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Synthesis, characterization and biological evaluation of new heterocyclic compounds containing benzimidazole ring

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Abstract

A new derivatives of benzimidazole containing Schiff base moiety has been synthesized. The reaction was achieved through cyclization of 4-methyl-1,2- phenylene diamine with a various of amino acids (glycine, alanine, phenyl alanine and tyrosine) to yielded derivatives of benzimidazole compounds 1(a-d). Condensation of these compounds 1(a-d) with a variety of aromatic aldehyde yielded the new benzimidazole compounds containing imine group. The chemical structure of synthesized compounds were confirmed by FT-IR, ^{1}H,^{13}C-NMR, and ^{13}C-NMR dept135 spectroscopy. Some selected compounds were tested in vitro for their antibacterial activity by disc diffusion method against two types of Gram-positive bacteria namely (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria namely (*Pseudomonas aeruginosa*, *Escherichia coli*). The results displayed that most of the prepared compounds have a good antibacterial activity when compared with the standard antibiotic ampicillin and ciprofloxacin.

Keywords: Benzimidazole, amino acid, Schiff base, 4-methyl-1, 2- phenylenediamine

INTRODUCTION

Benzimidazole is a fused heterocyclic compound, which consists from benzene ring attached with one face of the imidazole ring , It is an important compound and interest structure in pharmaceutical chemistry [1]. The study of biological activity of benzimidazoles and their derivatives is of significance importance due to their wide use in many areas of chemical industry [2] Various studies have shown different uses for benzimidazoles and their derivatives, especially as antagonists [3] potent inhibitors of tyrosine kinase [4] antipyretic [5], Benzimidazole derivatives have shown potential for applications in a variety of pharmacological targets and have attracted a wide interest in clinical applications [6]. Benzimidazoles have played an important role in medicinal chemistry [7] and biochemistry [8]. Compounds carrying benzimidazoles nucleus are reported to elicit certain biological activities such as antiviral [9], antifungal [10], anti-inflammatory [11], antibacterial [12], antimicrobial [13], anticancer [14], antitumor[15], anti-HIV [16]. many derivatives of benzimidazoles consider intermediates in organic synthesis Therefore, a large interests have been attracted to the synthesis of benzimidazole and its derivatives recently [17]. Schiff bases considered as privileged structure of organic compounds, especially in the medicinal and pharmaceutical field. Thus, synthesis and development of novel Schiff base derivatives as potential chemotherapeutics still attract attention of organic and medicinal and wide range of biological activities including antibacterial [18] and antimicrobial [19].

MATERIALS AND METHODS

Melting points were taken in an electrically heated using Stuart SMP^{3} instrument and are uncorrected. FT-IR spectra were recorded on (Shimadzu FT-IR- 8400S spectrophotometer at the Chemistry department/ College of education for pure scince/ University of Diyala) by using KBr disc(v,cm^{-1}). The ^{1}H and ^{13}C-NMR spectra were recorded on (Bruker 400MHz at the Jordan University for science and technology /Jordan) by using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent. The purity of the compounds was checked by TLC on silica gel plates using ultraviolet lamp(365nm and 254nm).

General procedure for synthesis of compounds 1(a-d)[20]

A solution of 4-methyl-1,2- phenylene diamine (0.02 mol) and amino acids (glycine, phenylalanine, alanine and tyrosine) (0.04 mol) in 4N HCl (25 ml) was heated to reflux with stirring for 9-12hrs. The progress of the reaction was monitored by TLC plate. On completion of the reaction , the product was cooled to room temperature and the pH was arrangement to 7.2 using 1N NaOH solution to obtain buff colored product. The product was recrystallized using ethanol as solvent.

5-(methyl-1H-benzo[d]imidazol-2-yl)methanamine (1a)

Yellow, yield 66%., m.p: 230 – 231 °C, IR ν_{max} (KBr/cm^{-1}): NH_{2str} (3377, 3353), N-H_{str} benzimidazole (3278), aromatic C-H_{str} (3029), aliphatic C-H_{st} (2664, 2764), C=N_{str} (1639) , aromatic C=C_{str} (1458, 1593). ^{1}H –NMR (400 MHZ, DMSO – d_6) δ :2.34(3H,s,CH_3) 2.91 (2H, s, CH_2), 5.18 (1H, s, N-H benzimidazole), 8.48 (2H, s, NH_2), 6.9-7.5 (3H,m, Ar – H). ^{13}C – NMR (400 MHZ, DMSO) δ :20.2(CH_3), 44.8 (CH_2), 142.3 (C=N of benzimidazole), 114.7 , 117.3 , 134.8 . ^{13}C-Dept 135 NMR (400 MHZ, DMSO – d_6) δ : 44.8 (CH_2).

1-(5-methyl-1H-benzo[d]imidazol-2-yl)ethan-1-amine (1b)

Brown, yield 87%, m.p : 250 – 251 °C, IR ν_{max} (KBr/cm^{-1}): NH_{2str} (3377, 3336), N-H_{str} benzimidazole (3283), aromatic C-H_{str} (3027,3018), aliphatic C-H_{str} (2644, 2856), C=N_{str} (1643), aromatic C=C_{str} (1458-1593). ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 1.2 (3H, d, CH_3),2.5(3H, s, CH_3), 3.6 (1H, q, C-H), 5.6 (1H, s, N-H benzimidazole), 8.54 (2H, s, NH_2), 6.84-7.61 (3H, m, Ar – H).^{13}C–NMR (400 MHZ, DMSO) δ: 20.2,23.9 (CH_3), 54.6 (CH), 146.9 (C=N of benzimidazole), 114.9, 119.2, 127.1, 138.1,140.1.

1-(5-methyl-1H-benzo[d]imidazol-2-yl)-2-phenylethan-1-amine (1c)

Red, yield 67%, m.p : 270–271 °C, IR ν_{max} (KBr/cm^{-1}): NH_{2str} (3385,3363), N-H_{str} benzimidazole (3220), aromatic C-H_{str} (3024), aliphatic C-H_{str} (2752, 2855), C=N_{str} (1628). aromatic C=C_{str} (1486-1591).

4-(2-amino-2-(5-methyl-1H-benzo[d]imidazol-2-yl)ethyl)phenol (1d)

Yellow, yield 82%, m.p : 261 – 262 °C, IR ν_{max} (KBr/cm^{-1}): NH_{2str} and O-H_{str} bands overlapping in one broad band around (3431), N-H_{str} benzimidazole (3125), aromatic C-H_{str} (3064,3034), aliphatic C-H_{str} (2765, 2868), C=N_{str} (1639), aromatic C=C_{str} (1454-1561).

General procedure for the synthesis of compounds 2(a-l) [21]

Compounds 1(a-d) (0.02 mol) were add to asolution of the various substituted benzaldehydes (p-bromo benzaldehyde, p-nitro benzaldehyde, p-hydroxy benzaldehyde) (0.02 mol) in dry ethanol 30 ml in RBF. 2-3 drops of CH_3COOH were also added to the above mixture. The mixture was refluxed for 10-13h. The progress of the reaction was monitored by TLC plate, solvents were partially evaporated then poured in to water. The precipitates were collected by filtration, washed with ether, dried and compounds 2(a-l) were synthesized and recrystallized from the appropriate solvent like ethanol or ethanol-water.

1-(4-bromophenyl)-N-((5-methyl-1H-benzo[d] imidazol-2-yl) methyl) methanimine (2a)

Yellow, yield 80%, m.p : 237-238 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3321), aromatic C-H_{str} (3030,3055), aliphatic C-

H_{str} (2997, 2875), C=N_{str} (1610) , aromatic C=C_{str} (1448-1531), C-Br_{str} (744).

4-((((5-methyl-1H-benzo[d]imidazol-2-yl) methyl)imino) methyl) phenol (2b)

Yellow, yield 83%, m.p : 245-246 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole band and O-H_{str} band overlapping in one broad band (3259) , aromatic C-H_{str} (3098,3042), aliphatic C-H_{str} (2943, 2875), C=N_{str} (1620), aromatic C=C_{str} (1449-1514), ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 2.4(3H, s, CH_3), 3.37 (2H, s, CH_2), 5.50 (1H, s, N-H), 9.87 (1H, s, OH), 9.51 (1H, s, CH=N), 6.94-7.65 (3H, m, Ar – H). ^{13}C –NMR (400 MHZ, DMSO) δ :20.4 (CH_3), 49.4 (CH_2), 143.7 (C=N of benzimidazole), 156.5 (1H,s,C-OH), 156.7(1H,s,CH=N), 115.3 , 118.7 ,125.03, 127.4 131.5 , 139.19) ^{13}C-Dept 135 NMR (400 MHZ, DMSO – d_6) δ : 49.5 (CH_2).

N-((5-methyl-1H-benzo[d] imidazol-2-yl) methyl)-1-(4-nitrophenyl) methanimine (2c)

Yellow crystals, yield 81%, m.p : 258-259 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3321), aromatic C-H_{str} (3035,3075), aliphatic C-H_{str} (2954, 2859), C=N_{str} (1604), aromatic C=C_{str} (1445,1535), NO_{2str} (1340,1516).

1-(4-bromophenyl)-N-(1-(5-methyl-1H-benzo[d]imidazol-2-yl) ethyl) methanimine (2d)

Brown crystals, yield 69%, mp : 273-274 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3361), aromatic C-H_{str} (3089,3045), aliphatic C-H_{str} (2983, 2879), C=N_{str} (1633), C-Br_{str} (775), aromatic C=C_{str} (1466,1536), ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 1.56 (3H, s, CH_3),2.6 (3H, d, CH_3), 5.6 (1H, s, N-H), 3.17 (1H, s, CH), 9.21 (1H, s, CH=N), 6.94-7.83 (7H, m, Ar – H). ^{13}C –NMR (400 MHZ, DMSO) δ : 17.4,23.2 (CH_3), 61.6 (CH), 145.7 (C=N of benzimidazole), 160.7(1H,s,CH=N), 117.3 , 118.7 ,123.03, 130.4, 138.5 , 140.19.

4-(((1-5-methyl-1H-benzo[d]imidazol-2-yl) ethyl) imino)methyl) phenol (2e)

Brown, yield 71%, m.p:285– 286°C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3265), O-H_{str} (3398), aromatic C-H_{str} (3095,3019), aliphatic C-H_{str} (2852 , 2737), C=N_{str} (1625), aromatic C=C_{str} (1428-1536), ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 1.56 (3H, s, CH_3),2.6 (3H, d, CH_3), 5.7 (1H, s, N-H), 3.07 (1H, s, CH),9.1 (1H,s,OH) 9.31 (1H, s, CH=N), 6.94-7.83 (7H, m, Ar – H). ^{13}C –NMR (400 MHZ, DMSO) δ:19.4,25.2 (CH_3), 61.6 (CH), 149.7 (C=N of benzimidazole), 166.7(1H,s,CH=N), 117.3 , 119.7 ,123.03, 133.4, 138.5 , 142.19.

N-(1-(5-methyl-1H-benzo[d]imidazol-2-yl)ethyl)-1-(4-nitrophenyl)methanimine (2f)

Brown, yield 76%, m.p : 295-296 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3235), aromatic C-H_{str} (3127,3029), aliphatic C-H_{str} (2962, 2807), C=N_{str} (1628), aromatic C=C_{str} (1471-1596), NO_{2str} (1557,1348).

1-(4-bromophenyl)-N-(1-(5-methyl-1H-benzo[d] imidazol-2-yl)-2-phenylethyl) methanimine (2g)

Yellow crystals, yield 84%, m.p : 280 – 281 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3323), aromatic C-H_{str} (3109,3031),aliphatic C-H_{str} (2919, 2828), C=N_{str} (1624), aromatic C=C_{str} (1466,1547),C-Br_{str} (755).

4-(((1-(5-methyl-1H-benzo[d] imidazol-2-yl)-2-phenylethyl) imino) methyl)phenol (2h)

Yellow crystals, yield 76%, m.p: 289 – 290 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3265), O-H_{str} (3435), aromatic C-H_{str} (3137), aliphatic C-H_{str} (2981,2876), C=N_{str} (1634), aromatic C=C_{str} (1459,1537). ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 3.23 (2H, d, CH_2), 4.83 (1H, q, C-H), 5.93 (1H, s, N-H benzimidazole), 9.53 (1H, s, O-H), 8.39 (1H, s, N=C-H),6.87-8.10 (13H, m, Ar – H). ^{13}C –NMR (400 MHZ, DMSO–d_6) δ :25.3 (CH_3), 65.8 (C-H), 47.2 (CH_2), 159.8 (=C-H), 163.4 (C-O), 138.3 (C=N of benzimidazole), 113.3 , 117.4 , 120.5, 124.9, 128.7, 131.1 , 133.6 , 140.8 , ^{13}C-Dept 135 NMR (400 MHZ, DMSO – d_6) δ : 47.1(CH_2).

N-(1-(5-methyl-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)-1-(4-nitrophenyl) methanimine (2i)

Yellow crystals, yield 78%, m.p : 299–300 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3289), aromatic C-H_{str} (3097,2996),aliphatic C-H_{str} (2827, 2799), C=N (1615), aromatic C=C_{str} (1477-1561), NO_{2str} (1539,1344) ^{1}H –NMR (400 MHZ, DMSO – d_6) δ: 2.31(3H, s, CH_3), 3.33 (2H, d, CH_2), 4.93 (1H, q, C-H), 5.83 (1H, s, N-H benzimidazole), 9.33 (1H, s, O-H), 8.39 (1H, s, N=C-H), 6.87-8.10 (13H, m, Ar – H). ^{13}C –NMR (400 MHZ, DMSO– d_6) δ : 23.12 (CH_3), 69.8 (C-H), 47.2 (CH_2), 155.8 (=C-H), 163.4 (C-O), 138.3 (C=N of benzimidazole), 113.3 , 117.4 , 120.5, 124.9, 128.7, 131.1 , 133.6 , 140.8 , ^{13}C-Dept 135 NMR (400 MHZ, DMSO – d_6) δ : 47.3(CH_2).

4-(2-((4-bromobenzylidene) amino)-2-(5-methyl-1H-benzo[d]imidazol-2-yl) ethyl) phenol (2j)

Red crystals, yield 88%, m.p : 290 – 292°C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3211), aromatic C-H_{str} (3083,3059), aliphatic C-H_{str} (2881,2962), C=N_{str} (1618), aromatic C=C_{str} (1456-1594), C-Br_{str} (750).

4-(2-((4-hydroxybenzylidene) amino)-2-(5-methyl-1H-benzo[d] imidazol-2-yl) ethyl) phenol (2k):

Red crystals, yield 71%, m.p : 307– 308 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3219), aromatic C-H_{str} (3039,3024), aliphatic C-H_{str} (2961, 2885), C=N_{str} (1608), aromatic C=C_{str} (1456-1591), O-H_{str} (3426).

4-(2-(5-methyl-1H-benzo[d]imidazol-2-yl)-2-((4-nitrobenzylidene) amino) ethyl) phenol (2l)

Red, yield 66%, mp : 316 – 318 °C, IR ν_{max} (KBr/cm^{-1}): N-H_{str} benzimidazole (3215), aromatic C-H_{str} (3039,3029), aliphatic C-H_{str} (2960 , 2897), C=N_{str} (1608), aromatic C=C_{str} (1456-1591), NO_{2str} (1456,1591),), ^{1}H –NMR (400 MHZ, DMSO – d_6) δ : 2.61 (3H, s, CH_3), 3.56 (2H, s, CH_2), 5.70 (1H, s, N-H), 4.17 (1H, s, CH), 9.11 (1H, s, CH=N),9.54(1H,s,OH), 6.87-7.98 (11H, m, Ar – H). ^{13}C –NMR (400 MHZ, DMSO) δ :22.11(CH_3), 47.3 (CH_2), 63.6 (CH), 149.7 (C=N of benzimidazole), 167.7(=CH), 157(C-O) , 153(C-NO_2), 113.3 , 117.7 ,123.03, 131.4, 138.5 , 142.19 , 143.5 ^{13}C-Dept 135 NMR (400 MHZ, DMSO – d_6) δ : 47.4 (CH_2).

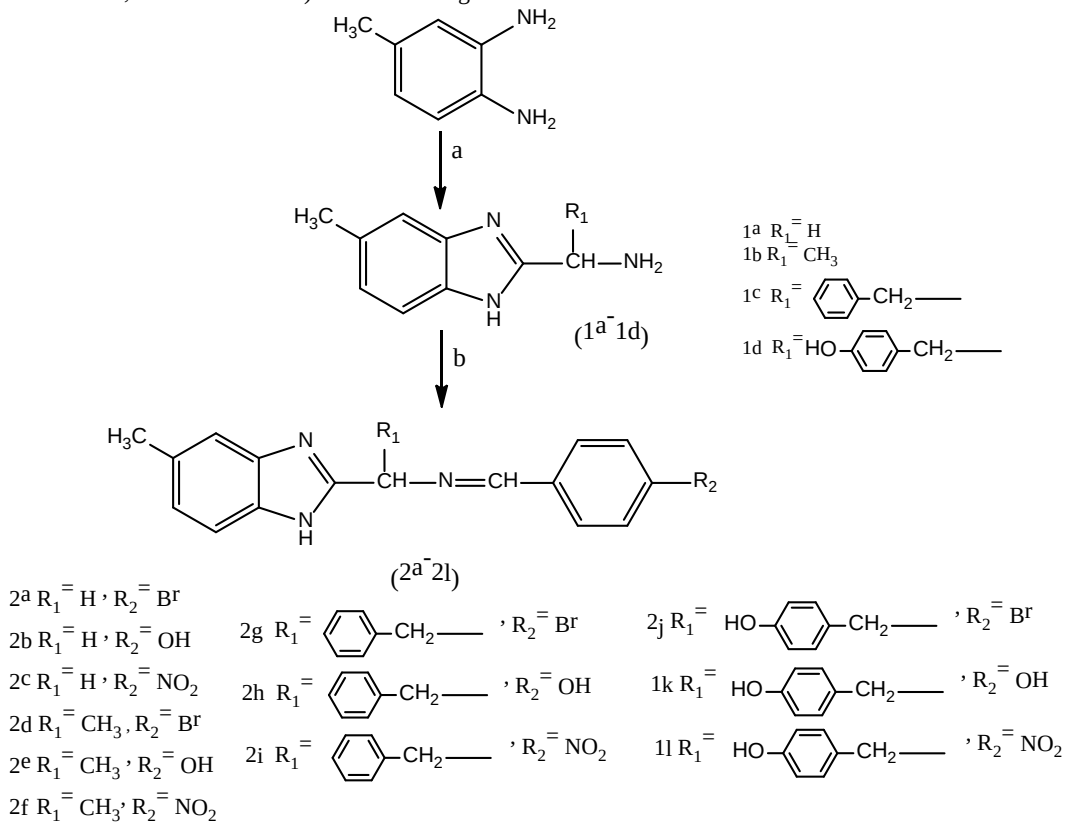
RESULT AND DISCUSSION

The target compounds (2a-2i) were synthesized by tow step procedure as depicted in scheme 1. The synthesis of title compounds started from cyclocondensation reaction of the 4-methyl-1,2- phenylene diamine with a various of amino acids (glycine, alanine, phenyl alanine and tyrosine)) in the presence 4N HCl. The IR spectra of these compounds exhibited broad absorption bands, one of which appearing at(3120-3288) was attributed to the N-H imidazole group. And other, observed at (3330-3385) was assigned to NH_2 stretching frequency. In^{1}H-NMR spectra of compounds 1(a,b) exhibited two different signals at(δ 8.48 and 8.54 ppm)which attributed to NH_2 protons and (δ 5.18 and 5.6 ppm)which assigned to N-H imidazole protons . The ^{13}C-NMR spectra of compounds 1(a,b) exhibited signals at(δ 142.5 and 146.9 ppm) which attributed to the(C=N) group. The Schiff bases compounds 2(a-l) were synthesized by the condensation reaction of compounds 1(a-d) with corresponding aromatic aldehyde in the presence of ethanol and few drops of acetic acid .the structure of all compounds 2(a-l) was confirmed by its IR spectra and compounds 2(b,d,e,h,i,l) by ^{1}H and ^{13}C-NMR, The IR spectra of these compounds exhibited broad absorption band at (3211-3365)cm^{-1} was attributed to the N-H imidazole group and band at(1608-1633) which assigned to imine group(N=CH).In ^{1}H-NMR spectra of compounds 2(b,d,e,h,i,l), the presence of proton of N=CH group was confirmed by one proton singlet at (8.39 -9.51)ppm, while signal for imidazole protons of NH group can be observed at (5.6-5.93),. The ^{13}C-NMR spectra

of compounds 2(b,d,e,h,i,l) exhibited signals at(δ 156.7–167.7 ppm) which attributed to the imine group (-N=CH-),and showed signal at about (δ138.3 – 149.7 ppm) related to benzimidazole (-C=N) group,.In ^{13}CNMR, DEPT-135 of compounds(2b,2h,2i and 2l)show negative signals at around (47.1 – 49.5) for CH_2 group

Antibacterial activity

The disk diffusion method was used to screened antibacterial activities of the some compounds synthesized herein(ref.). against different strains of Gram-positive bacteria namely (*Staphylococcous aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*) The compounds were tested at concentration of (10 mg /ml and 100 mg /ml). The zone of inhibition was measured in millimeters and was compared with reference standard antibiotic namely ampicillin and ciprofloxacin. The test compound were dissolved in DMSO to obtain solution of different concentration. The results show in (Table2) which demonstrates that most of compounds showed a significant activities when compared with the standard antibiotic ampicillin and ciprofloxacin.



Scheme 1: Synthetic route to the synthesized compounds. Reagents and conditions:(a) Corresponding amino acids, 4N HCl, reflux(9-12)hrs; (b) Corresponding aromatic aldehyde, EtOH/2-3 drops of CH_3COOH

Table 1: Physical properties of the compounds.

Comp no .	M.p (°C)	M . wt (g /mole)	M . Formula	Color	Yield %
1a	230-231	161.21	$C_9H_{11}N_3$	Yellow	66%
1b	250-251	175.24	$C_{10}H_{13}N_3$	Brown	87%
1c	261-262	251.33	$C_{16}H_{17}N_3$	Yellow	82%
1d	270-271	267.33	$C_{16}H_{17}N_3O$	Red	67%
2a	237-238	328.21	$C_{16}H_{14}BrN_3$	Yellow	80%
2b	245-246	265.32	$C_{16}H_{15}N_3O$	Yellow	83%
2c	258-259	294.31	$C_{16}H_{14}N_4O_2$	Yellow	81%
2d	273-274	342.24	$C_{17}H_{16}BrN_3$	Brown	69%
2e	285-286	279.34	$C_{17}H_{17}N_3O$	Brown	71%
2f	295-296	308.34	$C_{17}H_{16}N_4O_2$	Brown	76%
2g	280-281	418.34	$C_{23}H_{20}BrN_3$	Yellow	84%
2h	289-290	355.44	$C_{23}H_{21}N_3O$	Yellow	76%
2i	299-300	384.44	$C_{23}H_{20}N_4O_2$	Yellow	78%
2j	290-292	434.34	$C_{23}H_{20}BrN_3O$	Red	85%
2k	307-308	371.44	$C_{23}H_{21}N_3O_2$	Red	71%
2l	316-318	400.44	$C_{23}H_{20}N_4O_3$	Red	66%

Table 2: Antibacterial activity of synthesized compounds

Comp. No.	Concentration (mg / ml)	Zone of inhibition (in mm)			
		Gram-positive		Gram-negative	
		S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*
1b	10	15	17	22	18
	100	18	26	13	17
1d	10	12	15	-	-
	100	11	13	11	-
2a	10	12	20	19	17
	100	-	11	13	-
2d	10	14	27	19	21
	100	-	10	-	-
2h	10	12	18	20	19
	100	11	10	15	11
2j	10	15	-	12	-
	100	12	10	13	-
2k	10	14	16	14	17
	100	13	15	10	19
2i	10	17	19	22	18
	100	23	16	20	19
Ampicillin		22	23	-	10
ciprofloxacin		19	23	29	-
DMSO solvent		0	0	0	0

CONCLUSION:

New derivatives of benzimidazole containing Schiff base moiety were synthesized successfully by condensation reaction between compounds 1(a-d) which yielded from step one with a various of aromatic aldehydes. Some of these compounds shown good antibacterial activity.

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REFERENCES

1- Patil, A., Ganguly, S., and S.Surana "A Systematic Review of Benzimidazole Derivatives as an Antiulcer Agent".*Rasayan, J Chem.* 2008; 1(3):447-460.

2- Soni, B., "A Short Review on Potential Activities of Benzimidazole Derivatives". *PharmaTutor* 2014; 2(8):110-118.

3- Salahuddin, A., Shaharyar M., and A.Mazumder. "Benzimidazoles: A biologically active compounds". *Arabian Journal of Chemistry* 2017, 10(1):157-173.

4- Hasegawa, M., Nishigaki, N., Washio Y., Kano , K., Harris , P.A., Sato, H., Mori, I., West, R.I., Shibahara, M., Toyoda , H., Wang , L., Nolte, R.T., Veal J.M., and Cheung, M., "Discovery of Novel Benzimidazoles as Potent Inhibitors of TIE-2 and VEGFR-2 Tyrosine Kinase Receptors". *J Med Chem.* 2007, 50(18):4453-70.

5- Hamiduzzaman, M., Mannan, S.J., Dey A., and Abdur Rahman, S.M. , "Evaluation of analgesic, antipyretic, hypoglycemic and CNS depressant activity of 2-bromopopylamine hydrobromide, 3-bromo popyl ammonium bromide, ortho-amino aniline and benzimidazole-2-thiol in animal model". *Der Pharmacia Lettre* 2014; 6 (1):47-53.

6- Panwar, H., Dubey, R., Chaudhary N., and Ram T., "A green approach for the heterocyclization of 2-substituted benzimidazoles: Synthesis, characterisation and pharmacological evaluation" *Der Pharma Chemica* 2013; 5(6):192-200.

7- Rajasekhar, S., Maiti, B., Balamurali, M.M., and Chanda, K., "Synthesis and Medicinal Applications of Benzimidazoles: An Overview".*Current Organic Synthesis* 2017; 14(1):40-60.

8- Walia, R., Hedaitullah, Md., Naaz1 S.F., Iqbal K., and Lamba HS., "Benzimidazole Derivatives – an overview". *IJRPC* 2011; 1(3):565-574.

9- AL-Ebalsat, H.S.,"Synthesis and Biological Activities of Some Benzimidazoles Derivatives". *J. Appl. Sci. Environ. Manage* 2011; 15 (3) 451 - 454

10- Al-Ebaisat, H.S. ," Evaluation of Biological Activity of Some Benzimidazole Derivatives as Antifungal". *International Research Journal of Pure & Applied Chemistry* 2015; 8(1):19-25.

11- Nikalje A.P., and Ghodke M.,"One Pot Green Synthesis Of 2-Aryl/Heterylbenzimidazole As Anti Inflammatory Agents" *World Journal Of Pharmacy And Pharmaceutical Sciences* 2014; 3(2):1311-1322.

12- Kankeaw U., and Rawanna R.,"The Study of Antibacterial Activity of Benzimidazole Derivative Synthesized from Citronellal". *International Journal of Bioscience, Biochemistry and Bioinformatics* 2015; 5(5):280-287.

13- Yoon, Y.K., Ali, M.A., Ang C.Wei, Choon T.S., and Ismail, R.,"Synthesis and evaluation of antimycobacterial activity of new benzimidazole aminoesters" *European Journal of Medicinal Chemistry* 2015; 93(18):614-624.

14- Reddy, T.S., Kulhari, H., Reddy, V.G., Bansal, V., Kamal, A. and Shukla R.,"Design synthesis and biological evaluation of 1,3-diphenyl-1Hpyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents". *European Journal of Medicinal Chemistry* 2015; 101(58):790-805.

15- Sharma, A., Luxami V., and Paul K.,"Purine-benzimidazole hybrids: Synthesis, single crystal determination and in vitro evaluation of antitumor activities". *European Journal of Medicinal Chemistry* 2015; 93(17): 414-422.

16- Pan, T., He, X., Chen, B., Chen, H., Geng, G., Luo, H., Zhang H., and Bai, C.,"Development of benzimidazole derivatives to inhibit HIV-1 replication through protecting APOBEC3G protein". *European Journal of Medicinal Chemistry* 2015; 95(25):500-513.

17- Chen, R.H., Xiong, J.F. , Peng, P., MO, G.Z. , Tang, X.S. , Wang, Z.Y., and Wang, X.F. ," Synthesis of Benzimidazoles from Amino Acids with Solvent-free Melting Method". *Asian Journal of Chemistry* 2014; 26(3):926-932.

18- Alam , S.A.M. F., Ahmad, T., Nazmuzzaman , M., Rahman, S. Ray, S.K., Sharifuzzaman, M., Karim, M.R. , Alam, M.G., Ajam , M.M., Maitra , P., Mandol, D. Uddin M.E., and Ahammed, T.,"Synthesis of Benzimidazole Derivatives Containing Schiff Base Exhibiting Antimicrobial Activities". *nternational Journal of Research Studies in Biosciences (IJRSB)* 2017; 5(7):18-24.

19- Kumaravel G., and Raman, N.," A treatise on benzimidazole based Schiff base metal(II) complexes accentuating their biological efficacy:Spectroscopic evaluation of DNA interactions, DNA cleavage and antimicrobial screening". *Materials Science and Engineering* 2017; 70(1):184-194.

20- Vishwanathan B., and Gurupadayya, B.,"Synthesis and characterization of novel oxadiazole derivatives from benzimidazole". *Journal of the Korean chemical society* 2014; 58(5):450-455.

21- Noolvi, M., Agrawal, S. , Patel, H., Badiger, A., Gaba, M., and Zambre, A.,"Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1H-benzimidazole". *Arabian journal of chemistry* 2011; 7(2):219-226.