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New Benzimidazoles Bearin 2-Pyrazoline Moiety: Synthesis and Antimicrobial Activity

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Abstract

A new series of 5-(*1H*-Benzimidazol-2-yl)-4,5-dihydro-*1H*-pyrazol-3-yl] derivatives (1-9) were synthesized and characterized using spectral analysis. The first step includes the reaction of benzimidazole-2-carboxaldehyde with the *o,p*-aminoacetophenone to obtain the chalcone derivative (1, 2). The cyclization reaction of chalcone by the hydrazine hydrate afforded compound (3, 4), which represents the starting material for Schiff base derivatives. New Schiff bases (5-6) were synthesized from the reaction of benzimidazole derivative (2) with the corresponding benzaldehydes. The azetidin-2-one (7) and 1,3-oxazepane-4,7-dione derivatives (8-9) were synthesized from the corresponding aldehyde with chloroacetyl chloride and appropriate anhydride as depicted in the experimental section. All the derivatives were in vitro screened against Escherichia coli, Klebsiella spp. (Gram negative), Staphylococcus aureus, S.espidermi (Gram positive) as well as Candida albicans and found to exhibit moderate to potent activity.

Keywords: Benzimidazole, pyrazoline, azetidinone, oxazepane, antimicrobial.

1. Introduction

Microbial Infections (fungal and bacterial) have been reported to increase affected globally in present days and main reasons are toward the block resistance. Destruction of resistance results from several causes such as distortion, operations, immunosuppressive treatments, and old age. This case is exacerbated through rising rate of microbial resistance to the general antibiotics existing nowadays [1]. Therefore, there is an essential to develop new insignificant, harmless, and effective drugs with a wide range of antimicrobial action [2]. Heterocyclic compounds containing nitrogen have been gaining a lot of interest in the last

decade because of their eminent and diverse pharmacological activities. In medicinal chemistry, heterocyclic rings such as pyrazoline have drawn much attention due to their presence in antipyrine. For many years, pyrazolines have attracted researchers due to their various biological and pharmacological activities because it contains *N–N* bond, one of the important causes in their biological activities [3]. Pyrazoline nucleus is present in so many currently available drugs like metamizole or dipyrone (analgesic and antipyretic), phenylbutazone (anti-inflammatory) and sulfinpyrazone (chronic gout). Pyrazolines are reported to possess versatile activities such as antimicrobial [4], anti-inflammatory [5], analgesic [6], anticancer [7], antimalarial [8], antioxidant [9], Antiviral [10] and antidepressant [11]. The present work explores a novel benzimidazole derivatives containing 2-pyrazoline moiety as new antimicrobial agents. The new derivatives were synthesized and characterized using spectral analysis, then tested against several bacterial species as well as candida albicans.

2 Experimental Section

All starting materials and solvents were purchased from Sigma-Aldrich, or Fluka and used without further purification. Melting points were determined on an electro-thermal capillary apparatus and are uncorrected; FT-IR measurements were recorded on a Shimadzu model FTIR-8400S. Mass spectra were recorded on a Shimadzu GCMS-QP2010 Ultra apparatus. ^{1}H NMR spectra were obtained with a Bruker spectrophotometer model ultra-shield at 300 MHz in DMSO-d_6 and CDCl3 solution with the TMS as internal standard.

2.1 Synthesis of chalcone derivatives (1), and (2)

These compounds were prepared according to the procedure described in reference [12]. To a mixture of 1*H*-benzimidazole-2-carbaldehyde (1.46 g, 0.01 mol) and equimolar amount of corresponding substituted acetophenone dissolved in a minimum amount of ethanol, aqueous NaOH solution (0.25 mol, 40 %) was added drop wise. The reaction crude was stirred at room temperature until the completion of the reaction (monitored by TLC using DCM: MeOH; 97:3). The precipitate formed after the acidifying the reaction mixture was filtered off, washed thoroughly with cold distilled water then recrystallized from ethanol.

2.1.1 Characterization of 1-(2-Amino-phenyl)-3-(1*H*-benzoimidazol-2-yl)-propenone (1)

Orange powder, yield 91 %, m.p 220-222 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3481, 3319 (NH_2), 3433 (NH), 3057 (aromatic C-H), 2939, 2899 (aliphatic C-H), 1645 (C=O), 1614 (CH=CH), 1579 (C=N), 1531 (aromatic C=C). ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 6.62-6.65 (m, 1H, Ar-H), 6.63(d, 1H, Ar-H), 7.23-7.33 (m, 3H, NH_2, Ar-H), 7.49-7.67 (m, 5H, CH-chalcone, Ar-H), 7.96 (d, 1H, Ar-H), 8.25 (d, 1H, CH chalcone), 12.99 (s, 1H, NH benzoimidazol). GCMS (NCI) m/z: 264 M^+ For $C_{16}H_{13}N_3O$.

2.1.2 Characterization of 1-(4-Amino-phenyl)-3-(1*H*-benzoimidazol-2-yl)-propenone (2)

Dark yellow powder, yield 92 %, m.p 282-284 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3529, 3323 (NH_2), 3400 (NH-benzoimidazol), 3005 (aromatic C-H), 2931, 2889 (aliphatic C-H), 1649 (C=O), 1604 (CH=CH), 1579 (C=N), 1554 (aromatic C=C). ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 6.28 (s, 2H, NH_2), 6.66 (d, 2H, Ar-H), 7.24-7.25 (m, 2H, Ar-H),7.50 (d, 1H, CH-chalcone), 7.61-7.62(m, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 8.16 (d, 1H, CH-chalcone), 12.96 (s, 1H, NH benzoimidazol). LC-MASS m/z: 263.8 M^+ (10.48 min) 96 %, For $C_{16}H_{13}N_3O$.

2.2 Synthesis of 3, 5-disubstitutedarylpyrazolines

These compounds were prepared according to the procedure described in reference [13]. To an ethanolic solution of chalcone derivative (0.1 mol), a few drops of glacial acetic acid were added and the mixture stirring at 25 °C for 15 min. Then, hydrazine hydrate (0.25 mol, 80 %) was added drop wise and the reaction mixture was further stirred for 15 minutes. The completion of the reaction was checked by TLC using dichloromethane and methanol as eluent (94:6) The solid products were filtered, washed thoroughly with diethyl ether, and recrystallized from absolute ethanol.

2.2.1 Characterization of 4-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-phenylamine (3)

white powder, yield 83 %, m.p 232-234 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3529, 3323 (NH_2), 3444 (NH-pyrazoline), 3304 (NH-benzoimidazol), 3086 (aromatic C-H), 1635 (C=N pyrazoline), 1606 (C=N benzoimidazol), 1587 (aromatic C=C). ^{1}H NMR (300MHz,

DMSO-d_6) δ (ppm): 3.13-3.19 (m, 1H, Ha-pyrazoline), 3.37-3.44 (m, 2H, Hb-pyrazoline, NH-pyrazoline), 4.88-4.93 (m, 1H, Hx-pyrazoline), 6.53 (m, 2H, NH_2), 7.09-7.11 (m, 3H, NH-benzoimidazol, Ar-H), 7.31-7.47 (m, 6H, Ar-H). LC-MASS (NCI) m/z: 276 M^+ (9.23min) 84.5 %, For $C_{16}H_{15}N_5$.

2.2.2 Characterization of 2-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-phenylamine (4)

White powder, yield 90 %, m.p 220-222 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3414 (NH-pyrazoline), 3369 (NH-benzoimidazol) 3057 (aromatic C-H), 1620 (C=N pyrazoline), 1606 (C=N benzoimidazol), 1587 (aromatic C=C). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.38-3.46 (m, 2H, Ha-pyrazoline, NH-pyrazoline), 3.59-3.7 (m, 1H, Hb-pyrazoline), 4.94-5.02 (m, 1H, Hx-pyrazoline), 6.55-6.76 (m, 4H, NH_2 , Ar-H), 7.06-7.18 (m, 4H, Ar-H), 7.47-7.64 (m, 2H, Ar-H), 12.46 (s, 1H, NH benzoimidazol). GCMS (NCI) m/z: 277 M^+ for $C_{16}H_{15}N_5$.

2.3 Synthesis of Schiff bases (5), and (6)

These Schiff bases compounds were synthesized according to the procedure in reference [14]. A mixture of substituted benzaldehyde (1.5 mmol) dissolved in 1,4-dioxane (10 ml) with 2 drops of concentrated H_2SO_4 was mixed for 15 min at room temperature. Pyrazoline derivative (2) (1.5 mmol) was added to the mixture and stirred for two hours, and the completion of the reaction was monitored via TLC using n-hexane and ethyl acetate as eluent (6:1). The solid product filtered, dry and washed with distilled water then with diethyl ether.

2.3.1 Characterization of 3-({2-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-phenylimino}-methyl)-phenol (5)

A light-yellow powder, yield 58 %, m.p 280-282 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3540 (OH), 3480 (NH-pyrazoline), 3325 (NH-benzoimidazol), 3099 (aromatic C-H), 1640 (C=N pyrazoline), 1625 (C=N benzoimidazol), 1600 (CH=N), 1580 (aromatic C=C). ^{1}H NMR (300MHz, DMSO-d_6) δ (ppm): 3.46-3.54 (m, 1H, Ha-pyrazoline), 3.75-3.90 (m, 1H, Hb-pyrazoline,), 5.23-5.30 (m, 1H, Hx-pyrazoline), 6.42-8.03 (m, 15H, OH, NH pyrazoline, Ar-H), 8.63 (s, 1H CH=N), 9.94 (s, 1H, NH benzoimidazol). GCMS (NCI) m/z: 381.4 M^+ For $C_{23}H_{19}N_5O$.

2.3.2 Characterization of {4-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-benzylidene-amine (6)

A light-yellow powder, yield 68 %, m.p 320-322 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3400 (NH-pyrazoline), 3380 (NH-benzoimidazol), 3120 (aromatic, C-H), 1645 (C=N pyrazoline), 1631 (C=N benzoimidazol), 1595 (CH=N), 1572 (aromatic C=C). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.34-3.39 (m, 1H, Ha-pyrazoline), 3.67-3.89 (m, 1H, Hb-pyrazoline), 5.18 (m, 2H, Hx-pyrazoline, NH pyrazoline), 6.70 (m, 5H, Ar-H), 7.45-7.52 (m, 5H, Ar-H), 7.77 (m, 5H, Ar-H, CH=N, NH benzoimidazol). GCMS (NCI) m/z: 365.4 M^+ For $C_{23}H_{19}N_5$.

2.4 Synthesis of 1-{4-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-3-chloro-4-phenyl-azetidin-2-one (7).

Compound seven was synthesized according to the procedure in reference [15]. To a solution of Schiff base derivative (5), (0.365 g, 1mmol) in dioxane (10 mL) at 0-5 °C. Chloroacetyl chloride (0.17 g, 1.5 mmol) was added gradually with continuous stirring. After that, triethylamine (0.3 g, 3 mmol) was added, and the reaction crude was stirred for 30 minutes at 0-5 °C. The temperature of mixture arises to room temperature and stirring for one hour, then refluxed for eight hours. The completion of the reaction was checked by TLC using dichloromethane and methanol as eluent (98:2). The solid precipitate was filtered, and neglect and the filtrate added to iced water then, the product was collected, and wash with diethyl ether.

2.4.1 Characterization of compound (7)

The resulted yellow powder showed yield of 62 %, m.p 353-355 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3443 (NH-pyrazoline), 3379 (NH-benzoimidazol), 3032 (aromatic C-H), 1683 (C=O), 1670 (C=N pyrazoline), 1606 (C=N benzoimidazol), 1587 (aromatic C=C). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.67-3.73 (dd, 1H, Ha-pyrazoline), 3.90-3.96 (dd, 1H, Hb-pyrazoline), 4.72-4.85 (dd, 2H, CH-N, CH-Cl), 5.81-5.85 (dd, 1H, Hx-pyrazoline), 7.20-7.23 (m, 4H, , Ar-H), 7.56-7.59 (m, 4H, Ar-H), 7.77-7.86 (m, 5H, Ar-H), 10.72 (s, 1H, NH benzoimidazol).

2.5 Synthesis of oxazepane-4,7-dione derivatives (8), and (9)

These compounds were synthesized according to the procedure described in reference [16]. An appropriate anhydride compound (2 mmol) was dissolved in benzene (5 mL) was added to a solution of Schiff base (5) or (6) (0.365g, 1mmol) dissolved in benzene (10 mL), then the mixture was refluxed for ten hours. The progress of the reaction was checked by TLC using dichloromethane and methanol as eluent (97:3). The solid product filtered off, washed with benzene, and recrystallized from chloroform.

2.5.1 Characterization of 3-{4-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1H-pyrazol-3-yl]-phenyl}-2-phenyl-[1,3]oxazepane-4,7-dione (8).

Brown powder, yield 74 %, m.p 117-119 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3470 (NH-pyrazoline), 3400 (NH-benzoimidazol), 3090 (aromatic C-H), 2987, 2887(aliphatic C-H), 1716 (C=O), 1695(C=O), 1633 (C=N pyrazoline), 1606(C=N benzoimidazol), 1560 (aromatic C=C). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.31-3.40 (dd, 1H, Ha-pyrazoline), 3.68-3.78 (dd, 1H, Hb-pyrazoline), 5.27-5.34 (m, 1H, Hx-pyrazoline), 6.00 (m, 1H, , Ar-H), 6.75-6.84 (m, 3H, Ar-H, CH_2a-oxazepane), 7.38-7.60 (m, 5H, Ar-H, CH_2b-oxazepane), 7.77 (m, 7H, Ar-H, NH-pyrazoline, CHx-oxazepane), 10.29 (s, 1H, NH benzoimidazol).

2.5.2 Characterization of 3-{2-[5-(1*H*-Benzoimidazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]-phenyl}-2-(3-hydroxy-phenyl)-2,3-dihydro-[1,3]oxazepane-4,7-dione (9).

Light yellow powder, yield 66 %, m.p 102-104 °C; IR ($\bar{\upsilon}$ cm^{-1}): 3540 (OH), 3371 (NH-pyrazoline), 3340 (NH-benzoimidazol), 3026 (aromatic C-H), 2945, 2820 (aliphatic C-H), 1720 (C=O), 1680 (C=O), 1645 (NH-bending), 1622 (C=N pyrazoline), 1600 (C=N benzoimidazol), 1540 (aromatic C=C). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.83-3.98 (dd, 1H, Ha-pyrazoline, j = 0.15), 4.06-4.18 (m, 1H, Hb-pyrazoline), 5.82-5.88 (m, 1H, Hx-pyrazoline), 6.30 (s, 1H, , OH), 6.33-6.45 (m, 2H, Ar-H, CHa-oxazepane), 6.57-6.98 (m, 2H, Ar-H, CHb-oxazepane), 7.11-7.53(m, 8H, Ar-H, CHx-oxazepane), 7.60-7.84 (m, 3H, Ar-H), 9.93 (s, 1H, NH-pyrazoline), 10.94 (s, 1H, NH benzoimidazol).

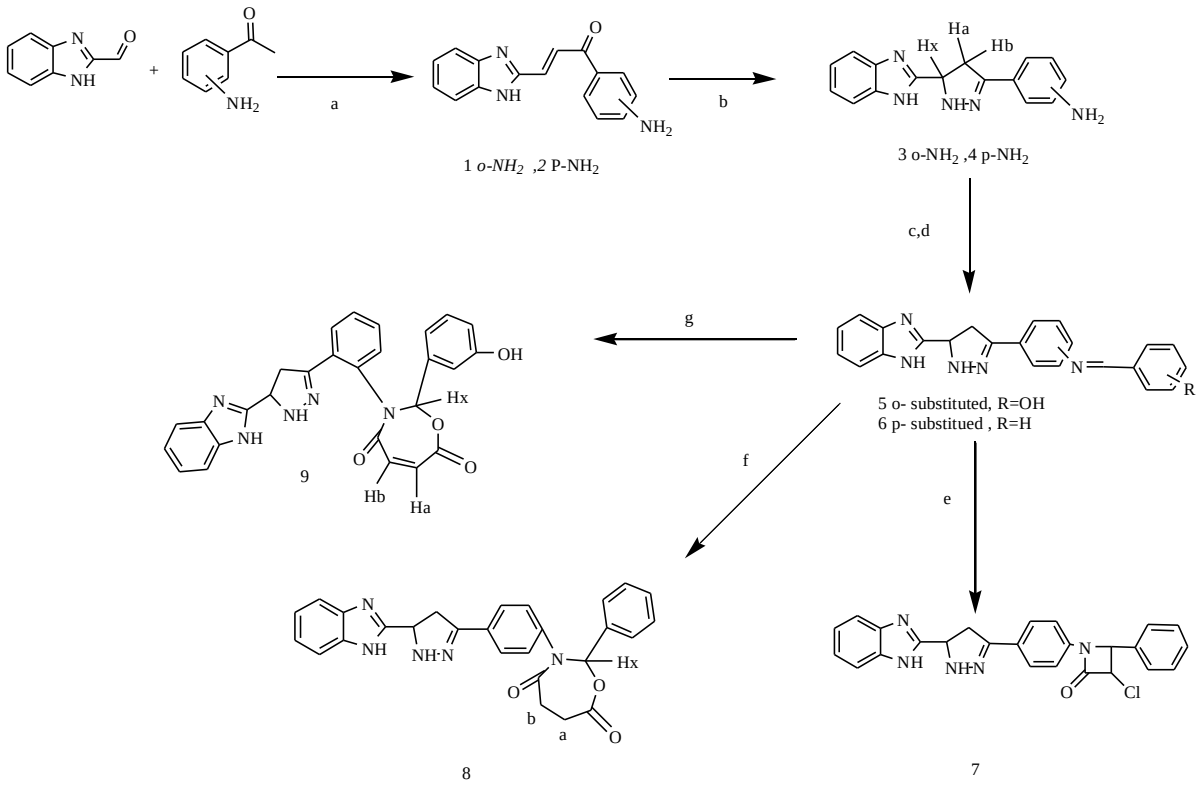
2.6 Biological activity evaluation

The synthesized benzimidazol derivatives (5-9) were tested for their antimicrobial activity against Escherichia coli, Klebsiella SPP (gram negative), Staphylococcus aureus, S. espidermi. (gram positive) as well as C. albicans using the well diffusion method table 1 [17]. The concentration for each compound was 1 mg/mL. Plates were prepared by spreading approximately 105 CFU/ml culture broth of each indicator bacterial isolates on Muller Hinton agar surface using sterile cotton swabs. The agar plates were left for 10 minutes before aseptically dispensing the 50 µl of each compound into the agar wells already bored in the agar plates. Then, plates were incubated at 37 °C for 24 hours. Zones of inhibition were measured and recorded in millimeter diameter. The Dimethyl sulfoxide was used as control.

3 Results and discussion

3.1 Synthesis of derivatives

Chalcones derivatives (1), and (2) were synthesized from the reaction of 1*H*-benzimidazole-2-carbaldehyde with the corresponding aminoacetophenone in EtOH using NaOH as a catalyst as shown in Scheme 1. Structures of synthesized compounds were confirmed by spectral analysis. The FT-IR spectrum of chalcone derivative (1) showed two absorption bands, the first band at 1645 cm^{-1}, and the second band at 1604 cm^{-1} regions are due to the stretching vibrations of the C=O, and CH=CH groups respectively. ^{1}H NMR spectra show singlet signal at 6.28 ppm that due to NH_2 with two doublet signals at 7.49 and 8.25 ppm due to CH=CH.



Scheme1: (a) NaOH 40 %, EtOH (b) hydrazine hydrate, glacial acetic acid, ETOH (c) benzaldehyde, H_2SO_4, 1,4-dioxane (d) p-hydroxy benzaldehyde, H_2SO_4, 1,4-dioxane (e) chloroacetyl chloride, triethyl amine, 1,4-dioxane (f) Succinic anhydride, benzene (g) Maleic anhydride, benzene

The cyclization reaction of compounds (1) and (2) by the action of hydrazine hydrate afforded pyrazoline derivatives (3), and (4). The FT-IR spectrum showed disappearance of the C=O and CH=CH and appearance absorption bands at 1635 and 1606 for C=N of pyrazoline and benzimidazole moiety for compound (3). While for compound (4) appeared at 1620, 1606 cm^{-1}. ^1H NMR spectra showed singlet signals at 3.13-3.46 ppm related to NH proton for compounds (3), (4) and a singlet signal at 7.77-10.20 due to NH proton for compound (4) with appearance of three multiple signals at 3.13-3.46, 3.37-3.7, and 4.48-5.02 ppm due to CHa, CHb and CHx of pyrazoline derivative. Schiff bases (5), and (6) were synthesized from the reaction of pyrazoline compound (3), and (4) with different aromatic aldehydes in acidic ethanolic solution scheme1. The FT-IR spectra of benzoimidazol derivatives (5), and (6) showed absorption bands at, 1595-1606 cm^{-1} region due to the stretching vibration of the CH=N group. The disappearance of the NH_2

stretching frequencies a good evidence of prepared target compounds. ^{1}H NMR spectra of benzoimidazol derivatives (5), and (6) showed singlet signal at the range of 7.77-8.63 ppm due to CH=N group with the absent of the singlet signal at 6.53- 6.76 related to NH_2 group in compound (3), and (4).

The 2-azetidinone derivatives (7) were obtained by the reaction of Schiff base (5) with the chloroacetyl chloride in triethyl amine. The IR spectrum of compound (9) showed characteristic peak at 1683 cm^{-1} due to C=O group. The ^{1}H NMR spectrum of compound (7) showed doublet of doublet signal at 4.72, and 4.85 ppm due to CH-N and CH-Cl groups. The reaction between the Schiff bases (5), and (6) with Succinic and maleic anhydride were carried out as described in scheme 1 to produce the oxazepine derivatives (8), and (9). Structures of [1,3]-oxazepane-4,7-dione derivatives were confirmed using FT-IR spectroscopy. The stretching of two carbonyl groups appeared in 1716, 1695 and 1720, 1680 cm^{-1} for compound (8), and (9) respectively. ^{1}H NMR spectrum showed multiple signals at 6.75-6.84, and 7.38-7.60 ppm due to CH_2a and CH_2b oxazepane and doublet signal at 6.33-6.45, and 6.57-6.98 ppm due to CHa and CHb oxazepane for compounds (6), and (7) respectively. CHx oxazepane appeared as singlet signal at 7.11-7.77 ppm for both compounds.

3.2 Antimicrobial activity

The in vitro assay of the synthesized compounds (5-8) against several microbial species was achieved using 1mg /mL concentration as illustrated in table 1. The tested derivatives exhibited promising activity against different species. Compounds (5), (6), and (7) were the potent agents against gram +ve, gram –ve as well as Candida Albicans as shown in table 1.

Table 1: In Vitro antimicrobial inhibition zone (mm) of the synthesized compounds.

benzimidazol derivatives	Gram positive		Gram negative		fungi
1mg /mL	*E.coli*	*Klebseilla SPP*	*S.aureus*	*S.espidermi.*	*C. albicans*
5	12	11	12	-	-
6	11	11	14	-	-
7	11	11	14	11	15
8	11	11	-	-	11

(-) exhibit no activity at specific concentration.

4 Conclusion

Novel benzimidazol derivatives bearing pyrazoline, azetidin-2-one and oxazepane scaffolds were designed, synthesized, and evaluated as antimicrobial agents. All synthesized products were evaluated as antimicrobial agents against two-gram negative (Escherichia coli and Klebseilla SPP), two gram-positive (Staphylococcus aureus and S.espidermi.) and one fungi (Candida albicans) species and exhibited promising results.

5 References

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