RESEARCH ARTICLE

Synthesis of Benzimidazole and Mannich Bases Derivatives from 4-Methyl ortho phenylenediamine and Evaluation of their Biological Activity

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ABSTRACT

Benzimidazole derivatives (A_1, A_2, A_3) were synthesized through the reaction of compound 4-methylorthophenylenediamine with both oxalic acid in the presence of ammonium chloride as a catalyst for the compound (A_1)., as well as with (CS_2) and KOH for the compound (A_2) as well as with chloroacetic acid in the presence of acetic anhydride to compound (A_3). The Manich bases of the compounds (A_4, A_5, A_6, A_7) were synthesized by mixing compounds (A_1, A_2) with formaldehyde and primary amines. While the Manich bases of (A_8, A_9) compounds were synthesized by mixing compound (A_3) with formaldehyde and primary amines. These reactions were carried out using the microwave irradiation method. The synthesized compounds were identified using infrared (IR) and TLC confirmed proton nuclear magnetic resonance spectroscopy (^{1}H-NMR), completing the reaction and purity of the compounds. Most of the tested compounds show significant anti-fungal and antibacterial activity.

Keywords: Benzimidazole, Biological Activity, Mannich Bases.

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INTRODUCTION

Benzimidazole is a heterocyclic aromatic compound. Its molecular formula is $C_7H_6N_2$, molecular weight is 118.14 g/mol and it is also known as: 1H-Benzimidazole, 1,3-benzodiazole, o-benzimidazole, 3-azaindole and benzoglyoxaline. Benzimidazoles have limited solubility in water; consequently, minor differences in solubility tend to affect absorption significantly. Benzimidazole's production and use as a chemical intermediate in the production of agricultural fungicides may result in its release to the environment through various waste streams. It is important pharmacophores and a privileged structure in medicinal chemistry. Benzimidazole is bicyclic, which consists of the fusion of benzene and imidazole. Now a days is a moiety of choice which possesses many pharmacological properties.[1-4] The most prominent benzimidazole compound in nature N-ribosyldimethyl-benzimidazole, which serves as an axial ligand for cobalt in vitamin B12.[5]

Benzimidazole derivatives play an important role in the medical field with so many Pharmacological activities such as analgesic, anti-inflammatory,[6] antibacterial,[7] anti-fungal,[8] antiviral,[9] antihelmenthic,[10] anticancer,[11] antihypertensive,[12] anti-diabetes,[1] anti-fertility,[1] antioxidant,[13] and treat ulcers,[14] treatment of malaria,[15] anti-HIV,[16] effective against tuberculosis,[17] anti-allergic,[18] anti-psychiatric,[19] anti-asthma,[20] antihistamine.[21] Manich reactions are the reaction of compounds containing acid hydrogen as in (ketones, acetylenes, phenols, and aliphatic nitro compounds) with formaldehyde and secondary (or primary) amines and sometimes ammonia by the reaction of Manich, and the result is from the amino-methyl derivatives called Manich bases.[22,23]

Experimental Materials and Physical Measurements

All the chemicals applied in our study are obtainable from Fluka. In addition, Sigma Aldrich. Electro-thermal capillary apparatus has specified the melting points. Com-pleating of the reaction was monitored by thin-layer chromatography (TLC) using Merck silica-coated plates and as mobile phase, a mixture of hexane and ethyl acetate. Infrared spectra were obtained using ATR technique Shimadzu 8400S, Fourier Transforms Infrared spectroscopy SHIMADZU in the range (400-4000) cm^{-1}. The 1H-NMR spectra were obtained on a VARIAN model ultra-shield 400MHz in the Chemistry Department, Faculty of Science, University of Jordan laboratories. We used tetramethylsilane (TMS) as internal reference and DMSO-d6 as solvent.

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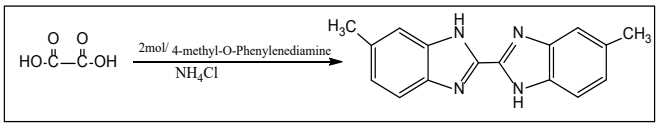
Synthesis of Benzimidazole Derivatives

1. Synthesis of compound (A_1)

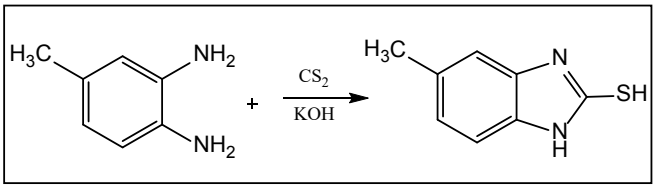
To a mixture of (0.004 mol) oxalic acid and (0.008mol) 4-methyl-o-phenylenediamine in (20mL) of ethanol, then adding (NH_4Cl) (0.004 mol) to the reaction mixture. The reaction mixture was refluxed in the microwave for 4–8 minutes (400 watt). The completion of the reaction was confirmed by TLC (ethyl acetate: hexane,1:2 v/v). After the reaction was completed, the reaction was cooled to room temperature, and then the sediment was filtered and collected, and it was dried and purified by recrystallization from ethanol to give the pure product. Color =white, M.P=286-287, Yield = 79 %, R_f = 0.22.



The equation for the synthesis of compound (A_1)

2. Synthesis of compound (A_2)

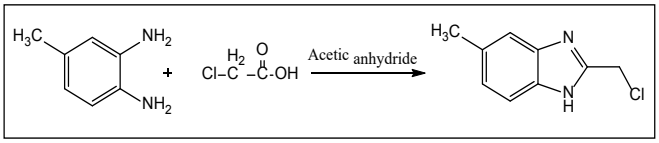
Dissolve (0.002 mol) KOH in methanol and after dissolving 4-methyl-o-phenylenediamine (0.002 mol) dry was added to it and then (CS_2) (0.12 mL) was added to the reaction mixture with continuous stirring for 10 minutes. The reaction mixture was refluxed in the microwave for 3–6 minutes (400watt). The completion of the reaction was confirmed by TLC (ethyl acetate: hexane,1:2 v/v). After the completion of the reaction, the reaction mixture was cooled and poured into the ice-cold water. The granular solid was obtained. It was crystallized from the ethanol. Color =white, M.P=277-279, Yield =90 %, R_f =0.24.



The equation for the synthesis of compound (A_2)

3. Synthesis of Compound (A_3)

Mixture of 4-methyl-o-phenylendiamine (0.004 mol), chloroacetic acid (0.004 mol) in (20 mL) of ethanol,after the dissolution is completed, add (2 mL) from acetic anhydride. The reaction mixture was stepped in the microwave for 5-10 minutes (400 watt). The completion of the reaction was confirmed by TLC (ethyl acetate: hexane,1:2 v/v). The reaction mixture was cooled at room temperature; crystals were obtained, filtered, washed with cold water twice, dried, and recrystallized using ethanol. Color = white, M.P = 210-213, Yield = 78 %, R_f = 0.25. Tables 1 and 2 shows physical properties.



Equation for the synthesis of compound (A_3)

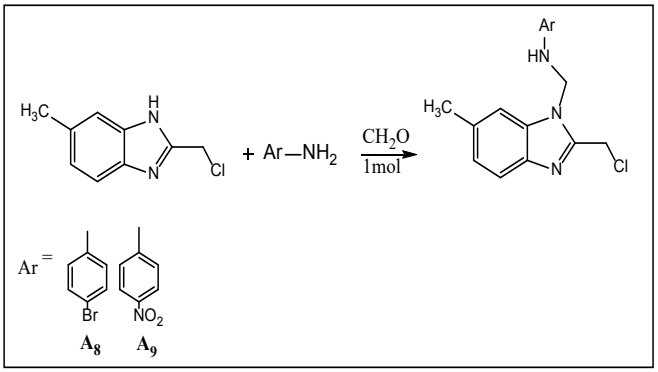
Synthesis of Mannich Bases Derivatives

1. Synthesis of Mannich Bases Compounds (A_4-A_7)

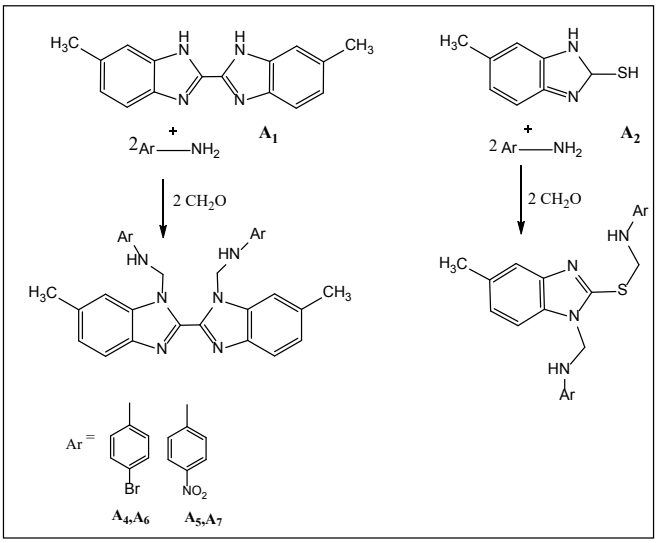
The mixture of benzimidazole derivatives (A_1, A_2) (0.4 g, 0.004 mol) and (5 mL, 0.008 mol) formaldehyde in (20 mL) of ethanol with continuous stirring for one hour. and then add a cold solution of primary amine (0.008 mol) and gradually drops. The reaction mixture was stepped in the microwave for (4–8) minutes (400 watt). After confirming the end of the TLC reaction, the resulting mixture was left at room temperature until the solvent evaporated from it; the sediment was filtered and dried and recrystallized by absolute ethanol.

2. Synthesis of Mannich Bases compounds (A_8, A_9)

Mixture of benzimidazole derivative (A_3) (0.5 g, 0.004 mol) and (5 mL, 0.004 mol) formaldehyde in (20 mL) of ethanol with continuous stirring for one hour and then add a cold solution of primary amine (0.004 mol) and gradually drops. The reaction mixture was stepped in the microwave for (4–8) minutes (400 watt). After confirming the end of the reaction using the TLC, the resulting mixture stayed at room temperature until the solvent evaporated from it; the sediment was filtered, dried, and recrystallized by absolute ethanol.



Equation for the synthesis of Mannich bases compounds (A_8, A_9)



Scheme 1: Synthesis of Mannich bases compounds (A_4-A_7)

RESULTS AND DISCUSSION

The IR of compound 5,6'-dimethyl-1H, 1'H-2,2'-bibenzo[d] imidazole (A_1) was showed starching bands of N-H benzimidazole at (3334). In addition, C-H aromatic at (3016), aliphatic C-H (2977, 2906). And C=N (1635), C=C aromatic (1585, 1510), and C-N(1299). The ^{1}H-NMR of compound (A_1) (400MHz, DMSO- d^6) was showed signals; δ:2.47ppm (3H,s, CH_3) assign to the Protons group (CH_3) of substituted to a benzene ring. In addition, δ2.51 assign to solvent (DMSO-d^6), δ3.38 assign to Protons (H_2O), δ6.80-7.91(6H,m, Ar-H) assign to Protons of benzene rings,12.49 (1H, s, NH) benzimidazole. The spectra are shown in Figure 1 for IR for compound (A_1).[24,25]

The IR (KBr/cm^{-1}) of compound 5-methyl-1H-benzo[d] imidazole-2-thiol (A_2): N-H benzimidazole (3263), C-H aromatic (3028), C-H aliphatic (2921, 2854), C=N (1654), C=C aromatic (1519, 1546), C-N(1296), C-S(1369). ^{1}H-NMR (400MHz, DMSO-d^6) δ2.02 (3H,s,CH_3) assign to Protons group(CH_3) connected to the benzene ring, δ2.51 assign to solvent (DMSO-d^6), δ3.38 assign to Protons (H_2O), δ6.85-8.38 (3H,m, Ar-H) assign to the Protons of the benzene ring, δ12.02 (1H,s,SH), δ12.62 (1H,s,NH) benzimidazole. The spectra are shown in Figure 2 for IR of compound (A_2).[24,25]

2-(chloromethyl)-5-methyl-1H-benzo[d]imidazole compound (A_3): IR νmax (KBr/cm-1): N-H benzimidazole (3282), C-H aromatic (3047), C-H aliphatic (2968, 2867), C=N (1666), C=C aromatic (1581, 1517), C-N(1242), C-Cl(572). ^{1}H-NMR(A_1) (400MHz, DMSO-d^6) δ2.39 (3H,s,CH_3) assign to Protons group(CH_3) connected to the benzene ring,δ2.51 assign to solvent (DMSO-d^6), δ3.30 assign to Protons (H_2O), δ4.67 (2H,s,CH_2) assign to Protons group(CH_2) connected to the imidazole ring, δ6.61-8.08 (3H,m,Ar-H) assign to the Protons of the benzene ring, δ 12.71 (1H,s,NH) benzimidazole. The spectra are shown in Figure 3 for IR of compound (A_3).[24,25]

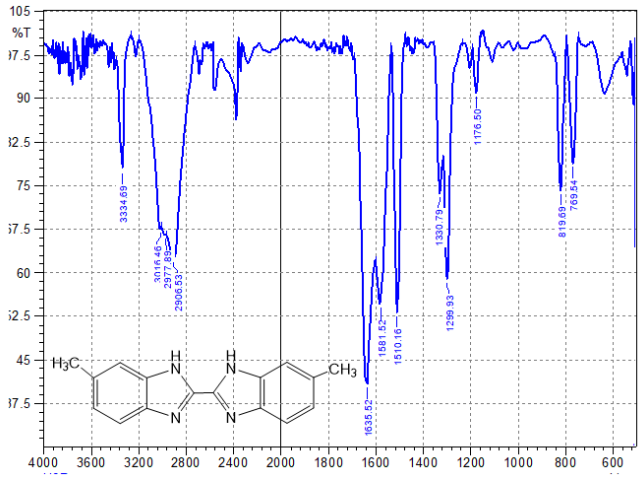


Figure 1: FT-IR Spectrum for compound (A_1)

Table 1: Some physical properties of the synthesized compounds (A_4-A_7)

Comp. No.	*Ar*	*Color*	*M.P. (°C)*	*Yield (%)*	R_f
A_4	Ph-Br	Yellow	158-161	74	0.23
A_5	Ph-NO_2	Yellow	171-173	77	0.41
A_6	Ph-Br	White	228-231	85	0.31
A_7	Ph-NO_2	Yellow	182-185	81	0.51

Table 2: Some physical properties of the synthesized compounds (A_8, A_9)

Comp. No.	*Ar*	*Color*	*M. P. (°C)*	*Yield (%)*	R_f
A_8	Ph-Br	Yellow	125-128	74	0.32
A_9	Ph-NO_2	Yellow	202-205	77	0.61

Synthesized Mannich Bases Derivatives for Compounds (A_4–A_7)

The IR spectrum of compounds (A_4–A_7) showed the absence of a *ν*(NH) for benzimidazole band and that presence of a band at (3234–3369 cm^{-1}) assign to *ν*(N-H) for amine groups in the Mannich Bases., also showed band within (1602–1645 cm^{-1}) assign to *ν*(C=N), also showed bands within (3047–3097 cm^{-1}) assign to *ν*(C-H) aromatic, also showed two bands (2921–2947 cm^{-1}) and (2846–2875cm^{-1}) assign to *ν*(C-H) aliphatic, also showed two bands (1529–1593 cm^{-1}) and (1469–1540 cm^{-1}) assign to *ν*(C=C) aromatic. also showed of other bands within (1230–1331 cm^{-1}) assign to *ν*(C-N), the rest of the bands maintained their normal ranges, as shown in (Table 3), which shows the results of infrared absorption of synthesis

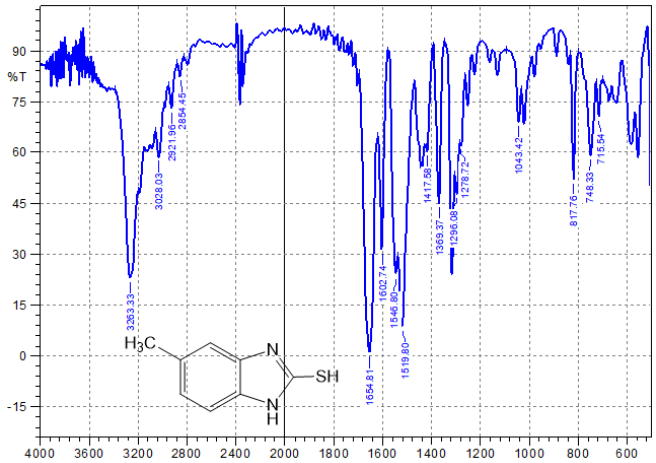


Figure 2: FT-IR Spectrum for compound (A_2)

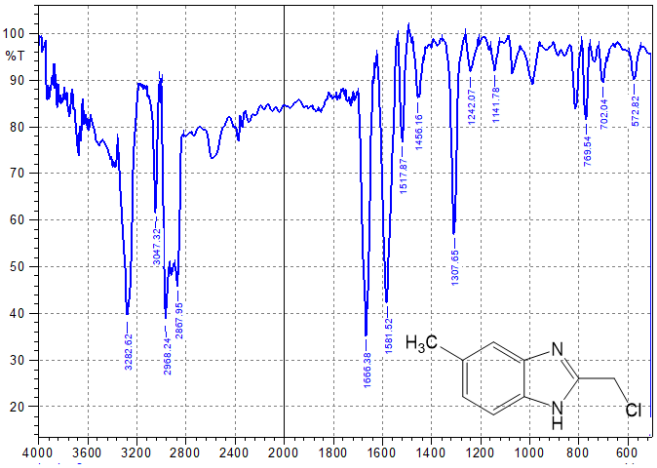


Figure 3: FT-IR Spectrum for compound (A_3)

compounds (A_4-A_7). ^{1}H-NMR (A_4) (400MHz, DMSO-d^6) δ2.51 assign to solvent (DMSO-d^6), δ2.84 (6H, s, CH_3) assign to Protons two groups (CH_3) related to benzene rings. In addition, δ3.38 assign to Protons (H_2O), δ5.29 (4H,s,CH_2) assign to Protons group (CH_2) connected to the groups (2NH), δ6.61-8.58 (14H,m,Ar-H) assign to the Protons of benzene rings, δ9.60 (1H,s,NH) assign to Protons two groups (NH) connected to the benzene rings. The spectra are shown in Figure 4 for IR of compound (A_4).[24,25]

Synthesized Mannich Bases Derivatives for Compounds (A_8, A_9)

The IR spectrum of compounds (A_8, A_9) showed the absence of a *v*(NH) for benzimidazole band and that presence of a band at (3345–3369 cm^{-1}) assign to *v*(N-H) for amine groups in the Mannich Bases., also showed band within (1602–1645 cm^{-1}) assign to *v*(C=N), also showed bands within (3014–3097 cm^{-1}) assign to *v*(C-H) aromatic, also showed two bands (2921–2939 cm^{-1}) and (2852–2856 cm^{-1}) assign to *v*(C-H) aliphatic, also showed two bands (1520–1590 cm^{-1}) and (1471–1502 cm^{-1}) assign to *v*(C=C) aromatic. It also showed other bands within (1267–1323 cm^{-1}) assign to *v*(C-N). The rest of the bands maintained their normal ranges, as shown in (Table 4), which shows the results of infrared absorption of synthesis compounds (A_8, A_9). ^{1}H-NMR (A_8) (400MHz, DMSO-d^6) δ2.42 (3H,s,CH_3) assign to the Protons group (CH_3) related to the benzene ring. In addition, δ2.51 assign to solvent (DMSO-d^6), δ3.30 assign to Protons (H_2O), and δ4.67 (2H,s,CH_2) assign to Protons group (CH_2) associated with (Cl), δ5.53 (2H,s,CH_2) assign to Protons group (CH_2) associated with (NH), δ6.61-8.04 (7H, m, Ar-H) assign to the Protons of benzene rings, and δ8.08 (^{1}H, s, NH) assign to Protons group (NH) related to the benzene ring. The spectra are shown in Figure 5 for IR of compound (A_8).[24,25]

Evaluation of the Biological Effectiveness of Some Synthesis Compounds

The effect of the synthesis compounds was studied on the type of fungus (*Candida*) and type of bacterial isolates of *Bacillus Puimilus*. The fungus standard fungicide (Nystatin) was used, and the standard antibiotic (Neomycin sulfate) of bacteria. The results indicate that the synthesized compounds can inhibit the fungus and bacteria used by using different concentrations of the concentrated compounds (5 mg/mL), (7.5 mg/mL),

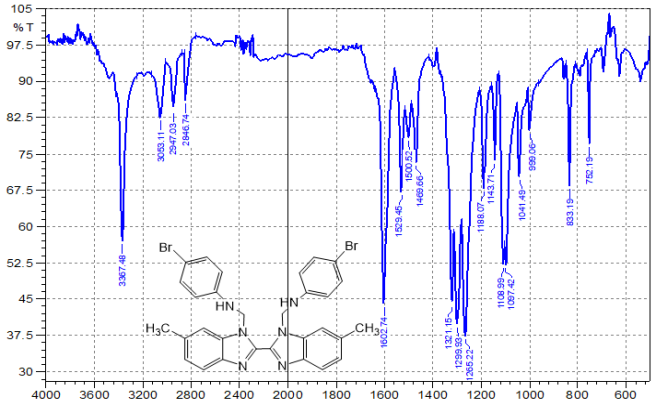


Figure 4: FT-IR Spectrum for compound (A_4)

Table 3: FT-IR spectral data for compounds (A_4-A_7)

	IR (KBr) cm^{-1}						
Comp No.	*v(N-H) Amine*	*v(C-H) Arom.*	*v(C-H) Aliph.*	*v(C=N)*	*v(C=C) Arom.*	*v(C-N)*	*Others*
A_4	3367	3053	2947 2846	1602	1529 1469	1265	ν(C-Br) 752
A_5	3369	3097	2921 2852	1645	1593 1502	1323	ν (NO_2). *asy*.(1455) *sym*.(1362)
A_6	3292	3047	2943 2875	1635	1565 1540	1331	ν(C-Br) 682
A_7	3234	3068	2925 2854	1627	1581 1512	1230	ν (NO_2). *asy*.(1455) *sym*.(1362)

Table 4: FT-IR spectral data for compounds (A_8,A_9)

	IR (KBr) cm^{-1}						
Comp No.	*v(N-H) Amine*	*v(C-H) Arom.*	*v(C-H) Aliph.*	*v(C=N)*	*v(C=C) Arom.*	*v(C-N)*	*Others*
A_8	3369	3014	2939 2856	1602	1520 1471	1267	ν(C-Br) 694 ν(C-Cl) 754
A_9	3345	3097	2921 2852	1645	1590 1502	1323	ν(C-Cl) 644 ν (NO_2). *asy*.(1455) *sym*.(1362)

Table 5: Antifungal activity of synthesized compounds (A_1–A_9)

Comp. No.	*Standard 10 mg/mL*	*5 mg/mL*	*7.5 mg/mL*	*10 mg/mL*
A_1	20.8	16.1	16.1	15.1
A_2	20.8	15.3	17.5	15.7
A_3	20	13.7	13.2	14.8
A_4	20	17.1	13.6	15.1
A_5	20.7	15.6	14.6	15.8
A_6	20.7	17.7	14.3	15.6
A_7	20.3	17	13.3	15.5
A_8	20.1	16.2	15.8	16.5
A_9	20.4	14.5	14.9	15.2

Table 6: Antibacterial activity of synthesized compounds (A_1–A_9)

Comp. No.	*Standard 10 mg/mL*	*5 mg/mL*	*7.5 mg/mL*	*10 mg/mL*
A_1	14.2	11.2	12.5	12.1
A_2	14.2	13.5	13.5	13.3
A_3	14.4	14.2	12.9	14.6
A_4	14.4	13.6	13.8	13.4
A_5	13.5	12.1	13.3	10.7
A_6	13.5	12.8	13.8	11.3
A_7	14.2	12.9	13.5	13.7
A_8	14.2	13.1	12.8	13
A_9	13.6	12.7	12.6	12.5

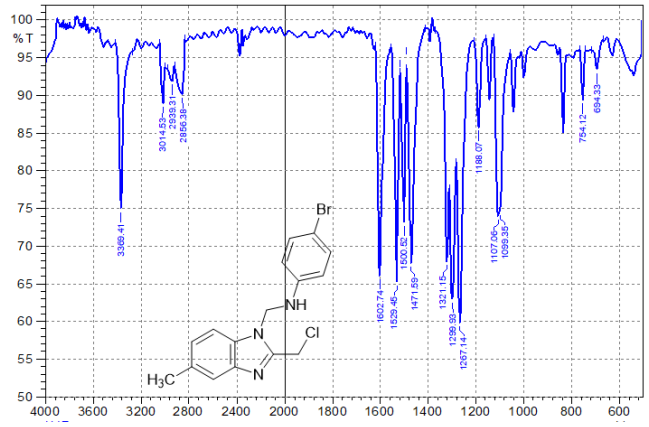
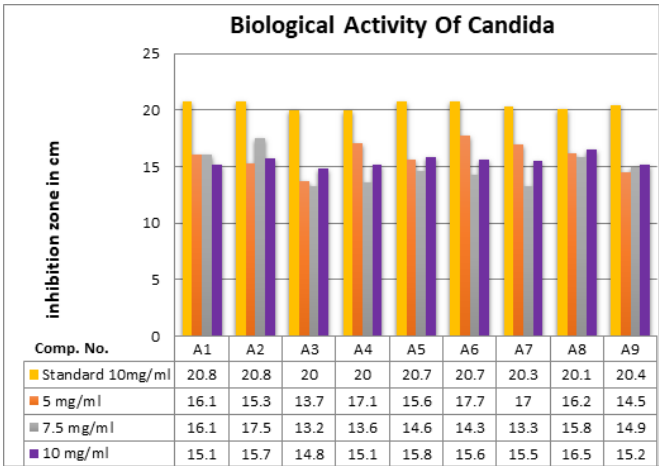


Figure 5: FT-IR Spectrum for compound (A_8)



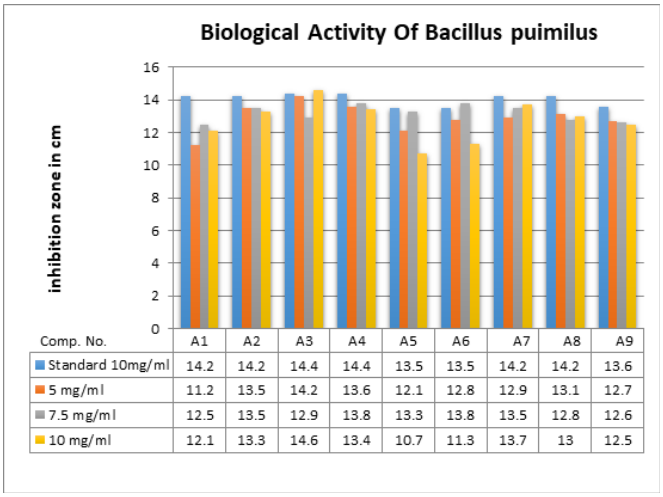
Comp. No.	A1	A2	A3	A4	A5	A6	A7	A8	A9
Standard 10mg/ml	20.8	20.8	20	20	20.7	20.7	20.3	20.1	20.4
5 mg/ml	16.1	15.3	13.7	17.1	15.6	17.7	17	16.2	14.5
7.5 mg/ml	16.1	17.5	13.2	13.6	14.6	14.3	13.3	15.8	14.9
10 mg/ml	15.1	15.7	14.8	15.1	15.8	15.6	15.5	16.5	15.2

Scheme 2: Inhibitory activity of synthesized compounds **(A_1–A_9)** anti-Candida fungus

(10 mg/mL) compared with the inhibition with the standard antibodies with concentration (10 mg/mL), synthesized compounds showed good inhibitory activity against bacteria and weak to medium inhibitory activity against fungi.

Candida albicans Fungus

All synthesized compounds (A_1–A_9) showed weak to medium activity at synthesized concentrations (5 mg/mL), (7.5 mg/mL), (10 mg/mL) as in Table 5.



Comp. No.	A1	A2	A3	A4	A5	A6	A7	A8	A9
Standard 10mg/ml	14.2	14.2	14.4	14.4	13.5	13.5	14.2	14.2	13.6
5 mg/ml	11.2	13.5	14.2	13.6	12.1	12.8	12.9	13.1	12.7
7.5 mg/ml	12.5	13.5	12.9	13.8	13.3	13.8	13.5	12.8	12.6
10 mg/ml	12.1	13.3	14.6	13.4	10.7	11.3	13.7	13	12.5

Scheme 3: Inhibitory activity of synthesized compounds (A_1–A_9) anti Bacillus Pumilus

Bacillus Puimilus

In these bacteria (Bacillus Puimilus), all compounds synthesized (A_1-A_9) showed good inhibitory activity at the concentrations (5 mg/mL), (7.5 mg/mL), and (10 mg/mL) as shown in Table 6.

CONCLUSION

In this research, new compounds containing benzimidazole ring and Mannich bases were synthesized, characterized, and study the biological activity of synthesized compounds, and the following can be concluded:

A good product ratio of synthesized compounds (A_1–A_9) was obtained, and the products were obtained directly using the microwave method and single-step, the tested compounds (A_1–A_9) showed good inhibitory activity anti-bacteria and weak to medium inhibitory activity anti-fungus.

REFERENCES

1. Srestha N, Banerjee J, Srivastava S. A review on chemistry and biological significance of benzimidaole nucleus. IOSR J Pharm. 2014;04(12):28-41.
2. Walia R, Hedaitullah M, Farha Naaz S, Iqbal K, Lamba H. International Journal of Research in Pharmacy and Chemistry Benzimidazole Derivatives–an Overview. Ijrpc. 2011;1(3):565-574.

3. Naga Prashant K, Ravi Kumar K. Green synthesis of benzimidazole derivatives: An overview of bulk drug synthesis. Int J PharmTech Res. 2015;8(9):60-68.
4. Townsend LB, Wise DS. The Synthesis and chemistry of certain anthelmintic benzimidazoles. Parasitol Today. 1990;6(4):107- 112.
5. Info A. Indo American Journal of Pharmaceutical Research, Indo Am J Pharm Res. 2015;5(02):1-6.
6. Shahare MB, Kadam VJ, Jagdale DM, Gandhi PS, Gaikwad PL. Synthesis and evaluation of novel anthelmentic benzimidazole derivatives. Int J Res Pharm Chem. 2012;2(1):132-136.
7. Barker Ha, Smyth Rd, Weissbach H, Toohey Ji, Ladd Jn, Volcani Be. Isolation and properties of crystalline cobamide coenzymes containing benzimidazole or 5, 6-dimethylbenzimidazole. J Biol Chem. 1960;235(2):480-488.
8. Shukla A. Synthesis and biological screening of benzimidazole derivatives. Int J Pharm Sci Res. 2012;3:922-927.
9. Alrazzak NAB, Saad ST, Aljamali NM. Synthesis, characterization and thermal analysis for new amoxil ligands. Asian Journal of Chemistry. 2019;31(5):1026.
10. Patil A, Ganguly S, Surana S. A systematic review of benzimidazole derivatives as an antiulcer agent. Rasayan J Chem. 2008;1(3):447-460.
11. Sugumaran M, Kumar MY. Synthesis and Biological Activity of Novel 2, 5-Disubstituted Benzimidazole Derivatives. Int J Pharm Sci Drug Res. 2012;4(1):80-83.
12. Schuck DC, Jordão AK, Nakabashi M, Cunha AC, Ferreira VF, Garcia CRS. Synthetic indole and melatonin derivatives exhibit antimalarial activity on the cell cycle of the human malaria parasite Plasmodium falciparum. Eur J Med Chem. 2014;78:375-382. doi.org/10.1016/j.ejmech.2014.03.055.
13. Ghafil, RAA, Alrazzak, NA, Aljamali, NM "Synthesis of triazole derivatives via multi components reaction and studying of (organic characterization, chromatographic behavior, chem-physical properties)" (2020) Egyptian Journal of Chemistry, 63 (11): 4163-4174
14. Shah K, Chhabra S, Shrivastava SK, Mishra P. Benzimidazole: A promising pharmacophore. Med Chem Res. 2013;22(11):5077-5104.
15. Sachin Parmar, Amit Gangwal NSD. Scholars Research Library. 2011;2(4):373-383.
16. Raj M, Padhi SK. Synthesis, Characterization, and Structure of Quinoline-based Benzimidazole Derivatives. J Heterocycl Chem. 2019;56(3):988-997. doi.org/10.1002/jhet.3481.
17. Jorani KRA-, Jabar A, Atia K, Lafta SJ, Al-bayti RI, Abdullah S. Antibacterial Activity of New Benzimidazole Moiety Synthesis via a Acid chloride and Related Heterocyclic Chalcones. J Pharm Sci Res. 2019;11(4):1195-1203.
18. Sravanthi A, Chetan S H , Subrahmanyam EVS , Shabaraya A R , Vinayak K. Synthesis of 1, 2 Disubstituted Benzimidazoles Using Sodium Acetate As Catalyst. Int Res J Pharm. 2019;10(3):181-184. DOI: 10.7897/2230-8407.1003101.
19. Tahlan S, Kumar S, Ramasamy K, Lim SM, Shah SAA, Mani V, et al. Design, Synthesis and biological profile of heterocyclic benzimidazole analogues as prospective antimicrobial and antiproliferative agents. BMC Chem. 2019;13(1):1-15. DOI: 10.1186/s13065-019-0567-x.
20. Kaur S, Kaur M, Kaur J, Bansal Y, Bansal G. Synthesis, Antimicrobial Evaluation and Chemical Stability Studies of Novel Trisubstitued Benzimidazoles. 2019;10(1):788-799.
21. Methodologies C. Green Synthesis of Benzimidazole Derivatives: an Overview on Green Chemistry and Its Applications. Chem Methodol. 2019;3:684-695.
22. Eberson L, Schäfer H. Organic electrochemistry. In: Organic Electrochemistry. Springer; 1971. p. 1-182.
23. Douh MH Al, Fatlawy AA Al, Abid Oh. Synthesis And Characterization Of 2-(N-Benzoyl N-Pyrid-3-Yl Aminobenzyl)-Aminobarbituric Acids Via N-Benzylidene Pyridine-3-Amines. October 2003.
24. Silverstein RM.; Webster FX.; Kiemle DJ.; Bryce DL. Spectrometric identification of organic compounds. John wiley & sons; 2014. Sep29.
25. Sabu Thomas, Raju Thomas, Ajesh Zachariah, Raghvendra Mishra. Nuclear Magnetic Resonance Spectroscopy. Publisher: Elsevier. June 2017.