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Synthesis and Estimate of Antimicrobial Efficacy of New Benzoic Acid Hydrazide Derivatives Substituted by Piperidine

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Abstract. *Background: Several of the best-selling small-molecule medications and natural alkaloids contain piperidine, a crucial saturated heterocyclic scaffold with a wide variety of biological functions. The hydrazide-hydrazone moiety's exceptional use in the pharmacological and biological domains made it particularly appealing. Objective: Designing and synthesizing a novel set of 4-Piperidin-1-yl-benzoic acid substituted hydrazides, Ac1-c3 and Bc1-c5, as potentially antimicrobial agents and characterizing them using IR, 1H-NMR, and mass spectroscopy. Methods: By esterifying 4- Piperidin-1-yl-benzoic acid Ac1 and then treating with hydrazine hydrate it to produce Ac3 in a good yield. The hydrazide Ac3 was condensed with the proper aldehydes or ketone to synthesis the hydrazones Bc1–c5. The in vitro bacterial activity was evaluated anti two Gram-negative bacteria, Pseudomonas aeruginosa, and Candida albicans, as well as two Gram-positive bacteria, Staphylococcus aureus and Bacillus subtilis. Results: The majority of tested compounds demonstrated significant efficacy anti Pseudomonas aeruginosa, Candida albicans. Notably, compound Bc3 emerged as the most effective derivative within the series. Conclusions: The Compounds (Bc1–c4) that were synthesized demonstrated moderate to good antimicrobial activity against a number of bacterias species and Candida albicans.*

Keywords: *antimicrobial, carboxylic acid, ester, hydrazone/hydrazide, Piperidine.*

1. INTRODUCTION

The widespread misapplication of conventional antimicrobial drugs contributed to the appearance of strains of multi-drug-resistant bacteria and fungi, which pose serious threats worldwide and demand a rapid and continuous effort to search for new-generation drugs [1]. In addition, the incidence of serious infections brought on by yeast is rising proportionally to the dearth of new antifungal medications. one among the most prevalent opportunistic fungus that causes these infections is *Candida albicans*. One of our most important tools for combating bacterial infections is antibiotics [2]. Therefore, for researchers and chemists, it became of interest to synthesize new antimicrobial agents. The advancement of pharmaceutical development can be significantly enhanced through the utilization of hydrazone and hydrazide derivatives, which feature the highly reactive azomethine group NHN=CH [3]. The synthesis of acid hydrazides and their derivatives remains a focal point of interest among organic chemists, owing to their distinctive properties. The excellent application of compounds with hydrazide and hydrazone moiety in biological and pharmacological fields, such as antimicrobial [4], anthelmintic, antidiabetic, and trypanocidal [5], anticonvulsant [6], anti-inflammatory and analgesic [7, 8], antibacterial and antifungal [9], antituberculous [10], antiparasite [11], antioxidant [12], antiviral [13],

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antimalarial [14], and anti-cancer [15], showed particular appeal. Furthermore, these were discovered to be beneficial, particularly in the management of autoimmune disorders, osteoarthritis, malignancies, cardiovascular disorders, respiratory disorders, cachexia, fever, hemorrhage, and sepsis. [16]. Examples of current drugs that possess hydrazide-hydrazone moieties include isoniazid and isocarboxazid (anti-tuberculosis), nifuroxazide (intestinal antiseptic), vitivazid (antibacterial), and iproniazid (antidepressant) [17]. Furthermore, hydrazones' low metabolic stability makes them the most crucial substances for prodrug creation. [18–21]. Prodrugs' plasma stability is crucial for their quick conversion in plasma. [22].

Hydrazones synthesis is an appropriate process for prodrug production. [23–26]. They hydrolyze readily into active medications in vivo. Our decision to create this new 4-peridin-1-yl-benzoic acid was motivated via these characteristics. The design strategy for these compounds involves incorporating hydrazones and hydrazides into the piperidine core structure to enhance biological activity. Piperidine, with the molecular formula $(CH_2)_5NH$, is a prominent heterocyclic amine clarified by a six-membered ring comprising five methylene groups and one nitrogen atom [27]. This heterocyclic moiety is widely distributed and exhibits various biological effects, including antibacterial and anti-inflammatory activities. antihypertensive, anticonvulsant, antimalarial, antiviral, and anticancer qualities, were demonstrated by piperidine and its derivatives. [28]. This work's primary goal was to production a new series of 4-Piperidin-1-yl-benzoic acid derivatives, Ac1-c3 and Bc1-c5, and use spectrum data to characterize them. Tested in vitro anti a variety of bacterial species, the 4-Piperidin-1-yl-benzoic acid (substituted)-hydrazide derivatives Bc1-c4 were found to exhibit moderate to strong effects.

2. MATERIALS AND METHODS

Experimental

1. General

All materials were procured from saleable suppliers with a clarity of 95–98% and used in default of purification. Melting points of compounds were outline in capillary tubes utilizing a Gallen-Kamp MFB-600 melting spot kit. FT-IR were recorded with an FT-IR-8400S spectrophotometer from Shimadzu. Mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX spectrometer. Proton NMR were acquired on a Bruker 500 MHz spectrometer, employing DMSO as the solvent and Tetramethylsilane (TMS) as standard.

2. Synthesis of 4-Piperidin-1-yl-benzoic acid(Ac1)

25 mL of methanol were used to dissolve 0.3 g (0.001 mol) of 4-chlorobenzoic acid before the addition of 0.056 g (0.001 mol) of KOH to the mixture. Piperidine (0.1 ml, 0.001 mol) was added to the mixture after refluxing for 30 minutes. Under TLC observation, the reaction was refluxed at 180 °C for 12 hours. To separate the acid from its salt, 10% HCl was added. After filtering and washing with methanol, the precipitate yielded targeted compound Ac1. [29–32].

Product, white solid, yield :60 %; M.P: 143°C; M.F: $C_{12}H_{15}NO_2$; M.W; 205.25; FT-IR (cm^{-1}): 3200-2200 (OH, Carboxylic acid), 3094-3051 (C-H, aromatic), 2948-2837 (C-H, aliphatic), 1679 (C=O, Carboxylic acid), 1574 (C=C, aromatic), 1460 (CH_2, bending), 1306 (C-N, stretching), 1282 (C-O).MS-EI (m/z, %): 204.9 (M^+,2500), 50.1 (160000), 75.1(260000), 111(400000), 149(500000), 158(200000), 159.3(530000).

3. Synthesis of 4-Piperidin-1-yl-benzoic acid methyl ester(Ac2)

After dissolving the compound Ac1 (0.23g, 0.001 mol) in 20 ml of hot methanol and stirring, 2-3 drops of strong sulfuric acid were added. Compound Ac1 reaction mixture was refluxed for 20 hours (The completeness of the reaction was tracked using TLC.), after then it was allowed to cool, neutralized with sodium bicarbonate (NaHCO3), and filtered. The compound Ac2 was synthesized by allowing the filtrate to evaporate at room temperature [33].

Product pink gummy, yield 50%; M.P: under 40°C; M.F: $C_{13}H_{17}NO_2$; M.W; 219.28; FT-IR (cm^{-1}): 3093-3050 (C-H, aromatic), 2952-2850 (C-H, aliphatic), 1722 (C=O, Ester), 1593 (C=C, aromatic), 1434 (CH_2, bending), 1360 (CH_3, bending), 1306 (C-N, stretching), 1272 (C-O).

4. Synthesis of 4-Piperidin-1-yl-benzoic acid hydrazide(Ac3)

In order to generate a good yield of the acid hydrazide Ac3, the synthesized ester Ac2 (0.9 g, 0.004 mol) and hydrazine hydrate (1 mL) were added to a 100 mL RB flask with 15 mL of ethanol as a solvent. This reaction was refluxed for 24 hours. TLC was used to checked the product formation utilizing a solvent system of 3:7 n-hexane to ethyl acetate. Once the reaction was complete, the mixture was allowed to cool to ambient temperature and allowed the solvent to evaporate. The precipitate was filtered, recrystallized from ethanol and dried at room temperature. [34].

Product off-white solid, yield 50%; M.P: 180-182°C; M.F: $C_{12}H_{17}N_3O$; M.W; 219.28; FT-IR (cm^{-1}): 3335 (NH), 3181-3104 (NH_2), 3093-3053 (C-H, aromatic), 2955-2849 (C-H, aliphatic), 1652 (C=O, Amide), 1594 (C=C, aromatic), 1424 (CH_2, bending), 1314 (C-N, stretching).

5. Synthesis of 4-Piperidin-1-yl-benzoic acid (substituted)-hydrazide derivatives(Bc1-c5)

A solution of substituted aldehyde or ketone (0.03 mol) in ethanol (20 mL) was mixed with three drops of glacial acetic acid were add the acid hydrazide compound Ac3 (0.03 mol). While the reaction was monitored by TLC using the 5:5 and 3:7 ethyl acetate:hexane systems, the mixture was refluxed for 10–12 hours. After drying and recrystallizing the precipitate from ethanol, it was filtered and washed with methanol [35].

4-Piperidin-1-yl-benzoic acid (4-nitro-benzylidene)-hydrazide(Bc1)

Product orange solid, yield 67%; M.P: 110-112°C; M.F: $C_{19}H_{20}N_4O_3$; M.W; 352.39; FT-IR (cm^{-1}): 3107 (NH), 3079-3045 (C-H, aromatic), 2955-2848 (C-H, aliphatic), 1703 (C=O, Amide), 1650 (CH=N), 1605(C=C, aromatic), 1531-1342 (NO_2), 1422 (CH_2, bending), 1324 (C-N, stretching). MS-EI (m/z, %): 352 (M^+, 300), 51.1(10000), 65.1(10000), 83.1(3000), 104(3800), 121.1(4000), 135.1(2000), 151.2(11000), 167(1000), 188(980), 218(2200), 244.1(1500).

4-Piperidin-1-yl-benzoic acid (4-hydroxy-benzylidene)-hydrazide(Bc2)

Product yellow solid, yield 59%; M.P: 105-107°C; M.F: $C_{19}H_{21}N_3O_2$; M.W; 323.39; FT-IR (cm^{-1}): 3204 (OH), 3172 (NH), 3045-3000 (C-H, aromatic), 2970-2887 (C-H, aliphatic), 1662 (C=O, Amide), 1650 (CH=N), 1588(C=C, aromatic), 1420 (CH_2, bending), 1314 (C-N, stretching). ^{1}H NMR (500 MHZ, DMSO-d_6, δ ppm): 2.26-2.40(m, 6H, 3CH_2, piperidin), 3.18-3.34(m, 4H, 2 CH_2, piperidin), 6.93(d, J=8.5Hz, 6H, aromatic), 7.77(d, J=8.6Hz, 2H, aromatic), 8.56 (s, 1H, CH=N), 9.79 (s, 1H, *p*-OH), 10.65 (s, 1H, N-NH).

4-Piperidin-1-yl-benzoic acid [1-(4-hydroxy-phenyl)-ethylidene]-hydrazide (Bc3)

Product yellow solid, yield 55%; M. P180-182°C; M.F: $C_{20}H_{23}N_3O_2$; M.W; 337.42; FT-IR (cm^{-1}): 3400 (OH), 3307 (NH), 3093-3053 (C-H, aromatic), 2955-2850 (C-H, aliphatic), 1683 (C=O, Amide), 1600 (C=N), 1593(C=C, aromatic), 1444 (CH_2, bending), 1365(CH_3 bending), 1306 (C-N, stretching). ^{1}H NMR (500 MHZ, DMSO-d_6, δ ppm): 0.83-0.89(m, 6H, 3CH_2, piperidin), 1.96(s, 3H, CH_3), 2.21-2.41(m, 4H, 2 CH_2, piperidin), 6.71(d, J=8.7Hz, 2H, aromatic), 6.82 (d, J=8.7Hz, 2H, aromatic), 7.45 (d, J=8.7Hz, 2H, aromatic), 7.47(s, 1H, *p*-OH), 7.77(d, J=8.7Hz, 2H, aromatic), 9.49 (s, 1H, N-NH).

4-Piperidin-1-yl-benzoic acid thiophen-3-ylmethylene-hydrazide(Bc4)

Product red solid, yield 64%; M.P: 122-124°C; M.F: $C_{17}H_{19}N_3OS$; M.W; 313.42; FT-IR (cm^{-1}): 3107 (NH), 3084-3017 (C-H, aromatic), 2979-2848 (C-H, aliphatic), 1688 (C=O, Amide), 1616 (CH=N), 1550(C=C, aromatic), 1411 (CH_2, bending), 1295 (C-N, stretching). MS-EI (m/z, %): 313 (M^+, 1600), 281.1(1000), 255 (800), 220(9600), 192(7700), 160(1200), 139.2(11400), 111.2(9900), 83.1(10200), 57.1(10300).

4-Piperidin-1-yl-benzoic acid (3-nitro-benzylidene)-hydrazide(Bc5)

Product off-white solid, yield 63%; M.P:201-203 °C; M.F: $C_{19}H_{20}N_4O_3$; M.W; 352.39; FT-IR (cm^{-1}): 3369 (NH), 3079-3045 (C-H, aromatic), 2955-2877 (C-H, aliphatic), 1689 (C=O, Amide), 1610 (CH=N), 1580(C=C, aromatic), 1530-1348 (NO_2), 1445 (CH_2, bending), 1300 (C-N, stretching). MS-EI (m/z, %): 352.1 (M^+, 200), 69.1(6400), 83.2(4400), 97.1(4450), 111.1(3810), 129.1(2850), 149.1(4120), 205.1(2600), 222.1(2300), 234(1000), 251.1(1550), 277.1(2650), 298.1(3150).

6. In vitro antimicrobic activity

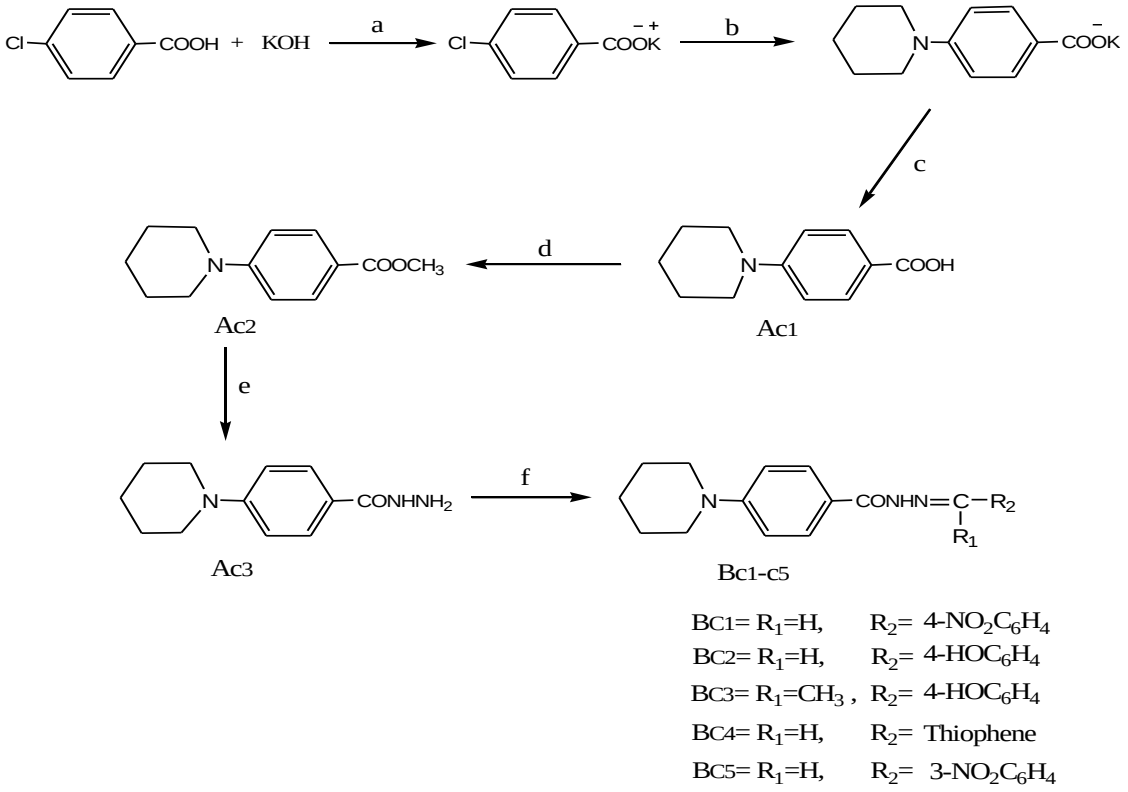
The effectiveness of derivatives Bc1-c4 anti pathogenic bacteria under aerobic conditions was examined using the well diffusion method. Following the growth of B. subtilus, S.aureus, (two gram-positive bacteria), P. auruginosa, E. coli, (two Gram-negative bacteria), and Candida albicans (yeast) in a nutrient broth, the antimicrobial activity anti all pathogenic microorganisms was evaluated using Mueller-Hinton agar. Each compound had a concentration of 600 µg /mL. Agar plates were made by inoculating a 0.5 McFarland tube with 1.5*108 (CFU)/ml of bacteria for bacteria strains and 1.5*106 (CFU)/ml for fungi. A sterile corn borer with a width of 6 mm was employed to produce wells in the Mueller-Hinton agar plates. Later, 100µl of the check compounds were added to each well after a 15-minute growth period. The plates were growth at 37°C for 24 hours to assess antibacterial activity, and at 28°C for 72 hours to evaluate antifungal activity. The inhibitory zone diameters (mm) were measured to determine activity [36]. Dimethyl sulfoxide (DMSO) served as the control solvent to ensure it did not influence microbial growth, with the same dilutions used in the test medium. The microorganisms were discovered to be unaffected by DMSO at the concentrations tested [37]. Each compound underwent a triplicate experiment, with the average reading being recorded.

3. DISCUSSION

Chemistry

The synthetic methodologies employed to synthesize. the compounds are depicted in Scheme 1. Several novel hydrazone and hydrazide derivatives were conceptualized utilizing 4-piperidin-1-yl benzoic acid Ac1 as the precursor. This compound was synthesized via nucleophilic aromatic substitution (SNAr) of 4-chlorobenzoic acid with piperidine[38]. The intermediate, 4-piperidin-1-yl benzoic acid hydrazide Ac3, was produced through esterification of Ac1 in methanol with sulfuric acid under reflux conditions. Subsequently, this ester, Ac2, was reacted with hydrazine hydrate [39]. The condensation of acid hydrazide Ac3

with various substituted aldehydes or ketones in ethanol, in the existence of glacial acetic acid, with reflux conditions, yielded a series of new 4-piperidin-1-yl-benzoic acid (substituted)-hydrazide derivatives Bc1-c5[40].



Scheme 1: (a) MeOH (b) piperidine (c) Hydrochloric acid 10% (d) MeOH, Concentrated Sulfuric acid (e) EtOH, hydrazine hydrate (f) EtOH, aldehyde or ketone, glacial acetic acid.

The structures of the derivatives Ac1-c3 and Bc1-c5 were validated by the FT-IR, 1H NMR, and mass spectrum. the FT-IR spectra of compounds (Ac1-c3) outline the bands at 1679 cm-1, 1722 cm-1 and 1652 cm-1 regions via to the vibrations of the c=o carboxylic acid, ester and hydrazide. Besides this The disappearance of the wide band for the OH stretch Carboxylic acid at 3200-2200 and appearance of NH2 and NH stretching at 3181-3104 cm-1 and 3335 cm-1 frequencies hydrazide a good evidence of prepared target compounds. Bc1-c5 revealed the bands of absorption at 3369-3107 cm-1 related to the vibrations of the NH and at 1703-1662 cm-1 related to the vibrations of the C=O hydrazide and at 1650–1600 cm-1 areas because of the CH=N, C=N groups vibrations. The elimination of the NH2 frequencies is a reliable indicator of target compounds that have been synthesized. The 1H NMR spectra of compounds Bc2 and Bc3 showed multiplet at 0.83-3.34 ppm regions due to CH2 piperidine groups and showed signal at 10.65 ppm and 9.49 ppm related to NH group, and the signal at 8.56 ppm related to CH=N group in compound Bc2. Mass spectra of all 4-peridin-1-yl-benzoic acid derivatives revealed [M++1], which validated the molecular formula. In the experimental section, the specific data are displayed.

In Vitro Antimicrobial Assays

The synthetic compounds (Bc1-c4) were tested against multiple bacteria species in vitro at a concentration of 600 µg /mL, as proved by Table 1. Promising activity against many species was demonstrated by the tested compounds. Compound Bc3 had the highest antibacterial activity in comparison with other compounds, with an inhibition zone diameter ranging between 11-16 mm. Bc4 and Bc1 have the highest activity against Candida albicans in comparison with other compounds, with an inhibition diameter of 29 and 28 mm, individually. It is obvious that Bc3 is more active compared to other compounds because it is the only one that includes a CH_3 group in its structure. We note the clear differences in biological activity between Bc3 and Bc2, which are similar in structure except for the presence of a CH_3 group in Bc3 [41]. Figure 1 shows the inhibition zone of compound derivatives.

Table 1: Evaluation of the Antimicrobial Efficacy of Compounds Bc1-C4

Compounds	Inhibition diameter (mm)				
	S. aureus (G+)	*Bacillus subtilus (G+)*	*P. aeruginosa (G-)*	*E. coli (G-)*	*Candida albicans*
DMSO	-	-	-	-	-
Bc1	9	11	15	9	28
Bc2	10	12	14	10	16
Bc3	16	15	16	11	25
Bc4	13	14	15	12	29
Amoxicillin	44	30	40	42	16

(-) exhibit no activity at specific concentration

A

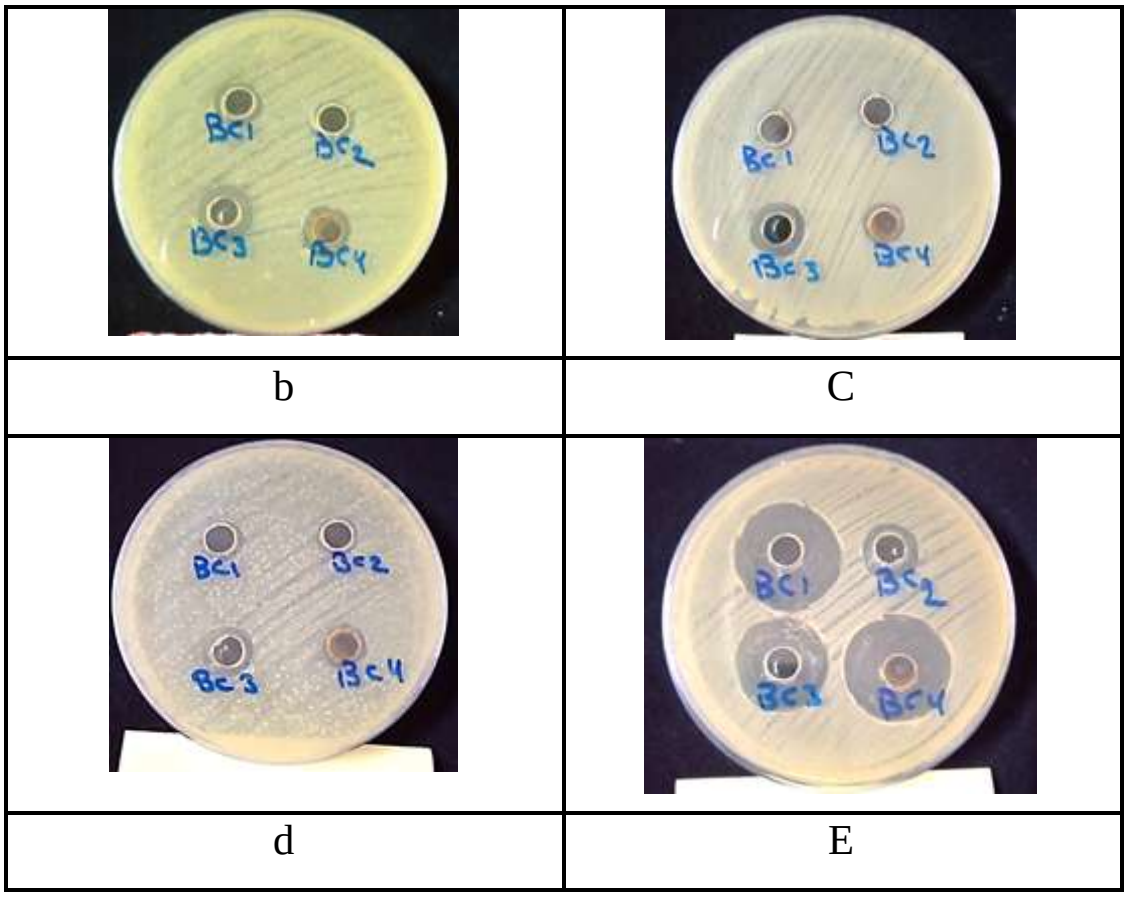


Figure 1: Inhibition zone of compounds Bc1-c4 against a- Escherichia coli, b- Pseudomonas aeruginosa (gram –ve), c- Staphylococcus aureus, d- Bacillus subtilus (gram+ve) e- C.albicans.

4. CONCLUSION

A new series of 4-Piperidin l-1-yl benzoic acid hydrazide (*Ac1-c3 and Bc1-c5*) were synthesized, chemically characterized, and biologically evaluated as antimicrobial agent. 4-Piperidin l-1-yl benzoic acid were synthesized and used as starting materials to synthesized new ester Ac2, hydrazide Ac3 and Hydrazone/hydrazide derivatives Bc1-c5. The sythesized compounds Bc1-c4 shown moderate to outstanding antibacterial efficacy against a number of antimicrobial species.

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