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Synthesis and Evaluation of Antimicrobial Activities of New Piperidine Derivatives

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Abstract: Nitrogen heterocycles with piperidine rings are the most prominent structural features and frequently utilized by pharmaceuticals. In this study, we have disclosed the synthesis of new compounds with piperidine motif. The synthesis of these derivatives was achieved using Wittig olefination, O-alkylation, and nucleophilic substitution reaction. The antimicrobial activity was performed by disc diffusion method utilizing *Staphylococcus aureus as* gram-positive *and Escherichia coli* as a gram-negative bacterial pathogen, respectively.

Keywords: N-Heterocycles; Piperidine; Antimicrobial; Wittig olefination; O-alkylation.

1. Introduction

The heterocyclic compounds are known from the centuries and play an essential role in chemistry, biology, and medicine [1]. Moreover, molecules with the presence of heterocycles, both natural products and synthetic drugs, showed excellent bioactivity [2–6]. Over the past three decades, these structural features of heterocycles have been thoroughly exploited by researchers [7–9].

Among them, the nitrogen-containing heterocycles have attracted due to their broad applications in natural products [10–13], alkaloids [14], pharmaceutical drugs [15], or drug-like molecules [16–17], synthetic building blocks [18–23], electronics, material science [24–25], polymers [26], Dyes [27–28], and agrochemicals [29]. Interestingly, the saturated N-heterocycles are associated with certain advantages such as better solubility of drugs to enhance their metabolism [30–31], than the corresponding aromatic N-heterocycles. Mainly, the piperidine moieties are a fascinating class of N-heterocycles, found in therapeutic agents [32–34], and chiral molecules [35–36], with significant biological activity, for example, antihypertensive, antibacterial [37–38], antimalarial [39], anticonvulsant [40], anti-inflammatory [41-42], antiproliferative, antitubercular and antioxidant [43–44].

Due to the importance of the piperidine scaffold, several functionalized derivatives have been investigated to find the lead compound (Figure 1) [45]. Cinnamic acid derivatives such as esters, amides, and hydrazide have been exploited due to their essential antioxidant and anti-inflammatory activities [46–47]. Although a great variety of piperidine derived bioactive molecules have been studied, the combination of piperidine with α,β-unsaturated esters (cinnamate) is not known in the literature. Earlier, we have reported the asymmetric syntheses of piperidine-based molecules [48–50]. We present here an efficient method to synthesize

piperidine derivatives and investigation of their antimicrobial bioactivity against pathogens *Escherichia coli* as gram-positive and *Staphylococcus aureus* as gram-negative bacteria.

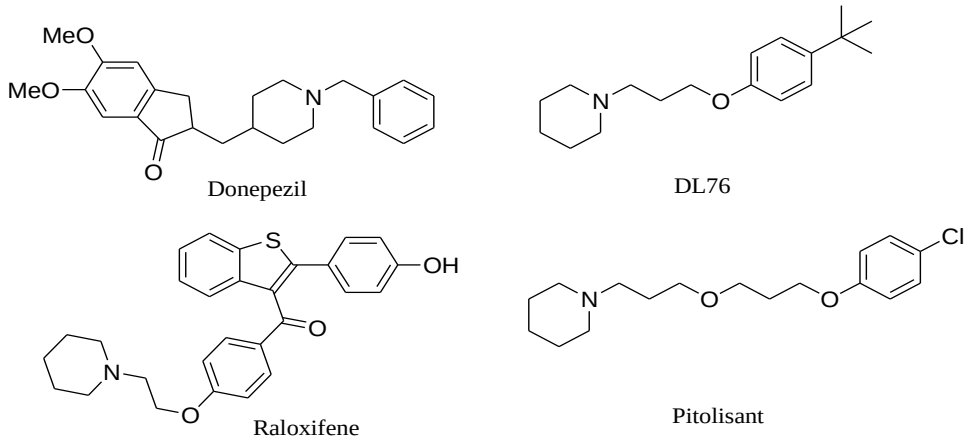


Figure 1. Lead drugs and bioactive molecules with piperidine core.

2. Materials and Methods

4-Hydroxy benzaldehyde, Wittig reagent [(carbethoxymethylene) triphenylphosphorane], and piperidine were purchased from Sigma-Aldrich, South Korea. The solvents and reagents (analytical grade) were procured from India, and it was used as such without any purification. The progress of the reaction was monitored using thin-layer chromatography (TLC), and the appearance of TLC spots was visualized by UV-lamp at 254 and 365 nm. The purification of products was performed using a chromatographic method using 60-120 mesh silica gel and a combination of solvents hexane:EtOAc. All the obtained products were characterized using FTIR, melting points, ^{1}H- and ^{13}C-NMR and DEPT NMR. Melting points (m.p.) were recorded on the MEL-TEMP instrument in closed capillaries without correction. A FT-IR spectrum has been recorded on Shimadzu 4000 FT-IR using KBr pellet. Bruker instrument has been utilized to measure ^{1}H-NMR of synthesized compounds, including ^{13}C-NMR at 400 MHz for proton spectra and 100 MHz for carbon spectra, respectively.

2.1. Synthesis.

2.1.1. Synthesis of 3-(4-Hydroxyphenyl)-(*E*)-ethyl propenoate (6).

A round bottom flask (100 mL) along-with magnetic bar, (Ethoxycarbonylmethylene) triphenylphosphorane (**7**) (10.45 g, 30 mmol) and deionized water (60 mL) was introduced successively. The resulting solution was stirred at 25 ^{o}C for 5 minutes. Then, 4-hydroxybenzaldehyde (**8**) (2.44 g, 20 mmol) was slowly added to the flask. Again the whole mixture was allowed to stir for 5 minutes at room temperature and further heated to 80-90 °C (2 h) with continuous stirring. The reaction was monitored with the help of TLC. After completion of the reaction, it was cooled to 25 ^{o}C, and then transferred to a separatory funnel, and CH_2Cl_2 (3 × 40 mL) was used as an extraction solvent.[51] The combined organics was treated with water (15 mL) and anhydrous Na_2SO_4. Removal of CH_2Cl_2 was carried out using a rotary evaporator resulted in the oil as a crude product. The crude product **6** was subjected to the chromatographic purification using 60-120 meshed silica gel, elution of 20% EtOAc in *n*-hexane to provide 3-(4-Hydroxyphenyl)-(*E*)-ethyl propenoate in 85% (3.264 g) as a colorless solid.

Melting point: 68-72 ^{o}C; FTIR in KBr (cm^{-1}): 680, 979, 1110, 1205, 1291, 1380, 1473, 1595, 1610, 1716, 2922, 3224; ^{1}H-NMR in $CDCl_3$ (300 MHz) δ= 7.58 (d, 1H, $H^{\beta}C=CH^{\alpha}R$, *J* = 16 Hz), 7.42 (multiplet, 2H), 6.90 (m, 2H), 6.30 (d, 1H, $H^{\beta}C=CH^{\alpha}$-R, *J* = 16 Hz), 5.40 (brs, 1H, H-O-Ar), 3.80 (q, 2H, OCH_2, *J* 7.2 Hz & *J* 6.8 Hz), 1.37 (t, 3H, CH_3, J 7.2 Hz & J 6.8 Hz); ^{13}C-NMR in $CDCl_3$ (100 MHz) δ= 168.58, 158.81, 145.38, 130.10, 126.49, 116.08, 114.78, 60.88, 14.28.

2.1.2. Synthesis of (E)-ethyl 3-(4-(2-bromoethoxy)phenyl)acrylate (3).

Wittig product 3-(4-Hydroxyphenyl)-(*E*)-ethyl propenoate (**6**) (2.88 g, 15 mmol) was dissolved using 25 mL of dimethyl formamide. Then the resulting solution was allowed to stir at 25 ^{o}C, and KOH (2.52 g, 45 mmol) was introduced in one portion. Subsequently, 1,2-dibromoethane (**5**) (4.133 g, 22 mmol) was introduced with the help of a syringe. This whole mixture was allowed to heat (80 ^{o}C) for 3 h. The development of the reaction was monitored using TLC [52]. After completion of the reaction, the flask was cooled to 25 ^{o}C, extracted with EtOAc (40 mL x 3). Then ethyl acetate (EtOAc) layer was treated with anhydrous Na_2SO_4 followed by evaporation of ethyl acetate using a rotary evaporator. Thus the obtained crude residue (**3**) was subjected to chromatographic purification using a column packed with (60-120 mesh) silica gel and eluent as EtOAc:hexane (5%) affording pure (E)-ethyl-3-(4-(2-bromoethoxy)phenyl)acrylate (**3**) in 70% (3.142 g) yield as white solid.

Melting point: 45-50 ^{o}C; FTIR in KBr (cm^{-1}): 627, 645, 810, 1007, 1054, 1152, 1173, 1225, 1280, 1491, 1597, 1712, 2845, 2910, 2997; ^{1}H-NMR in $CDCl_3$ (400 MHz) δ= 7.50 (d, 1H, $H^{\beta}C=CH^{\alpha}R$, *J* 16 Hz), 7.65 (d, 2H, *J* 8.4 Hz), 6.93 (d, 2H, *J* 8.8 Hz), 6.34 (d, 1H, $H^{\beta}C=CH^{\alpha}R$, *J* 15.6 Hz), 4.34 (t, 2H, OCH_2, *J* 6.2 Hz), 4.27 (q, 2H, OCH_2, *J* 7.2 Hz), 3.67 (t, 2H, $BrCH_2$, *J* 6.2 Hz), 1.35 (t, 3H, CH_3, *J* 7.0 Hz); ^{13}C-NMR in $CDCl_3$ (100 MHz) δ= 167.25, 159.75, 143.99, 129.76, 127.92, 116.26, 115.01, 67.86, 60.40, 28.79, 14.28.

2.1.3. Synthesis of (E)-ethyl 3-(*p*-(2-(piperidin-1-yl) ethoxy) phenyl) acrylate (1).

A 500 mL clamped flask charged with commercially available piperidine (**4**) (2.55 g, 30 mmol) followed by addition of ethanol (250 mL). The solution was stirred at 25 ^{o}C for 5 minutes, followed by the addition of (E)-ethyl-3-(4-(2-bromoethoxy)phenyl)acrylate (**3**) (4.488 g, 15 mmol). Subsequently, K_2CO_3 (6.219 g, 45 mmol), then the catalytic portion of KI in water (20 mL) was introduced to the above reaction mixture [53]. The whole solution was refluxed up to 24 h, and the progress of the reaction was observed using TLC. After 24 h, the reaction flask was cooled to ambient condition. It was observed that white solid appeared at the bottom of the flask, which was separated using filter paper, and the resulting organic layer was evaporated using a rotary evaporator. Finally, obtained oil was again mixed with CH_2Cl_2 (100 mL) followed by treatment with HCl (0.5%) and NaOH (0.5%) and H_2O (40 mL). The solvent was exposed to Na_2SO_4. The solvent was removed using a rotary evaporator to afford product **1** in crude form. The residue of product **1** was then purified using the chromatographic technique by (60-120 mesh) silica gel and eluted with 30% mixture of ethyl acetate in *n*-hexane as to isolate pure (E)-ethyl 3-(*p*-(2-(piperidin-1-yl) ethoxy) phenyl) acrylate (**1**) in 25% yield (1.14 g) as a brown liquid.

FTIR neat (cm^{-1}): 670, 710, 873, 953, 1069, 1163, 1210, 1239, 1305, 1452, 1643, 1720, 2940, 2963; ^{1}H-NMR in $CDCl_3$ (400 MHz) δ= 7.55 (m, 2H), 7.02 (d, 1H, $H^{\beta}C=CH^{\alpha}R$), 6.51 (m, 2H), 6.22 (d, 1H, $H^{\beta}C=CH^{\alpha}R$), 3.45 (q, OCH_2, 2H), 3.29 (t, OCH_2, 2H), 2.34-1.64 (m, 6H,

-C*H*$_2$ of Pip) 1.04-0.67 (m, 6H, Piperidine 3,4,5-*H*) 0.52 (t, 3H, CH_3); ^{13}C-NMR in $CDCl_3$ (100 MHz) δ= 171.17, 157.45, 139.03, 130.06, 128.73, 113.19, 78.01, 65.33, 59.33, 57.41, 54.46, 26.41, 24.50, 13.51.

2.1.4. Synthesis of (E)-methyl 3-(*p*-(2-(piperidin-1-yl) ethoxy)-phenyl) acrylate (2).

To the round bottom flask (E)-ethyl 3-(p-(2-(piperidin-1-yl) ethoxy)-phenyl) acrylate (**1**) (0.607 g, 2 mmol) was dissolved in MeOH (15 mL) and allowed to stir at 25 ^{o}C. To this solution, anhydrous Na_2CO_3 (0.212 g, 2 mmol) has been introduced and further heated to reflux (5 h), and the development of reaction was observed by TLC. Then the flask was cooled to 25 ^{o}C,[54], and the solvent (MeOH) was evaporated under vacuum. The obtained crude residue was dissolved with a mixture of EtOAc–*n*-hexane (1:1, 10 mL) followed by filtration in order to remove unwanted salts. Evaporation of the solvent gave crude product **2** as oil, which was subjected to chromatographic separation using (60-120 mesh) silica gel and elution with 30% EtOAc:*n*-hexane to provide pure (E)-methyl 3-(p-(2-(piperidin-1-yl)ethoxy)-phenyl) acrylate (**2**) in 85% yield (4.13 g) as a brown oil.

FTIR neat (cm^{-1}): 665, 715, 745, 868, 945, 1052, 1155, 1223, 1247, 1318, 1460, 1610, 1645, 1715, 2923, 2976; ^{1}H-NMR in $CDCl_3$ (400 MHz) δ= 7.55 (m, 2H, Ar-H), 6.97 (m, 2H, Ar-H), 6.46 (d, 1H, $H^{\beta}C=CH^{\alpha}R$ *J* = 8.0 Hz), 6.17 (d, 1H, $H^{\beta}C=CH^{\alpha}R$, *J* 8.0 Hz), 3.40 (t, 2H, -O-CH_2, *J* 8.0 Hz), 2.90 (s, 3H, O-CH_3), 2.26 (t, 2H, N-CH_2, *J* 7.2), 2.12 (m, 2H, N-CH_2, *J* 7.2 Hz & *J* 6.8 Hz), 1.90 (m, 2H, N-CH_2), 1.12 (m, 2H, R-CH_2R *J* 6.8 Hz); ^{13}C-NMR in $CDCl_3$ (100 MHz) δ= 171.48, 157.42, 143.70, 130.10, 128.55, 114.21, 113.17, 78.01, 65.02, 57.40, 54.43, 26.49, 24.54.

2.2. Evaluation of antibacterial activity.

The *in-vitro* antibacterial screening of piperidine derivatives **1** and **2** were tested using two bacteria, namely *Escherichia coli* and *Staphylococcus aureus*, using the disc diffusion method. The disc diffusion method was performed with Whatman No.1 filter paper making discs measuring in 6 mm diameter. The compounds **1-2** and standard compounds were dissolved using ethanol with a concentration of 10 mg/mL. The aliquots of 10 µL and 20 µL of the sample and standard solutions were added out to the discs, each in triplicate. The paper discs impregnated with the aliquots of 10 µL and 20 µL of the sample was transferred to a petri dish where the bacteria was cultivated. Sampling Petri dish was poured with a 20 mL Mueller-Hinton agar medium with 0.1 mL of the corresponding microorganism, which was spread through glass rod. Then the petri dish was incubated, keeping temperature 37 °C, for 24 h. The antibacterial activity was calculated based on measuring the area of inhibition zone in diameter. All these tests were carried out in triplicate, and the mean of inhibition zone (dm), was calculated and presented as mean ± standard deviation. The results obtained were compared with commercially available drug chloramphenicol as standard.

2.2.1. Preparation of media.

The *in-vitro* antibacterial screening of newly synthesized compounds **1** and **2** were tested against two bacterial species, namely *Escherichia coli* and *Staphylococcus aureus*, using the disc diffusion method.[55] Mueller-Hinton agar (MHA) was used as a medium to study biological assay, which was made by dissolving 3.8 g MHA and 100 mL distilled water. In order to make a homogeneous solution, the medium was heated gently with frequent agitation

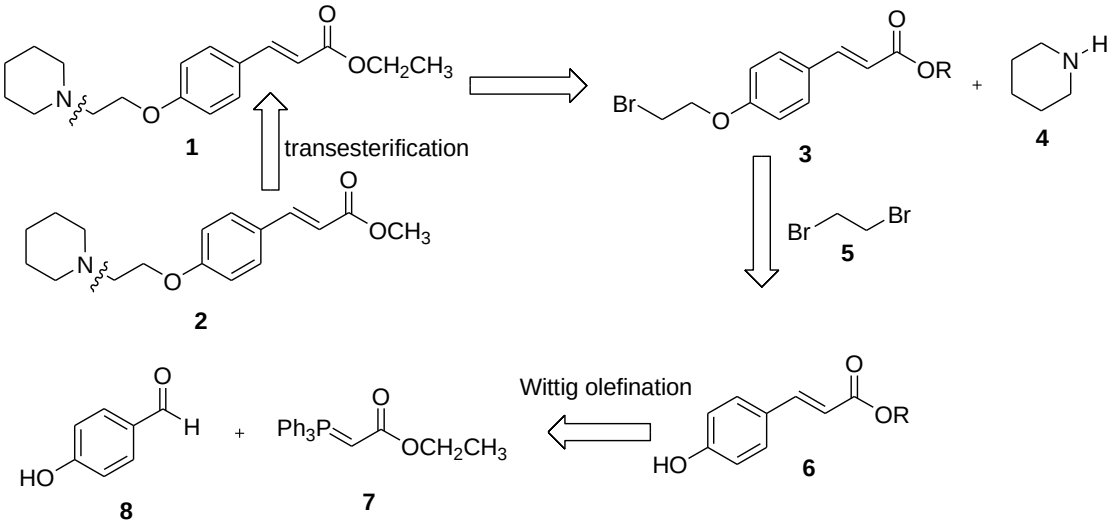
and then boiled for one minute. Later, the medium was autoclaved, keeping temperature 121 ^{o}C, 15 min., which was further cooled to 25 ^{o}C. The pH of the medium was maintained at 7.1.

3. Results and Discussion

3.1. Synthesis of designed piperidine derivatives.

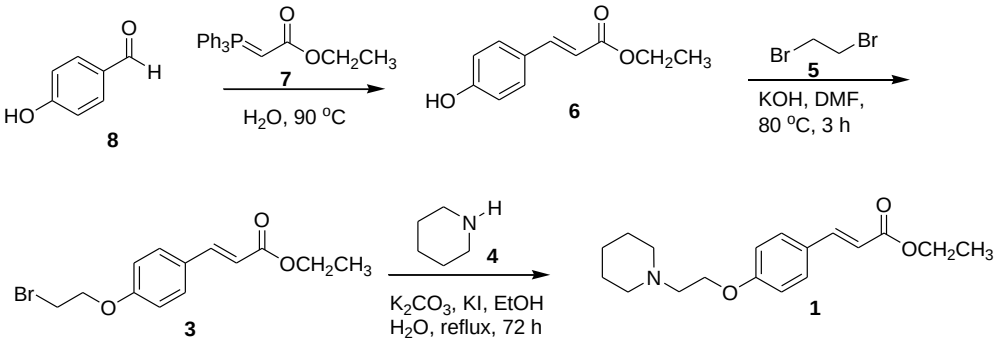
Both piperidine and cinnamic acid esters are associated with important biological properties. In the literature, there is no report to combine these two molecules as lead structures. Therefore we have chosen to synthesize new derivatives with a combination of piperidine and cinnamic acid esters based on the fact that they are highly bioactive substances. The retrosynthetic analysis of the newly designed piperidine derivatives **1** and **2** is represented in Scheme 1. In order to find the shortest synthetic route, the first disconnection could be possible between C-N bond of target compounds (**1** and **2**), which resulted in the two fragments **3** and **4**. These two intermediate **3** and **4** possibly join through nucleophilic substitution reaction to give target **1**.

Further, the intermediate **3** envisaged synthesizing by employing O-alkylation reaction of 1,2-dibromoethane (**5**) with α-β-unsaturated ester **6**. The α-β-unsaturated ester (**6**) could be further obtained from 4-hydroxylbenzaldehyde **8** via Wittig olefination reaction (**7**). While the target compound **2** could be achieved by a transesterification reaction of **1** with methanol.



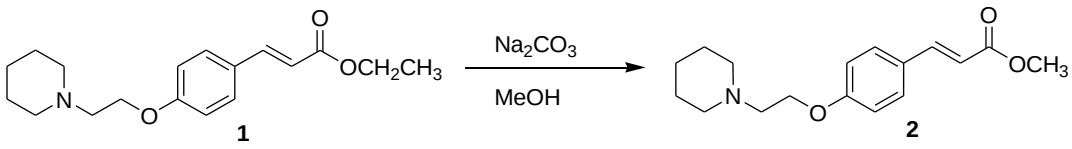
Scheme 1. Retrosynthetic analysis of designed piperidine derivatives.

The synthesis of desired piperidine compounds (**1** and **2**) was achieved by employing Wittig olefination, O-alkylation, and nucleophilic displacement reactions outlined in Scheme 2. The α-β unsaturated ester **6** was obtained by employing Wittig olefination of 4-hydroxy benzaldehyde (**8**) and phosphonate ester (7) in aqueous conditions at 90 ^{o}C. Obtained α-β unsaturated ester **6** was then reacted with potassium hydroxide in DMF followed by alkylating agent 1,2-dibromoethane (**5**), which resulted in the formation of O-alkylated-α-β unsaturated ester in good yield. Finally, the introduction of piperidine moiety was accomplished by subjecting a nucleophilic substitution reaction. Thus, the reaction of O-alkylated-α-β unsaturated **3** with piperidine (**4**) under alkaline conditions K_2CO_3 and KI as a catalyst in the presence of aqueous ethanol produce the compound1 in good yield.



Scheme 2. Synthesis of (E)-ethyl 3-(p-(2-(piperidin-1-yl)ethoxy)phenyl)acrylate (**1**).

In order to synthesize compound **2** we utilized a transesterification strategy (Scheme 3). Therefore, compound **1** was treated with carbonate and methanol at ambient conditions to give the desired compound **2**.



Scheme 3. Synthesis of (E)-methyl 3-(p-(2-(piperidin-1-yl) ethoxy)-phenyl)-acrylate (**2**).

3.2. In-vitro antibacterial study.

The antibacterial activities of the target products (1-2) were tested against pathogenic bacteria strains by using the disc diffusion method. The newly synthesized compounds were examined, against *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative) bacterial species grown in Mueller-Hinton agar (MHA). The results were compared with the commercially available antibiotic drug chloramphenicol as a reference. The test results obtained for the synthesized compounds **1** and **2**, which was exposed to bacterias species *Staphylococcus aureus* and *Escherichia coli*, are presented in Table 1.

Table 1. Antibacterial activities of piperidine derived analogs .[a]

Antibacterial activities (Inhibition zone)			
Samples	Microorganism	Inhibition zone in mm Concentration in 10mg/ml	
		10 µL	20 µL
Compound **1**	*Escherichia coli*	6± 0.82	9± 1.41
	Staphylococcus aureus	17± 1.63	22± 4.32
Compound **2**	*Escherichia coli*	8± 0.82	12± 0
	Staphylococcus aureus	18± 2.94	24± 3.26
Ethanol	*Escherichia coli*	--	--
	Staphylococcus aureus	--	--
Chloramphenicol	*Escherichia coli*	28± 2.16	31± 3.56
	Staphylococcus aureus	19± 1.63	23± 2.45

[a] Procedure for sample preparation is presented in the materials and methods section.

From Table 1, it was observed that piperidine derivatives were active against *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative) bacteria. From the inhibition data of synthesized compounds, compound **2** was more active than the corresponding analogs **1**. Additionally, compound **2** showed good activity with respect to the commercially available standard drug chloramphenicol against gram-positive bacteria (*Staphylococcus aureus*). This activity resulted from the decrease of the hydrocarbon chain of the ester part. Compounds **1** and **2** were active against *E. coli*, gram-negative bacteria as compared with standard drug chloramphenicol.

4. Conclusions

We have described the synthesis of new compounds namely (E)-ethyl 3-(*p*-(2-(piperidin-1-yl)ethoxy)phenyl)acrylate (**1**) and (E)-methyl 3-(*p*-(2-(piperidin-1-yl)ethoxy)phenyl)-acrylate (**2**) employing simple reaction conditions for example Wittig olefination, O-alkylation and nucleophilic displacement reaction. Furthermore, the synthesized compounds (**1** and **2**) were evaluated for their antibacterial activity using the disc diffusion method. The compounds **1** and **2** have been investigated employing *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative) bacteria, respectively. Interestingly, compound **1** showed moderate antibacterial activity, while compounds **2** displayed excellent antibacterial activity as compared with standard drugs.

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Conflicts of Interest

The authors declare no conflict of interest.

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