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Synthesis and Antibacterial Effect of 2-(Benzylthio) Methyl-1h-Benzimidazole Derivatives on Two Bacteria of Medical Interest

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Abstract

This work involved the synthesis of ten (10) novel 2-benzylthiomethyl-1*H*-benzimidazole derivatives (5a-d) and evaluation of their antibacterial activities. These new compounds were synthesized by reacting the isothiouronium-1*H*-benzimidazole salts (3a and 3b) with the benzyl halides (4) to ethanol reflux in the presence of a sodium hydroxyde solution. The obtained compounds were characterized by nuclear magnetic resonance ^{1}H, ^{13}C NMR and High-Resolution Mass Spectrometry (HRMS). These compounds were evaluated for antibacterial activity on two bacterial strains, *Escherichia coli* and *Staphylococcus aureus*. The results showed that on *S. aureus*, six compounds (5b, 5d, 5e, 5f, 5g and 5j) were significantly potent with antibacterial activity MIC values ranging from 140 to 320 µg/mL. On the bacterial strain *E. coli*, five compounds (5b, 5e, 5g, 5h and 5j) showed a significant antibacterial effect with MIC ranging from 140 to 400 µg/mL.

Keywords: Isothiouronium-1H-benzimidazole, antibacterial activity, bactericidal, bacteriostatic.

Introduction

Bacteria, viruses, fungi and parasites evolve over time and are increasingly resistant to drugs [1]. This resistance becomes a major factor complicating the treatment of bacterial infections and increasing the risk of spread [2]. Recently, the rate of resistance to ciprofloxacin, an antibiotic frequently used to treat urinary tract infections, has ranged from 8.4% to 92.9%. Enterobacteria such as *E. coli*, *Klebsiella*, are resistant to carbapenems. Colistin, the only treatment of last resort for deadly infections caused by these enterobacteria, has been found inactive on some bacteria in some parts of the world [3]. In 2019, according to a UN report on the environment, antibiotic-resistant infections caused nearly 5 million deaths. Thus, this report tells us that without immediate action, these infections could cause up to 10 million deaths per year by 2050 [4]. Antibiotic resistance is now one of the most serious threats to global health, food security and development. This problem has led several research groups to develop new antibacterial agents [5-7]. In order to contribute to this research, we looked at the benzimidazole scaffold. This compound is present in the family of cobalamins in the form of vitamin cyano-cobalamin [8]. The benzimidazole nucleus has been widely described in the

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literature because of its various biological properties, such as antihypertensive, antifungal, antioxidant, antiviral and topoisomerase inhibitor, anti-proliferative, anti-allergic, antitumoral, anti-kinase, anticanceral, cytotoxicity and anti-HIV-1 [9-29]. Many approved drugs have benzimidazole as the major moiety or substructure [30,31]. Also, the different modulations carried out around the benzimidazole scaffold have led to very effective drugs Omeprazole, Lansoprazole, Rabeprazole and Pantoprazole [32]. In this study, pharmacomodulation will be carried out by introducing benzylthiomethyl groups at the -2 position of the benzimidazole scaffold and then evaluate their antibacterial activities.

Materials

Materials of Chemistry

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75MHz or 400 and 101 MHz or 600 and 151MHz, respectively, in $CDCl_3$, solution. Chemical shifts are reported in ppm on the $\boldsymbol{\delta}$ scale. Multiplicities are described as s (singlet), d (doublet), dd (doublet of doublet, m (multiplet) and further qualified as app (apparent), br (broad) coupling constants, *J* are reported in Hz. HRMS were measured in the electrospray (ESI) mode on a LC-MSD TOF mass analyzer

Biological Materials

The microbial support consisted of clinical strains of *E. coli* (Gram-negative bacteria) and *S. aureus* (Gram-positive bacteria) which are resistant to Piperacillin and Erythromycin, respectively. The strains were supplied by the Laboratory of Bacteriology-Virology of the Institute Pasteur in Côte d'Ivoire. These strains are all pathogenic and multi-resistant. *S. aureus* strains are resistant to Erythromycin, sensitive to Cefoxitin and Clindamycin. Those of *E. coli* are all resistant to Piperacillin/Tazobactam, sensitive to Ceftriaxone and Ticarcillin/Clavulanic Acid. The culture medium used was Mueller-Hinton broth (Oxide) and Mueller-Hinton agar (Lab.Conda s.a). Dimethyl sulfoxide (DMSO) and distilled water were used as solvents for chemical solubilization.

Methods

Methods of Synthesis

General procedure for the synthesis of 2-(chloromethyl)-1H-benzimidazoles (1a and 1b)

To 1g (9.3 mmol) of orthophenylenediamine, was added 1.5eq of chloroacetic acid and 10 mL of hydrochloric acid (4N). The mixture was let under reflux for 2 hours. Then 5% potassium hydrogenocarbonate ($KHCO_3$) solution was added. The precipitate formed was purified on silica gel in a solvent mixture ethyl-hexane acetate (80/20).

2-(chloromethyl)-1H-benzimidazole (1a)

Yellow powder, Yield = 80%, ^{1}H NMR (DMSO-*d6*) δ (ppm): 7.19-7.24 (m, 2H, H_{Ar}), 7.54-7.58(m, 2H, H_{Ar}) 4.92 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d6*) (δ ppm): 149.57, 138.52, 122.28, 115.26, 38.29. HRMS(ESI) Calc for $C_8H_8ClN_2$ $(M+H)^+$: 167.7312, Found: 167.7316.

2-(chloromethyl)-5-nitro-1H-benzimidazole (1b)

Black powder, Yield = 88%, ^{1}H NMR (DMSO-*d6*) δ (ppm): 8.39 (m, 1H, H_{Ar}), 8.09 (m, 1H, H_{Ar}), 7.66 (m, 1H, H_{Ar}), 4.64 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d6*): 141.5, 142.7, 118.6, 116.0, 111.4, 41.8. HRMS(ESI): Calc for $C_8H_7ClN_3O_2$ $(M+H)^+$: 212. 4928, Found: 212.4931

Synthesis method of 2 methyl-1H-benzamidazole thiourunium chloride salt (3a and 3b)

To a solution of 2-(chloromethyl)-1*H*-benzimidazole (1 eq, 57.2 mmol) in 50 mL of acetonitrile, thiourea (1 eq, 57.2 mmol) was added. The mixture was brought to reflux for 1.30 hours. After cooling to room temperature, a precipitate was formed, filtered, washed several times with ethyl acetate and then dried in the open air to afford yellow powder.

2-[(1H-benzimidazol-2-yl) methyl] isothiouronium (3a)

Yellow powder, Yield = 88%, HRMS(ESI): Calc for $C_9H_{12}ClN_4S$ (M+H) +: 243.1127, Found: 243.1132

2-[(5-nitro-1H-benzimidazol-2-yl) methyl] isothiouronium (3b)

Yellowish-orange powder, Yield = 70%, HRMS(ESI): Calc for $C_9H_{11}ClN_5O_2S$ $(M+H)^+$: 288.0411, Found: 243.0415

Synthesis method of 2-[(thiobenzyl) methyl]-1H-benzimidazole

To a solution of 2-methylbenzimidazole thiourunium chloride salt (1 eq, 2.1 mmol) in 15 mL of absolute ethanol was added (2.5 eq, 0.35N) of sodium hydroxide solution. The mixture was stirred under reflux, then benzyl chloride derivative (1.2 eq, 2.52 mmol).

was added. The reaction stayed like this for two more hours. After cooling to room temperature, the mixture was diluted in dichloromethane and washed several times with water. The organic phase was dried over anhydrous Na_2SO_4. and the solvent was evaporated *in vacuo*. The residue obtained after evaporation of solvent was purified by silica column chromatography (hexane / ethyl acetate: 85 / 15) to give compound **5(a-j).**

2-[(benzylthio) methyl]-1H-benzimidazole (FIG.1)

Yellow powder, Yield = 53%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65–7.47 (m, 2H, H_{Ar}), 7.34–7.17 (m, 7H, H_{Ar}), 3.93 (s, 2H, CH_2), 3.71 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.52, 137.45, 128.99, 128.65, 127.30, 122.65, 36.72, 29.49. HRMS(ESI): Calc for $C_{15}H_{15}N_2S$ $(M+H)^+$: 255.1685, Found: 255.1689

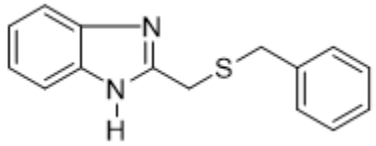

FIG. 1 **Compound 5a**

2-{[(4-chlorobenzyl) thio] methyl}-1H-benzimidazole (FIG.2)

Yellow powder, Yield = 59%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60–7.54 (m, 2H, H_{Ar}), 7.30–7.15 (m, 6H, H_{Ar}), 3.92 (s, 2H, CH_2), 3.66 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 130.28, 128.70, 123.13, 115.10, 35.50, 29.20, HRMS(ESI): Calc for $C_{15}H_{14}ClN_2S$ $(M+H)^+$: 289. 1127, Found: 289.1131

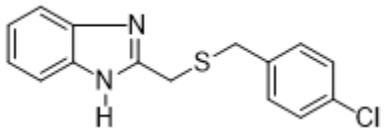

FIG. 2 **Compound 5b**

2-{[(4-fluorobenzyl) thio] methyl} -1H-benzimidazole (FIG.3)

Oil, Yield = 59%, ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 10.74 (s, 1H, NH), 7.65 – 7.56 (m, 2H, H_{Ar}), 7.33 – 7.26 (m, 2H, H_{Ar}), 7.20 – 7.14 (m, 2H, H_{Ar}), 6.92 – 6.83 (m, 2H, H_{Ar}), 3.93 (s,2H, CH_2), 3.66 (s, 2H, CH_2).^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) : 162.73, 161.10, 151.54, 138.52, 132.92, 130.50, 115.46, 115.32, 115.05, 35.94, 29.13, HRMS(ESI): Calc for $C_{15}H_{13}FN_2S$ $(M+H)^+$: 373.1328, Found: 373.1332

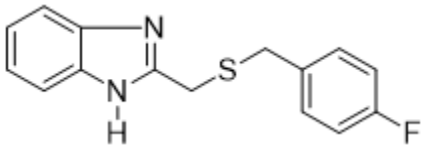

FIG. 3 **Compound 5c**

Benzoate, 4-methyl{[(1H-benzimidazol-2-yl) methyl] thio} methyl (FIG.4)

Oil, Yield = 61%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):8.47 (s, 1H, NH), 7.88 (dd, *J* = 8,3, 3,5 Hz, 2H, H_{Ar}), 7.60 – 7.54 (m, 2H, H_{Ar}), 7.33 – 7.24 (m, 4H, H_{Ar}), 3.92 (s, 2H, CH_2), 3.90 (s, 3H, CH_3-O), 3.73 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.67, 151.16, 142.84, 129.82, 128.96, 123.19, 115.26, 52.12, 36.01, 29.03, HRMS(ESI): Calc for $C_{17}H_{17}N_2$ O_2S $(M+H)^+$: 313.1224, Found: 313.1227

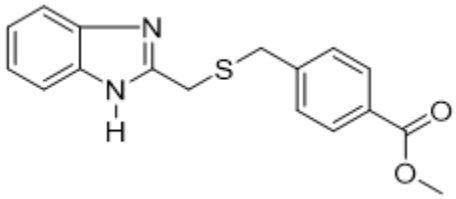

FIG. 4 **Compound 5d**

2-{[(4-nitrobenzyl) thio] methyl} -1H-benzimidazole (FIG.5)

Brown powder, Yield = 55%, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.07–8.00 (m, 2H, H_{Ar}), 7.60–7.52 (m, 2H, H_{Ar}), 7.44–7.35 (m, 2H, H_{Ar}), 7.32–7.22 (m, 2H, H_{Ar}), 3.93 (s, 2H, CH_2), 3.76 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.56, 146.88, 145.07, 129.77, 123.66, 123.06, 35.60, 29.16, HRMS(ESI): Calc for $C_{15}H_{14}N_3O_2S$ $(M+H)^+$: 300.1366, Found: 300.1369

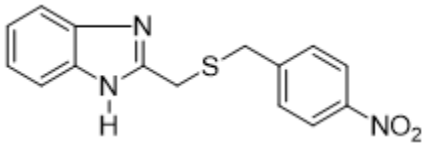

FIG. 5 **Compound 5e**

2-{[(3-nitrobenzyl) thio] methyl} -1H-benzimidazole (FIG.6)

Brown powder, Yield = 68%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (s, 1H, H_{Ar}), 7.96 (d, *J* = 7.4 Hz, 1H, HAr), 7.55 (d, *J* = 6.6 Hz, 3H, HAr), 7.28 (dd, *J* = 10.7, 8.8 Hz, 3H, H_{Ar}), 3.95 (s, 2H, CH_2), 3.79 (s, 2H, CH_2).^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 150.78, 148.09, 139.55, 135.06, 129.28, 123.66, 122.90, 122.09, 35.55, 29.33. HRMS(ESI): Calc for $C_{15}H_{14}N_3O_2S$ $(M+H)^+$: 300.1366, Found: 300.1369

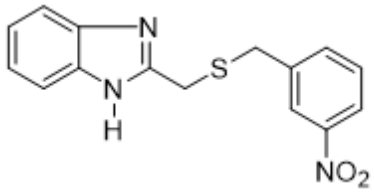

FIG. 6 **Compound 5f**

2-{[(4-methylbenzyl) thio] methyl} -1H-benzimidazole (FIG.7)

Yellow powder, Yield = 89%, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.24 (s, 1H, NH), 7.52 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.30–7.23 (m, 2H, H_{Ar}), 7.10 (dd, J = 35.6, 7.9 Hz, 4H, H_{Ar}), 3.93 (s, 2H, CH_2), 3.68 (s, 2H, CH_2), 2.30 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 151.76, 137.04, 134.37, 129.33, 128.88, 36.71, 29.49, 20.79. HRMS(ESI): Calc for $C_{16}H_{17}N_2S$ $(M+H)^+$: 369.1763, Found: 369.1770

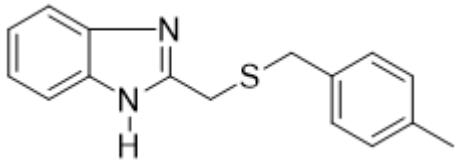

FIG. 7 **Compound 5g**

2-{[(4-(trifluoromethyl) benzyl) thio] methyl}-1H-benzimidazole (FIG.8)

Yellow powder, Yield = 64%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.00 (s, 1H, NH), 7.6–7.56 (m, 2H, H_{Ar}), 7.45 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.33 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.31–7.26 (m, 2H, H_{Ar}), 3.93 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). ^{13}C NMR (101MHz, CDCl3) δ (ppm): 151.04, 141.45, 138.30, 129.22, 125.45, 125.41, 122.95, 115.01, 35.74, 29.07. HRMS(ESI): Calc for $C_{16}H_{14}F_3N_2S$ $(M+H)^+$: 323.1131, Found: 323.1134

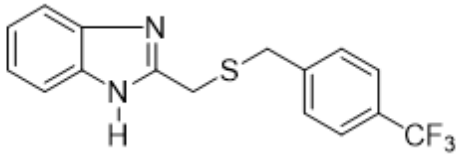

FIG. 8 **Compound 5h**

2-[(benzylthio)methyl]-6-nitro-1H-benzimidazole (FIG.9)

Oil, Yield = 68%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (dd, *J* = 8.9, 2.2 Hz, 1H, H_{Ar}), 7.31–7.15 (m, 7H, H_{Ar}), 3.97 (s, 2H, CH_2), 3.76 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 143.77, 137.30, 128.96, 128.77, 127.52, 36.85, 29.18, HRMS(ESI): Calc for

$C_{15}H_{14}N_3O_2S$ $(M+H)^+$: 300. 1366, Found: 300.1369

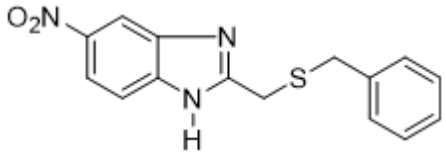

FIG. 9 **Compound 5i**

2-{[(4-chlorobenzyl) thio] methyl} -6-nitro-1H-benzimidazole (FIG.10)

Orange powder, Yield = 68%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 1.9 Hz, 1H, H_{Ar}), 8.22 (dd, *J* = 8.9, 2.2 Hz, 1H, H_{Ar}), 7.60 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.20 (s, 4H, H_{Ar}), 3.95 (s, 2H, CH_2), 3.71 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 155.70, 143.81, 135.55, 133.29, 130.25, 128.75, 118.83, 35.84, 28.98. HRMS(ESI): Calc for $C_{15}H_{13}ClN_3O_2S$ $(M+H)^+$: 334.0531 , Found : 334.0534

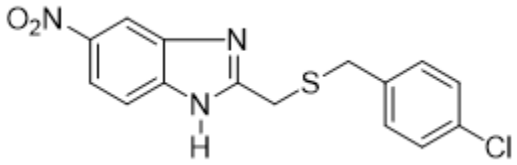

FIG. 10 **Compound 5j**

Biological Methods

The liquid micro dilution method was used to determine the Minimum Inhibitory Concentration (MIC) and the Minimum Bactericidal Concentration (BMC). A colony isolated from an 18 hours' bacterial culture was collected and homogenized in 10 mL of 0.9% NaCl and incubated for 3 hours at 37°C. From this bacterial suspension, 0.1 mL was added to 10 mL of 0.9 NaCl solution. This prepared bacterial suspension constituted the starting bacterial inoculum. To do this, the bacterial inoculum was homogenized and diluted from 10 to 10 until dilution 10-4. Four successive dilutions were obtained from 10-1 to 10-4. The initial bacterial inoculum and the 4 successive dilutions were inoculated with a 2 µL calibrated loop in Muller-Hinton agar boxes with 5 cm long streaks. This preparation represents Box (A) that will help to determine the BMC. Antibacterial testing was conducted using the liquid micro dilution method [33]. Final concentrations ranging from 100 to 3.12 mg/mL were achieved. In a series of 5 test tubes, a growth control tube and a sterility control tube, a volume of one milliliter of an extract known concentration from the concentration range was added to the test tubes. The growth control tube received 0.5 mL of sterile distilled water while all test tubes received 0.5 mL of bacterial inoculum. The sterility control tube received 1 mL of 0.9% NaCl solution. The tubes were incubated for 24 hours at 37°C. The MIC is the lowest concentration of extract for which no bacterial growth is observed. The contents of the tubes in which there was no visible growth were used to seed the Muller-Hinton agar on 5 cm ridges using a 2 µL calibrated loop. This Petri dish is called B. Analysis of the results after 24 hours of incubation allowed to calculate the CMB which corresponds to the lowest concentration that kills 99.99% of the bacteria in culture.

Results and Discussion

Chemistry

The orthophenylenediamine derivatives were condensed with 2-chloroacetic acid under reflux in a HCl (4N) solution following the Phillips reaction Yielded to 2-chloromethyl-1*H*-benzimidazole derivatives (**1a** and **1b**) (**Scheme 1**) **FIG.11** [34].

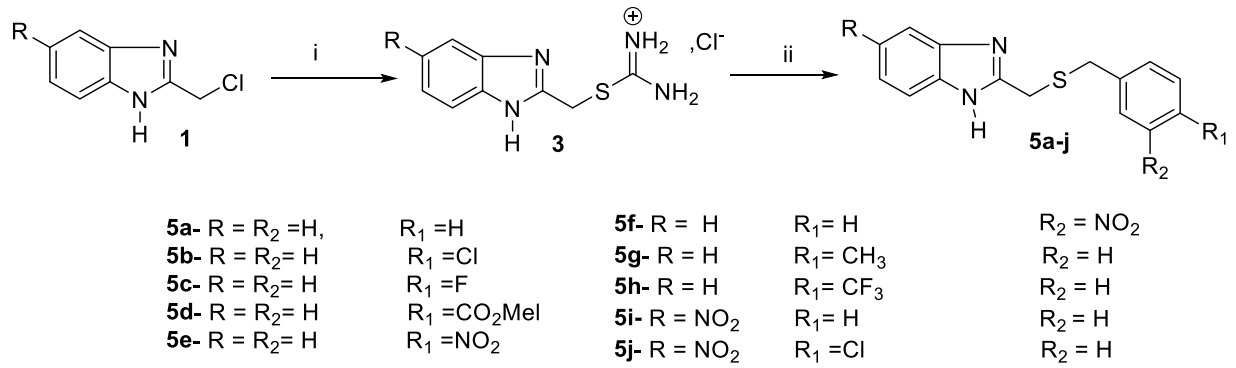

FIG.11.**Reaction conditions: 1(i) Thiourea (2), MeCN (reflux 2h); 3(ii) Benzyl chloride (4), NaOH, EtOH/ H_2O (reflux 2h).**

Scheme 1: Synthesis method of 2-((thiobenzyl)methyl)-1*H*-benzimidazole (5)

These two derivatives were condensed in acetonitrile (CH_3CN) under reflux with thiourea by adopting the protocol used by Farid et *al*., allowing the synthesis of the isothiouronium-1*H*-benzimidazole salts (**3a** and **3b**). The reactivity of these isothiouronium salts was studied by Oleynk et al. [35-36]. Thus, using the protocol, isothiouronium-1*H*-benzimidazole salts (**3a** and **3b**) were put in reaction with the benzyl halides (**4**) of under reflux in ethanol with the presence of sodium hydroxide to lead to the formation of 2-benzylthiomethyl-1H-benzimidazole derivatives **FIG.** (**5a-j**). Structures of these compounds **FIG.** (**5a-d**) were confirmed by ^1H, ^{13}C NMR spectroscopy and HRMS. ^1H NMR spectra of **FIG. 5a-j** compounds indicate presence of a singlet in the vicinity of 3.9 ppm corresponding to the methylene protons (C2-CH_2-S) located between the C2 carbon of the benzimidazole scaffold and the sulfur. Another singlet occurs around 3.7 ppm due to sulfur bound to benzyl methylene hydrogen (-S-CH_2-Φ). Analysis of ^{13}C NMR spectra of the synthesized compounds **FIG.** (**5a-j**) confirms the presence of the methylenic carbon's (C2-CH_2-S) around 27 ppm. Methylene carbon bound to benzyl (-S-CH_2-Φ) was also observed around 35 ppm.

Biology

The Minimum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration (BMC) and ratio (BMC/MIC) of each compound tested using the liquid micro dilution method were reported in **(TABLE 1)** below.

TABLE 1**. Bactericidal and Bacteriostatic effects of obtained compounds 3a-l on bacteria strains *E. coli* and *S. aureus* determined by MIC and BMC values.**

	S. aureus 2275C2021				***E. coli 2279C2021***			
Compounds	**MIC (µg/mL)**	**BMC (µg/mL)**	**BMC/ MIC**	**Effect**	**MIC (µg/mL)**	**BMC (µg/mL)**	**BMC/ MIC**	**Effect**
5a	-	-	-	-	-	-	-	-
5b	300	610	2	bc	150	610	4	bs
5c	-	-	-	-	-	-	-	-
5d	320	650	2	bc	-	-	-	-
5e	180	740	4	bs	180	740	4	bs
5f	140	590	4	bs	-	-	-	-
5g	280	570	2	bc	140	570	4	bs
5h	-	-	-	-	150	630	4	bs
5i	-	-	-	-	-	-	-	-
5j	200	830	4	bs	400	830	2	bc
Non-determined. bc means bactericidal, bs means bacteriostatic								

On *S. aureus* 2275C2021 six compounds including **FIG. 5b**, **5d**, **5e**, **5f**, **5g** and **5j** showed significant antibacterial activity with MIC ranging from 140 to 320 µg/mL. Of these six compounds, **FIG. 5b**, **5d** and **5g** showed bactericidal potency. Compounds **FIG. 5e**, **5f**, and **5j** showed bacteriostatic properties. Compounds **FIG. 5e** and **5f** possessing the nitro group (NO_2) on the benzyl were more potent with respective MICs of 180 and 140 µg/mL. On the bacterial strain *E. coli* 2279C2021, the compounds **FIG. 5b**, **5e**, **5g**, **5h** and **5j** showed significant antibacterial effect with MIC ranging from 140 to 400 µg/mL. Compounds **FIG. 5b** and **5g** with Electro-Donating Groups (EDG) such as methyl (CH_3) by inductive effect and chlorine (Cl) by mesomeric effect gave the best MICs (140 and 150 µg/mL). Compound **5j** with the nitro (NO_2) group on the 5-position of the benzimidazole scaffold yielded a MIC of 400 µg/mL and represents the only compound with bactericidal potency. Others tested compounds showed bacteriostatic potency.

Conclusion

This work resulted in the synthesis of ten (10) new derivatives of 2-benzylthiomethyl-1*H*-benzimidazole (compound **5a-j**) with yields between 72 and 79 %. Structures of all compounds were confirmed by the results of spectroscopic ^{1}H, ^{13}C NMR analyses and High-Resolution Mass Spectroscopy (HRMS). Antibacterial tests of the ten (10) compounds were explored on two bacterial strains of *E. coli* and *S. aureus*. Compounds **FIG. 5b**, **5d** and **5g** showed bactericidal potency on *S. aureus* while compounds **FIG. 5e**, **5f**, and **5j** showed bacteriostatic potency on the same strain. On the bacterial strain *E. coli*, the compound **FIG. 5j** showed antibacterial activity with bactericidal potency and **FIG. 5b**, **5e**, **5g** and **5h** were active with bacteriostatic potency.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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