g), the yield was 36.07 %, m.p. 156–158 °C. ^{1}H NMR (DMSO, 400 M, TMS, δ: ppm): 1.70–1.78 (m, 2H,$–CH–CH_2–$), 1.91–1.94 (d, 2H, $–CH–CH_2–$), 2.50–2.51 (m, 2H $S–CH_2–$), 2.87–2.89/ 5.39–5.48 (m, 2H, $C–CH_2–CH$), 3.02–3.04 (d, 2H, $–S–CH_2–$), 3.62–3.67 (m, 1H, CH–Ar),4.03 (s, 5H, Fc–H), 4.12 (m, 1H, C–CH–C), 4.13 (brs, 1H, N–H), 4.14–4.69 (m, 4H, Fc–H), 7.25–7.43 (m, 5H, Ar–H), 7.53/7.89 (s, 2H, pyrazole-H); ^{13}C NMR (DMSO, 100 M, TMS, δ: ppm): 29.23, 43.60, 46.00, 48.35, 59.43, 67.26, 67.86, 69.48, 70.59, 70.70, 74.89, 119.49, 124.56, 127.04, 130.24, 131.42, 143.88, 154.21; Anal. Calcd. for $C_{27}H_{29}FeN_3OS$: C, 64.93 %; H, 5.85 %; N, 8.41 %; Found: C, 64.90 %; H, 5.88 %; N, 8.38 %.

*1-Ferrocenyl-3-phenyl-3-((5-methyl-1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazol-4-yl)amino) propan-1-ketone (**4b**)*

The product of **4b** was yellow needle crystals (0.18 g), the yield was 31.19 %, m.p. 166–167 °C. ^{1}H NMR (DMSO, 400 M, TMS, δ: ppm): 1.70–1.74 (m, 2H, –CH–CH_2–), 1.89–1.91 (d, 2H,–CH–CH_2–), 2.13 (s, 3H, –CH_3), 2.50–2.51 (m, 2H, S–CH_2–), 2.76–2.81/5.38–5.46 (m, 2H, C–CH_2–CH), 3.00–3.03 (d, 2H, S-CH_2–), 3.48–3.57 (m, 1H, CH–Ar), 3.95 (s, 5H, Fc–H), 4.02 (m, 1H, C–CH–C), 4.04 (brs, 1H, N–H), 4.05–4.54 (m, 4H, Fc–H), 7.87 (s, 1H, pyrazole-H);^{13}C NMR (DMSO, 100 M, TMS, δ: ppm): 11.16, 29.02, 43.65, 46.07, 48.32, 59.44, 67.24, 67.82, 69.48, 70.57, 70.72, 74.89, 120.64, 124.34, 127.05, 130.25, 143.85, 153.99; Anal. Calcd. for $C_{28}H_{31}FeN_3OS$: C,65.49 %; H, 6.09 %; N, 8.18 %; Found: C,65.54 %; H, 6.06 %; N, 8.21 %.

*1-Ferrocenyl-3-phenyl-3-((1-(tetrahydro-2H-thiopyran-4-yl)-1H-1,2,4-triazol-3-yl)amino)propan-1-ketone (**4c**)*

The product of **4c** was yellow needle crystals (0.23 g), the yield was 46.00 %, m.p. 188–190 °C. ^{1}H NMR (DMSO, 400 M, TMS, δ: ppm): 1.74–1.82 (m, 2H, –CH–CH_2–), 1.96–1.98 (d, 2H, –CH–CH_2–), 2.55–2.60 (m, 2H, S–CH_2–), 2.74–2.78/ 5.40–5.49 (m, 2H, C–CH_2–CH), 3.02–3.04 (d, 1H, S–CH_2–), 3.48–3.57 (m, 1H, CH–Ar), 4.04 (s, 5H, Fc–H), 4.19–4.20 (m, 1H, C–CH–C), 4.21 (brs, 1H, N–H), 4.23–4.62 (m, 4H, Fc–H), 8.37 (s, 1H, triazole-H); ^{13}C NMR (DMSO, 100 M, TMS, δ: ppm): 28.98, 43.74, 45.75, 48.30, 59.24, 67.11, 67.70, 69.27, 69.32, 70.06, 70.72, 75.01, 127.07, 124.34, 127.99, 130.26, 142.46, 143.78, 153.87, 155.49; Anal. Calcd. for $C_{26}H_{28}FeN_4OS$: C, 62.40 %; H, 5.64 %; N, 11.20 %; Found: C,62.38 %; H, 5.68 %; N, 11.15 %.

Antimicrobial activity

Antibacterial activity

Antibacterial activity was determined in acetone by the filter paper disc method [43]. Five bacterial strains (*Escherichia coli*, *Saccharomyces aureus*, *Streptococcus*, *Actinomycete*, and *Saccharomyces cerevisiae*) were selected for the test.

Beef extract in agar medium was prepared by dissolving peptone (10 g), beef extract (5 g), sodium chloride (5 g), and agar (20 g) in distilled water (1,000 mL) and adjusting the pH to 7.5 or 7.6, and sterilized by dry heat at 120 °C for 30 min. Normal saline was used to make a suspension of strains for lawning. A loopful of a particular strain was transferred to normal saline to get a suspension of the corresponding species (10^6 cfu/mL). Agar medium (15 mL) was poured into each sterile Petri dish. Sterile filter paper discs (6 mm in diameter) saturated with the solution of test compounds (0.01 g of the synthesized compounds were dissolved separately in acetone to get a concentration of 5 mg/mL) were placed on the surface of an agar plate inoculated with 0.1 mL suspension. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium

Table 1 Antimicrobial activity of the compounds **1, 3a–c** and **4a–c**

Compound no. (5 mg/mL)	Zone of Inhibition (mm)				
	E. coli	*S. aureus*	*Streptococcus*	*Actinomycete*	*S. cerevisiae*
1	18.3	5.6	8.3	6.1	6.5
3a	26.7	6.9	8.9	9.7	7.4
3b	24.6	6.2	8.0	8.7	6.9
3c	20.3	5.5	7.1	6.3	5.5
4a	32.1	12.2	15.5	13.7	12.9
4b	30.0	11.1	14.8	12.5	11.8
4c	28.2	8.4	11.3	10.0	10.6
Acetone	-	-	-	-	-
Ampicillin	28.4	7.8	10.4	8.7	15.5

The data in the table are average values of three experiments, Acetone as blank, - indicates no antimicrobial activity, Ampicillin was used as reference drug

supplemented with the filter paper discs (6 mm in diameter) saturated with acetone and treated as blank in the experiments. The plates were prepared in triplicate and were incubated at 37 °C for 2–4 days for evaluating antimicrobial activity. The diameters of inhibition zones (in mm) of triplicate sets were measured and the results are given in Table 1. Ampicillin was used as reference drug.

For the antibacterial activity, the compounds were dissolved in acetone. Further dilutions of the compounds and reference drug in the test medium were prepared at the required quantities of 256, 128, 64, 32, 16, 8, 4, 2, and 1 μg/mL concentrations with Mueller–Hinton agar. The minimum inhibitory concentrations (MIC) were determined using the agar dilution method. A control test was also performed containing inoculated broth supplemented with just acetone at the same dilutions used in our experiments and found to be inactive in the culture medium. All the compounds were tested for their in vitro growth inhibitory activity against different bacteria and the results are summarized in Table 2.

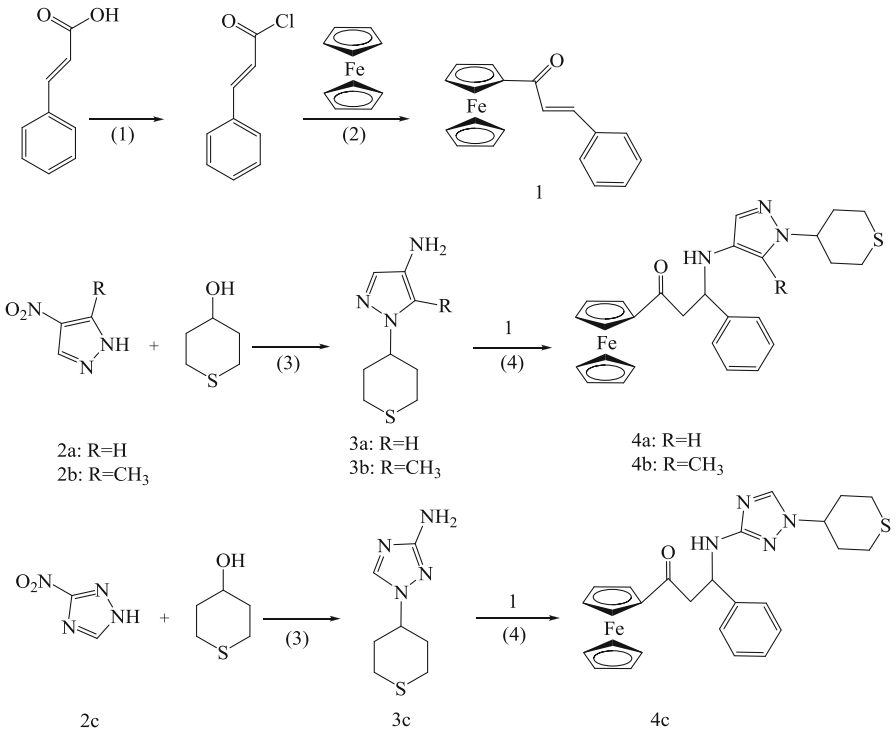
Table 2 Minimum inhibitory concentrations (MIC) of the compounds **1, 3a–c** and **4a–c** in μg/mL

Compounds no.	*E. coli*	*S. aureus*	*Streptococcus*	*Actinomycete*	*S. cerevisiae*
1	8	128	64	64	64
3a	2	64	64	64	64
3b	4	64	64	64	64
3c	8	128	64	64	128
4a	1	32	16	32	32
4b	2	32	16	32	32
4c	64	64	32	32	32
Ampicillin	2	64	32	64	16

Acetone as blank; Ampicillin was used as reference drug

Results and discussion

In this study, we report the synthesis of novel heterocyclic compounds containing a ferrocene unit. The synthetic strategy for desired compounds **4a–c** in three steps is depicted in Scheme 1. The compound 1 (ferrocenylchalcone) was traditionally synthesized by using acetylferrocene and aromatic aldehyde as starting materials. In order to avoid problems in the purification process of acetylferrocene, we designed one-pot synthesis of compound **1** by Friedel–Crafts acylation of cinnamic acid with ferrocene using phosphorus pentachloride as acylating agent in 85.84 % yields. This method had the advantage of easily available starting materials, easy procedure, and good yields. The characteristic vibration of the carbonyl group in the ferrocenylchalcone scaffold was observed at 1,648/cm. In the ^{1}H NMR spectra of compound **1**, the olefinic H_α and H_β protons have two bound doublets at δ (7.81–7.83) and (7.14–7.18) ppm. These indicate that the carbonyl group and olefinic group are present in the ferrocenylchalcone scaffold. The rest of the signals for protons appeared in the expected regions. In addition, protons of the amino group of compounds **3a–c** appeared as a singlet at δ 2.79, 2.82, and 2.87 ppm in the ^{1}H NMR spectra, respectively. The synthesized compounds **3a–c** were then treated with



Scheme 1 Synthesis route of compounds **1, 3a–c**, and **4a–c**. R:a,-H:b,-CH_3. Reaction reagents and conditions: (**1**) PCl_5, 20 °C, 2 h; (**2**) $CS_2/AlCl_3$, 45 °C, 3 h; (**3**) i: DEAD, PPh_3, THF, rt; ii: Fe, 95 %ethanol, HCl, reflux 4 h; (**4**) triethylamine, ethanol, rt

compound **1** to obtain target compounds **4a–c**. Successful synthesis of compounds **4a–c** was confirmed by the disappearance of the signals at δ (7.81–7.83) and (7.14–7.18) ppm in ^{1}H NMR spectra of the compound **1** which are related to the olefinic H_{α} and H_{β} protons, respectively, coupled with two broad multiplet δ (1.70–1.78) and (1.91–1.94) ppm, δ (1.70–1.74) and (1.89–1.91) ppm, δ (1.74–1.79) and (1.96–1.98) ppm in ^{1}H NMR spectra of the compounds **4a–c** which are related to –CH-CH_2-, respectively. In ^{1}H NMR spectra of compounds **4a–c**, a broad single at δ 4.13, 4.04, and 4.21 ppm due to N–H protons, respectively. The target compounds were well characterized by data of ^{13}C NMR.

The antimicrobial activity of test compounds was assessed in side-by-side comparisons with blank experiments and reference drug. The investigation of combined data revealed that some tested compounds showed moderate to excellent antibacterial activities against five tested strains and the synthesized compounds **1**, **3a–c**, and **4a–c** showing MIC values between 8 and 128, 2 and 128, and 1 and 64 μg/mL, respectively. Compounds **3a** and **4c** exhibited the best inhibitory activities against *E. coli* besides reference drug; their zones of inhibition were 26.7 and 28.2 mm, respectively. Compounds **3a** and **3b** showed better inhibitory activities against *Actinomycete* than reference drug; their zones of inhibition were 9.7 and 8.9 mm, respectively. Compounds **4a–c** showed stronger inhibitory activities against *S. aureus*, *Streptococcus*, and *Actinomycete* in comparison to reference drug and MIC values between 1 and 64 μg/mL. Among these tested compounds, compounds **4a** and **4b** exhibited the broadest spectrum and stronger inhibitory activities.

From what has been discussed above, we draw out from these novel heterocyclic compounds containing a ferrocene unit some speculative antimicrobial mechanisms. Ferrocenylchalcone had a relatively strong inhibitory effect on microbials, while heterocyclic compounds containing a ferrocene unit displayed a stronger antibacterial activity than ferrocenylchalcone due to the group of heterocyclic compounds of pyrazolyl or triazolyl derivatives being introduced. On the other hand, **4a** and **4b** showed different antimicrobial activities against the five tested strains since the substituent's steric hindrance of **4a** is less than for **4b**.

Conclusion

In summary, we have developed a simple and efficient method for the synthesis of ferrocenylchalcone. A series of novel heterocyclic compounds containing a ferrocene unit were synthesized and their antimicrobial activity has been tested. Compounds **4a** and **4b** showed the best inhibitory activity. This work offers an excellent framework in this field, which may lead to the discovery of potent antibacterial agents.

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