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Design, Synthesis and Antibacterial Activity Evaluation of 4,5-Diphenyl-1*H*-Imidazoles Derivatives

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Abstract

Due to the continuous emergence and rapid spread of drug-resistant strains of bacteria, there is an urgent need for the development of novel antimicrobials. Along this line, the synthesis and antibacterial activity of 4,5-diphenyl-imidazol-2-thiol derivatives **2a-g** and **6a-e** are reported. The structures of the synthesized compounds were confirmed by Nuclear Magnetic Resonance (NMR) and High Resolution Mass Spectrometry (HRMS). All compounds were screened *in vitro* for their antibacterial activity against *Pseudomonas aeruginosa* and *Escherichia coli* (Gram-negative bacteria) and also against *Staphyloccocus aureus* and *Enterococcus faecalis* (Gram-positive bacteria). The results showed most of the synthesized compounds have no antibacterial activity. However compound **6d** was two-fold potent than ciprofloxacin against *Staphylococcus aureus* with Minimum Inhibitory Concentration (MIC) of 4 μg/mL and **6c** showed moderate biological activity against *Staphylococcus aureus* (16 μg/mL) and *Enterococcus faecalis* (16 μg/mL).

Keywords

Synthesis, 4,5-diphenylimidazole-2-thiol, Benzimidazole, Antibacterial Activity, Drug-Resistant

1. Introduction

Infectious diseases caused by bacterial pathogens represent a major public health issue in recent years due to the emergence and spread of new strains of bacteria [1] and the widespread occurrence of drug resistance [2]. Thus, the development

of new types of antibacterial drugs, especially those with a new drug target and/or with the ability to overcome drug resistance [3] is an urgent need. Structural modification of antimicrobial drugs to which resistance has developed, has been shown to be an effective way to prolong the lifespan of antifungal agents such as azoles [4], antiviral agents such as nonnucleoside reverse transcriptase inhibitors [5], and various antibacterial agents including imidazole and benzimidazole [6] [7] [8] [9]. Currently, some of the various marketed drugs available (**Figure 1**) have imidazole or benzimidazole in their structures.

Because the heterocyclic ring includes the core of the active moiety or pharmacophores, we have been interested in working on structural modification of imidazole and benzimidazole. Besides this, these two heterocyclics containing nitrogens can be substituted in different positions to give several compounds with antibacterial activity [10] [11].

Considering the importance of both moieties imidazole and benzimidazole, we hypothesize their presence in the same structure would lead to compounds with higher potent. In the present study, we report the design, synthesis and antibacterial activities of some compounds containing both imidazole and benzimidazole motifs (**Scheme 1** and **Scheme 2**), modified from 4,5-diphenyl-imidazol -2-thiol. All the structures of the synthesized compounds were confirmed by NMR (^{1}H and ^{13}C) and HRMS spectra and their activities were illustrated against some gram-positive and gram-negative bacteria.

2. Materials and Methods

2.1. Chemistry

All chemical reagents and solvents used were of reagent grade or purified using standard methods. NMR spectra were recorded at ^{1}H (400 MHz or 600 MHz) and ^{13}C (101 MHz or 400 MHz) on a Bruker instrument. Coupling constants (J) and chemical shifts (δ) are given in hertz and ppm respectively, using TMS (^{1}H NMR) and solvents (^{13}C NMR) as internal standards.

High resolution mass spectrometry (HRMS) analyses are performed on a hybrid quadrupole time-of-flight mass spectrometer (Micromass-Waters Q-TOF Ultima global), equipped with an electrospray ionization source and a MALDI source. All these analyses are carried out at the Laboratory of Glycochemistry, Antimicrobials and Agroresources (LG2A) of the University of Picardie Jules Verne, Amiens. The melting points were measured using a KOFLER bench.

The purification of the products is carried out by flash chromatography on

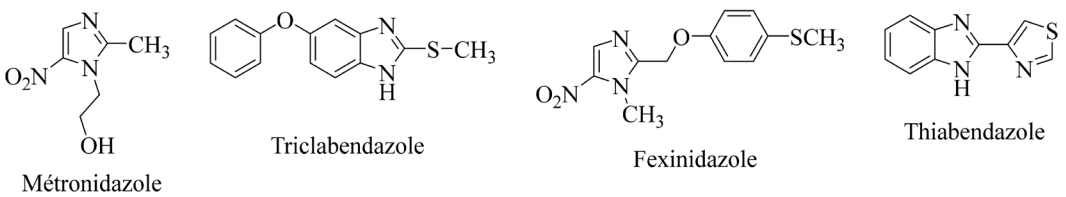


Figure 1. Chemical structure of some imidazole and benzimidazole-supported anti-infective compounds.

silica gel (Silica gel 60) pushed by compressed air using a mixture of cyclohexane/ethyl acetate eluent in variable proportions. Thin layer analytical chromatography (TLC) was performed on silica gel on aluminum support (Merck DC-Autofolien Kiesegel 60 F_{254} commercial plates, silica thickness 0.2 mm in normal phase). The products are then revealed under UV lamp (wavelength 254 nanometer).

General procedure for the synthesis of 2-(benzylthio)-4,5-diphenyl-1*H*-imidazoles 2a-g

The synthesis of 2-(benzylthio)-4,5-diphenyl-1*H*-imidazoles **2a-g** was carried out in two steps from benzoin. First, 4,5-diphenyl-1*H*-imidazol-2-thiol **1** was prepared by the condensation of benzoin with thiourea in dimethylformamide (DMF) at 150˚C using the reported procedure [12]. Then, to a solution of 4,5-diphenyl-imidazol-2-thiol (50 mg; 0.1985 mmol) in absolute ethanol (10 mL), an appropriate benzyl bromide derivative (1.2 eq) was added. The mixture was refluxed for 3 hours. After cooling to room temperature, the reaction mixture was placed in an ice bath then neutralized with sodium hydrogen carbonate solution (5%). The mixture was diluted in ethyl acetate and washed several times with water. The organic phase was dried over anhydrous sodium sulphate, filtred and the solvent was evaporated under reduced pressure.

The residue obtained was purified by silica gel chromatography (cyclohexane/ethyl acetate: 30/70) to give the compounds **2a-g**.

2-(benzylthio)-4,5-diphenyl-1*H*-imidazole 2a [13]

White crystals, yield = 85%, m p: 186˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.57 (s, 1H, NH), 7.49 - 7.19 (m, 15H, H-Ar) 4.40 (s, 1H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 138.52 (C=N), 128.61 (2C, CH-Ar), 128.38 (2C, CH-Ar), 128.12 (2C, CH-Ar), 127.91 (2C, CH-Ar), 127.54 (2C, CH-Ar), 127.35 (1C, CH-Ar), 126.92 (1C, CH-Ar), 126.68 (2C, CH-Ar), 126.26 (1C, CH-Ar), 36.97 (SCH_2). HRMS: m/z calculated for $C_{22}H_{19}N_2S$ $[M + H]^+$: 343.1269; found: 343.1272.

2-(4-nitrobenzylthio)-4,5-diphenyl-1*H*-imidazole 2b

Yellow crystals, yield = 70%, m p: 168˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.13 (d, 2H, H-Ar), 7.46 - 7.42 (m, 6H, H-Ar), 7.33 - 7.28 (m, 6H, H-Ar), 4.34 (s, 1H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d6) δ: 146.61 (NO_2-C-Ar), 146.54 (CH2-C-Ar) 139.59 (C=N), 129.86 (4C, CH-Ar), 128.40 (1C, CH-Ar), 127.93 (1C, CH-Ar), 127.55 (1C, CH-Ar), 127.43 (1C, CH-Ar), 126.66 (1C, CH-Ar), 126.32 (1C, CH-Ar), 123.23 (4C, CH-Ar), 36.03 (SCH_2). HRMS: m/z calculated for $C_{22}H_{18}N_3O_2S$ $[M + H]^+$: 388.1120; found: 388.1108.

2-(4-trifluorobenzylthio)-4,5-diphenyl-1*H*-imidazole 2c

White crystals, yield = 78%, m p: 182˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.58 (s, 1H, NH), 7.68 (d, 2H, H-Ar), 7.47 - 7.19 (m, 10H, H-Ar), 4.46 (s, 2H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 143.31 (CH_2-C-Ar) 138.98 (C=N), 129.67 (2C, CH-Ar), 128.67 (2C, CH-Ar), 128.20 (2C, CH-Ar), 127.82 (2C, CH-Ar), 127.69 (1C, CH-Ar), 126.94 (2C, CH-Ar), 126.58 (1C, CH-Ar), 125.26 -

125.22 (2C, CH-Ar), 36.24 (SCH_2). HRMS: m/z calculated for $C_{23}H_{18}F_3N_2S$ [M + H]$^+$: 411.1143; found: 411.1154.

2-(4-chlorobenzylthio)-4,5-diphenyl-1*H*-imidazole 2d

Light yellow crystals, yield = 73%, m p: 150˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.58 (s, 1H, NH), 7.49 - 7.47 (m, 2H, H-Ar), 7.42 - 7.37 (m, 8H, H-Ar), 7.33 (td, 1H, H-Ar), 7.29 (t, 2H, H-Ar), 7.23 - 7.20 (m, 1H, H-Ar), 4.38 (s, 2H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 139.24 (C=N), 130.73 (2C, CH-Ar), 128.67 (2C, CH-Ar), 128.34 (2C, CH-Ar), 128.20 (2C, CH-Ar), 127.82 (2C, CH-Ar), 127.66 (1C, CH-Ar), 126.95 (2C, CH-Ar), 126.56 (1C, CH-Ar), 36.12 (SCH_2). HRMS: m/z calculated for $C_{22}H_{18}ClN_2S$ [M + H]$^+$: 377.0879; found: 377.0880.

2-(3,5-dichlobenzylthio)-4,5-diphenyl-1*H*-imidazole 2e

White crystals, yield = 76%, m p: 178˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.60 (s, 1H, NH), 7.48 - 7.20 (m, 13H, H-Ar), 4.33 (s, 2H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d6) δ: 142.91 (CH_2-C-Ar), 138.59 (C=N), 128.67 (2C, CH-Ar), 128.20 (2C, CH-Ar), 127.81 - 127.80 (4C, CH-Ar), 127.71 (1C, CH-Ar), 126.95 (2C, CH-Ar), 126.65 (1C, CH-Ar), 126.61 (1C, CH-Ar), 35.92 (SCH_2). HRMS: m/z calculated for $C_{22}H_{17}Cl_2N_2S$ [M + H]$^+$: 411.0489; found: 411.0488.

2-(4-fluorobenzylthio)-4,5-diphenyl-1*H*-imidazole 2f [13]

Yellow crystals, yield = 88%, m p: 160˚C. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.59 (s, 1H, NH), 7.51 - 7.50 (m, 2H, H-Ar), 7.45 - 7.42 (m, 2H, H-Ar), 7.41 - 7.39 (m, 3H, H-Ar), 7.33 - 7.27 (m, 3H, H-Ar), 7.22 - 7.20 (m, 1H, H-Ar), 7.15 - 7.12 (m, 2H, H-Ar), 4.40 (s, 2H, SCH_2). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 162.15 and 160.54 (F-C-Ar), 139.44 (C=N), 130.86 (1C, CH-Ar), 130.81 (1C, CH-Ar), 128.65 (2C, CH-Ar), 128.19 (2C, CH-Ar), 127.82 (2C, CH-Ar), 127.62 (1C, CH-Ar), 126.97 (2C, CH-Ar), 126.54 (1C, CH-Ar), 115.21 (1C, CH-Ar), 115.07 (1C, CH-Ar), 36.13 (SCH_2).

2-(4-méthylbenzylthio)-4,5-diphenyl-1*H*-imidazole 2g

White crystals, yield = 88%, m.p: 164˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.57 (s, 1H, NH), 7.51 - 7.50 (m, 2H, H-Ar), 7.40 - 7.37 (m, 4H, H-Ar), 7.33 - 7.27 (m, 5H, H-Ar), 7.21 (t, 1H, H-Ar), 7.12 (d, 2H, H-Ar), 4.37 (s, 2H, SCH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 139,74 (C=N), 128.96 (2C, CH-Ar), 128.80 (2C, CH-Ar), 128.64 (2C, CH-Ar), 128.18 (2C, CH-Ar), 127.80 (2C, CH-Ar), 127.59 (1C, CH-Ar), 126.96 (2C, CH-Ar), 126.51 (1C, CH-Ar), 36.79 (SCH_2), 20.68 (CH_3). HRMS: m/z calculated for $C_{23}H_{21}N_2S$ [M + H]$^+$: 357.1425; found: 357.1423.

General procedure for the synthesis of 2-(chloromethyl)-1*H*- benzimidazoles 5a-e [14] [15] [16]

To a solution of orthophenylenediamine or derivatives **3** (50 mg; 0.1985 mmol) in 5 mL hydrochloric acid (4N), 1.5 equivalents of chloroacetic acid **4** was added. The mixture was refluxed for 15 hours. After cooling to room temperature, the reaction mixture was placed in an ice bath then neutralized with sodium hydrogen carbonate solution (5%). The mixture was diluted in ethyl acetate and washed several times with water. The organic phase was dried over

anhydrous sodium sulphate, filtred and the solvent was evaporated under reduced pressure.

The residue obtained was purified by chromatography on silica gel (cyclohexane/ethyl acetate: 30/70) to give compounds **5*a-e***.

2-[(1*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazole 6a [17]

White crystals, yield = 76%, m p: 152˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.92 (s, 1H, NH), 12.64 (s, 1H, NH), 754 - 7.32 (m, 12H, H-Ar); 7.18 (d, 2H, H-Ar); 4.62 (s, 2H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 151.14 (C=N), 139.31 (C=N), 30.57 (SCH_2). HRMS: m/z calculated for $C_{23}H_{19}N_4S$ $[M + H]^+$: 383.1330; found: 383.1346.

2-[(5'-nitro-1*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazole 6b

Solid, yield = 68%, m.p: 260˚C - 266˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.26 (s, 1H, NH), 12.78 (s, 1H, NH), 7.69 (d, 1H, H-Ar); 743 - 7.28 (m, 10H, H-Ar), 4.66 (s, 2H, SCH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.94 (C=N), 138.52 (C=N), 30.69 (SCH_2). HRMS: m/z calculated for $C_{23}H_{18}N_5O_2S$ $[M + H]^+$: 428.1181; found: 428.1177.

2-[(5'-trifluoromethyl-1*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazole 6c

White crystals, yield = 70%, m.p: 220˚C. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.88 (d, 2H, 2NH), 7.89 - 7.47 (m, 3H, H-Ar); 751 - 7.30 (m, 10H, H-Ar), 4.63 (s, 2H, SCH_2); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 138.72 (C=N, imidazole), 30.65 (SCH_2). HRMS: m/z calculated for $C_{24}H_{18}F_3N_4S$ $[M + H]^+$: 451.1204; found: 451.1208.

2-[(5'-chloro-1*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazole 6d

White crystals, yield = 66%, m.p: 248˚C. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.80 (s, 2H, 2NH), 762 - 7.19 (m, 13H, H-Ar), 4.61 (s, 2H, SCH_2); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 152.58 (C=N), 138.95 (C=N), 30.55 (SCH_2). HRMS: m/z calculated for $C_{23}H_{18}ClN_4S$ $[M + H]^+$: 417.0941; found: 417.0959.

2-[(5'-methyl-1*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazole 6e

White crystals, yield = 77%, m.p: 248˚C - 250˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.92 (s, 1H, NH), 12.48 (s, 1H, NH), 746 - 7.32 (m, 12H, H-Ar), 6.99 (d, 1H, H-Ar); 4.58 (s, 2H, SCH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 151.44 (C=N), 139.38 (C=N), 30.57 (SCH_2), 21.30 (CH_3). HRMS: m/z calculated for $C_{24}H_{21}N_4S$ $[M + H]^+$: 397.1487; found: 397.1480.

2.2. Antibacterial Assay

Antimicrobial tests of synthesized compounds **2a**-**e** and **6a**-**e** were evaluated against *Pseudomonas aeruginosa* and *Escherichia coli* (Gram-negative bacteria) and then against *Staphyloccocus aureus* and *Enterococcus faecalis* (Gram-positive bacteria). The method used was the liquid medium micromethod performed in a

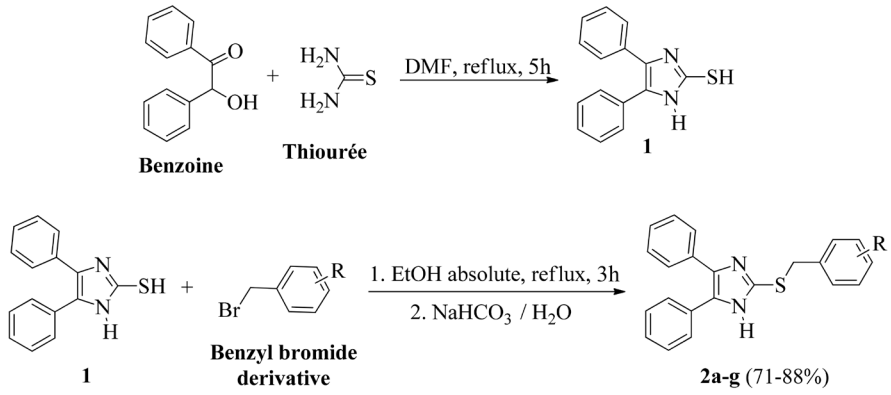
96-well plate [18]. The compounds were dissolved in sterile DMSO so that their concentration in the wells of column 12 was 256 µg/mL followed by a dilution range of order 2 in DMSO to obtain a concentration series of the sample solution (from 256 to 0.063 µg/mL). After this dilution, 225 µL of Mueller-Hinton culture medium (previously prepared according to the supplier's data) and 20 µL of the different inocula were added to 5 µL of the sample solution at different concentrations. Then the microplates were incubated at 37˚C for 24 hours. Absorbance measurements were performed at 600 nm with a plate reader. Bacterial growth results in a cloudiness in the well. Thus, if there is cloudiness in the well (Absorbance higher than 0.1), the bacteria has grown there; the compound has not allowed its inhibition (the compound has no antibacterial activity) at the corresponding concentration. In the opposite case, if there is absence of this disorder (Absorbance lower than 0.1), the compound has inhibited the growth of bacteria at the corresponding concentration (the compound has an antibacterial activity).

3. Results and Discussion

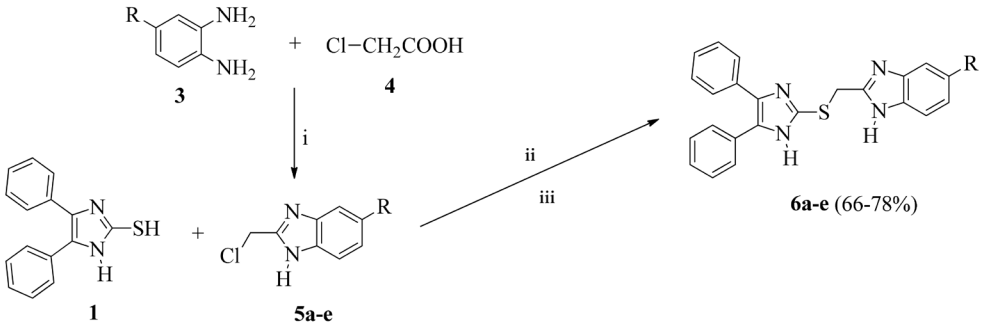
3.1. Chemistry

The synthetic route of the compounds **2a-g** and **6a-e** is outlined in Scheme 1 and Scheme 2 respectively. The synthesis of 2-(benzylthio)-4,5-diphenyl-1*H*-imidazoles **2a-g** was carried out in two steps from benzoin. First, 4,5-diphenyl-1*H*-imidazol-2-thiol **1** was prepared by the condensation of benzoin with thiourea using the reported procedure [12]. Then compound **1** was coupled with an appropriate benzyl bromide derivative in absolute ethanol at reflux temperature to furnish after neutralization in the presence of $NaHCO_3$ compounds **2a-g** (Scheme 1).

The 2-(benzylthio)-4,5-diphenyl-1*H*-imidazoles **2a-g** were obtained in good yields, from 71% to 85%, after purification by silica gel chromatography. The structures of all novel compounds were confirmed by ^1H and ^{13}C NMR spectra and mass spectrometry. The absence of the peak at 3.5 ppm attributed to the thiol proton (S**H**) in compound **1** and the appearance of the signals (protons and



Scheme 1. Synthesis of 2-(benzylthio)-4,5-diphenyl-1*H*-imidazoles **2a-g**.



Reagents and conditions: i : HCl (4N), Reflux, 5-10H; ii : EtOH absolute, Reflux, 3h ; iii : $NaHCO_3$ / H_2O

Scheme 2. Synthesis of 2-[(1-*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazoles **6a-e**.

Table 1. Melting points and yields of 2-(benzylthio)-4,5-diphenyl-1*H*-imidazoles **2a-g**.

Compounds No	R	Molecular formula	Melting point (˚C)	Color	Yield (%)
2a	H	$C_{22}H_{18}N_2S$	186	White	85
2b	4-NO_2	$C_{22}H_{17}N_3O_2S$	168	Yellow	71
2c	4-CF_3	$C_{23}H_{17}F_3N_2S$	182	White	73
2d	4-Cl	$C_{22}H_{17}ClN_2S$	150	Light yellow	78
2e	2,4-Cl	$C_{22}H_{16}Cl_2N_2S$	178	White	76
2f	4-F	$C_{22}H_{17}FN_2S$	160	Yellow	88
2g	4-CH_3	$C_{23}H_{20}N_2S$	164	White	81

carbons) of the (SCH_2) groups as well as the increase of the signals of the aromatic protons and carbons confirm the formation of compounds **2a-g**.

The structures of synthesized compounds **2a-g** and their physicochemical properties are given in Table 1.

Compounds 2-[(benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazoles **6a-e** were synthesized by coupling compound **1** with an appropriate 2-(chloromethyl)-1*H*-benzimidazoles **5a-e** at refluxed temperature in absolute ethanol. Compounds **5a-e** were obtained by condensation reaction between orthophenylenediamine derivatives **3** and chloroacetic acid **4** following a published procedure [19].

The 2-[(benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazoles **6a-e** were obtained after purification by silica gel chromatography in good yields, from 66 to 77%. Compounds **6a-e** were characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Their ^{1}H NMR spectra indicate the disappearance of the signal at 3.5 ppm corresponding to the thiol proton (S**H**) in compound **1** and the appearance of new signals attributed to the protons of the (SCH_2) group at 4.58 - 4.66 ppm. Chemical structures of synthesized compounds **6a-e** and their physicochemical properties are given in Table 2.

3.2. Antibacterial Activity

The synthesized compounds **2a-e** and **6a-e** were evaluated for their *in-vitro* an-

tibacterial activity against the gram positive *Staphylococcus aureus* and *Enterococcus faecalis* bacteria and the gram negative *Pseudomonas aeruginosa* and *Escherichia coli* bacteria. The MIC values were determined by using liquid medium micromethod performed in a 96-well plate. Ciprofloxacin was used as the reference antibacterial agents. All the biological results of the tested compounds are shown in Table 3. It was found that compounds **2a-e** and **6a,b,e** were not active against all bacteria tested at used concentrations. However two compounds **6c** and **6d** showed MIC values respectively at 16 µg/mL against gram positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*) and at 4 µg/mL against *Staphylococcus aureus*. Thus, the investigation of antibacterial screening revealed that most of the synthesized compounds were inactive but **6c** has shown half antibacterial activity against gram positive while **6d** has shown two fold antibacterial activity against *Staphylococcus aureus* compared to the reference ciprofloxacin. From the results, it is evident that the presence of chloride or trifluoromethyl at 5-position of benzimidazole leads to the appearance of

Table 2. Melting points and yields of 2-[(1-*H*-benzimidazol-2-yl)methylthio]-4,5-diphenyl-1*H*-imidazoles **6a-e**.

Compounds No	R	Molecular formula	Melting point (˚C)	Color	Yield (%)
6a	H	$C_{23}H_{18}N_4S$	252	White	76
6b	NO_2	$C_{23}H_{17}N_5O_2S$	260 - 266	Dark yellow	68
6c	CF_3	$C_{24}H_{17}F_3N_4S$	220	White	70
6d	Cl	$C_{23}H_{17}ClN_4S$	248	White	66
6e	CH_3	$C_{24}H_{20}N_4S$	250	White	78

Table 3. MIC test results of 4,5-diphenyl-1*H*-imidazoles derivatives **2a-e** and **6a-e**.

Compounds No	MIC: Minimum Inhibition Concentration (µg/mL)			
	Gram-negative bacteria		Gram-positive bacteria	
	Pseudomonas aeruginosa	*Escherichia coli*	*Staphyloccocus aureus*	*Enterococcus faecalis*
2a	–	–	–	–
2b	–	–	–	–
2c	–	–	–	–
2d	–	–	–	–
2e	–	–	–	–
6a	–	–	–	–
6b	–	–	–	–
6c	–	–	16	16
6d	–	–	4	–
6e	–	–	–	–
Ciprofloxacine	0.25	0.063	8	0.5

-No activity.

antibacterial activity.

Overall, the results indicate very useful information for researchers interested in designing antibacterial agents containing imidazole and benzimidazole moities in their structure for both improved potency and for avoiding the chemical space that would not be productive.

4. Conclusion

We have synthesized a series of heterocyclic compounds **2a-g** and **6a-e** from 4,5-diphenylimidazol-2-thiol **1**. The antibacterial activity of compounds **2a-e** and **6a-e** was evaluated against gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) and gram-positive bacteria (*Staphyloccocus aureus* and *Enterococcus faecalis*) in a 96-well plate using the liquid dilution method (liquid micromethod) and ciprofloxacin as a reference. Most of the synthesized compounds were inactive but **6c** has shown half antibacterial activity against gram-positive while **6d** has shown two-fold antibacterial activity against *Staphylococcus aureus* compared to the reference ciprofloxacin.

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Conflicts of Interest

The authors declare that have no conflict of interest regarding the publication of this paper.

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