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Synthesis and Antimicrobial Evaluation of Some Mannich Base Derivatives Bearing of 1,2-Substituted Benzimidazole Moiety

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ABSTRACT
The major objective of the present study is making derivatives of Mannich bases carrying a 1,2-substituted benzimidazole moiety, which are anticipated as being effective as antimicrobial agents with promising features for drug development. The research framework in the present study includes two approaches used in this research method design. First, the synthesis of a series of 2-(substituted phenyl) benzimidazoles (a1-3) by a reaction of benzaldehydes p-substituted with an o-phenylene diamine (OPDA), then it was utilized to synthesize Mannich bases (b1-3) in the presence of benzaldehyde and dimethylamine (DMA). Second, 2-(N-[Bis(dimethylamino)methylene]) benzimidazole (d) was prepared by reaction of N, N-Dimethylglycine (DMG) (c) with an o-phenylene diamine (OPDA), which was then utilized to synthesize Mannich bases (e1-3) in the presence of benzaldehydes p-substituted and dimethylamine (DMA). The newly created compounds' structures were verified by m.p., TLC, R_f values, FT-IR structural analysis, and ^{1}H-NMR spectral data. Using the cup-plate method and gram-positive (*S. aureus*) and gram-negative (*E. coli*) bacteria, the produced Mannich bases were tested for their in vitro antibacterial activity. Compounds e1, e2, e3, and b2 were shown to be the most effective against all tested bacteria among the produced compounds at a concentration of (100 µg/mL). Among these compounds having hydroxy group (e3) showed maximum activity followed by benzaldehyde, and p-bromo benzaldehyde. These outcomes suggest that interesting compounds are obtained compared to the current therapeutic drugs. This may be considered promising exploratory research if considered to investigate further in the future.

Keywords: Benzimidazoles, Mannich bases, Antimicrobial.

1. Introduction
Due to their extensive range of biological and pharmacological applications, benzimidazole and imidazole systems are of tremendous significance in medicinal chemistry [1-5]. These heterocyclic moieties are often called 'privileged' because of their wide recurrence in bioactive compounds that featured a large number of common biological activities, such as antifungal, antibacterial, and anthelmintic [6-10]. The ring framework where a benzene ring is intertwined to the 4,5-positions of the imidazole ring is assigned as benzimidazole [11, 12]. There are two main well-established synthetic methods for 2- (substituted phenyl) benzimidazoles in the literature. First is the method of condensation of an o-phenylene diamine with a series of carboxylic acids in the presence of different catalytic materials [13, 14]. Second is the method of condensation of an o-phenylene diamine with a series of substituted aliphatic or aromatic aldehydes in the presence of different catalytic materials [15, 16]. In this paper, we describe the synthesis of various novel Mannich bases obtained from 2-substituted benzimidazole and their in vitro antimicrobial testing. Melting Points (m.p.), Thin Layer Chromatography (TLC), Fourier-Transform Infrared Spectroscopy (FT-IR), and Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectral data were used to confirm the structural analysis of the compounds. Drugs with a substituted amino group at the 1 position of benzimidazoles, or bioactive heterocyclic core[17, 18], possess exclusive

antimalarial[19, 20], and analgesic activities have been reported[21-23] . Imidazole has been FDA (U.S. Food and Drug Administration) - approved as a key structural component of a number of drugs, including angiotensin II receptor antagonists[24], oral anti-inflammatory agents[25], protein kinase inhibitors[26], potent anticancer agents[27], and fungicides[28]. Our interest lies in Mannich bases for drug design, which in recent years played an important role in the development of synthetic pharmaceutical chemistry [29-32]. Various applications have been reported for Mannich bases, including antibacterial[33], anticancer [34], antimycobacterial [35], anti-malarial [36], antiparkinsonian to anticonvulsant[37, 38], analgesic[39] , antispasmodic[40], remarkable anti-HIV[41], antitubercular [42, 43] , and intermediates in drug synthesis [44, 45]. From this perspective, we hypothesized that a general and practical method that is successful in producing new Mannich base derivatives from 2-substituted benzimidazoles could produce substances with strong antimicrobial properties when using gram-positive bacteria (*S. aureus*) and gram-negative bacteria (*E. coli*) in accordance with the cup-plate method.

2. Experimental

In one-end open capillary tubes, the melting points of all the recently synthesized chemical structures were verified. On a Shimadzu 8400 spectrometer, FT-IR spectra were captured using the KBr pellet method. On a Bruker Ultra Shield (300 MHZ FT NMR) spectrometer, ^{1}H-NMR spectra were obtained using chemical shifts expressed in parts per million and TMS (Tetramethyl Silane) as an internal reference (ppm). TLC (Thin Layer Chromatography) was used on silica gel plates to determine the purity of the chemicals. Following the experiment, the spots were seen by being exposed to iodine vapors. Table 1 contains a list of the produced compounds' physical characteristics.

Table1: The produced compounds' physicochemical data.

Comp.	R (sub.)	M.F.	M.W.	M.P. (^{0}C)	Rf value	% Yield
a1	H	$C_{13}H_{10}N_2$	194	288-290	0.25	95
a2	Br	$C_{13}H_9N_2Br$	273	224-226	0.23	92
a3	OH	$C_{13}H_{10}N_2O$	210	166-168	0.28	90
b1	H	$C_{22}H_{21}N_3$	327	185-186	0.29	80
b2	Br	$C_{22}H_{20}N_3Br$	406	196-198	0.16	70
b3	OH	$C_{22}H_{21}N_3O$	343	203-204	0.24	68
c	-	$C_4H_9O_2N$	103	158-160	0.25	90
d	-	$C_{10}H_{13}N_3$	175	269-270	0.28	82
e1	H	$C_{19}H_{24}N_4$	308	220-222	0.22	87
e2	Br	$C_{19}H_{23}N_4Br$	387	300 d	0.29	75
e3	OH	$C_{19}H_{24}N_4O$	324	271-273	0.38	70

Eluants for TLC were value n- Hexane: ethyl acetate (7: 3).
Abbreviations: Comp. compounds; R. various substitutions used; M.F. molecular formula; m.p. melting point; R_f. retardation factor; d. decomposition.

2.1. Benzimidazole derivatives' synthesis

2.1.1. General method of 2-(substituted phenyl) benzimidazole synthesis (a1-3)

In a beaker, methanol (50 mL) and substituted benzoaldehyde (4.982 g, 0.048 moles) were combined. The mixture was continuously stirred as 10 mL of a saturated sodium metabisulfite solution was added in portions. More methanol was thereafter progressively added while the mixture was aggressively stirred. The finished combination was refrigerated for the night. The resultant precipitate was adequately filtered and dried, and the ultimate product yield was 95%. DMF (40 mL) was used to dissolve o-phenylene diamine (4.2g, 0.039 moles), and substituted benzaldehyde (8.0g, 0.039 moles) was then added. The mixture was heated for 4 hrs while in reflux. After cooling, the reaction mixture was placed into distilled water that was already cold. Filtered, dried, and then recrystallized from absolute ethanol was the precipitate that resulted.

2.1.2. Synthesis of 2- (2-N, N- dimethyl amino methyl) benzimidazole (d)

A mixture of o-phenylenediamine (8.6 gm, 0.092 moles) and (N, N – dimethylglycine) (DMG) (C) (0.1 moles) were dissolved in 20 mL absolute ethanol and mixture were refluxed for 6 hrs. The solvent was reduced and cooled to room temperature, then acidified with 10% HCl solution to yield the final product. The resultant precipitate was filtered, dried, and recrystallized from absolute ethanol.

2.1.2.1. Synthesis of 2 - (dimethyl amino) acetic glycine (DMG) (c)

A mixture of potassium hydroxide (0.728 gm, 0.013 moles) and dimethylamine (0.013 moles) was dissolved in (25 mL) absolute ethanol. Then chloroacetic acid (1.22 gm, 0.013 moles) was added and refluxed for 6 hrs. The solvent was removed and the formed solid was recrystallized from absolute ethanol.

2.2. Mannich base synthesis

2.2.1. General method for synthesis of 1- (N, N-dimethyl amino benzyl) -2-(substituted phenyl) benzimidazole (b 1-3)

The N-Mannich bases of 2- (substituted phenyl) benzimidazole were made using the following typical methods. Benzaldehyde (0.006 moles) and a secondary amine (0.006 moles) were added with stirring for 5 hrs to a solution of 2-(substituted phenyl) benzimidazoles (0.006 moles) in (10 mL) ethanol. The reaction mixture was then allowed to reflux for 3 hrs. In order to recrystallize from DMF after cooling, the product was filtered, dried, and recrystallized from DMF.

2.2.2. General procedure for synthesis of 1- (N, N – dimethyl amino substituted benzyl) - 2- (2-N, N-dimethyl aminomethyl) benzimidazole (e1-3)

The preparation steps were similar to the Mannich bases preparation method (b1-3).

2.3. Studies on antimicrobials

Staphylococcus aureus and *Escherichia coli* were used as test subjects for the freshly synthesized Mannich bases' antibacterial properties. As a reference standard for antibacterial activity, *ketoconazole* (10 µ/mL) and *amikacin* (10 µg/mL) were utilized, respectively. A concentration of 100 µg/mL was achieved by dissolving the synthesized substances and standards in DMSO. Test and standard chemical dilutions were made in nutrient broth for microorganisms. For 24 hrs, the samples were cultured for microorganisms at 37 °C. Following the incubation period, a millimeter vernier caliper was used to measure the diameter of the growth inhibition zones.

3. Results and Discussion

3.1. Chemistry

The procedure outlined in prior literature was used to create the Mannich bases of 2-substituted benzimidazole derivatives. A yield of 68–95% was obtained from the preparations (Table 1). In a short reaction period, a series of 2-substituted benzimidazole derivatives (a1-3) were produced in good to outstanding yields via condensation of o-phenylene diamine (OPDA) with benzaldehyde or substituted benzaldehydes such as p-bromobenzaldehyde and p-hydroxybenzaldehyde. By mixing a solution of 2-substituted benzimidazole derivatives (0.006 mol) in 10 mL ethanol with 0.006 mol of a secondary amine and 0.006 mol of benzaldehyde, and then refluxing the mixture for 5 hrs, the desired Mannich bases compounds (b1-3) were produced. TLC provided evidence that the reaction had ended. Using the open capillary tube method, the melting points (m.p.) of the produced compounds were determined. The majority of the synthetic compounds produced good FT-IR and ^{1}H-NMR spectra that were in agreement with the given structures. Schemes 1 and 2 describe the steps involved in synthesizing specific Mannich bases and benzimidazole derivatives. Table 1 lists the compounds' physicochemical characteristics. Using gram-positive bacteria (*S. aureus*) and gram-negative bacteria (*E. coli*), the produced Mannich bases were tested for their in vitro antibacterial activity using the cup-plate method.

3.2. Spectral and physical information on produced substances

3.2.1. 2-Phenylbenzimidazole (a1)

$C_{13}H_{10}N_2$, 95% yield, m.p. (288-290) °C, m.w.194, R_f value 0.25, IR (KBr, υ cm $^{-1}$), 3276 (N-H str.), 3145 (Ar-H str.),1600 (C=N str.), 1460 (C-N str.).

3.2.2. 2-(4-bromophenyl) benzimidazole (a2)

$C_{13}H_9N_2Br$, 92% yield, m.p. (224-226) °C, m.w. 273, R_f value 0.23, IR (KBr, υ cm^{-1}), 3270(N-H str.), 3015(Ar-H str.), 1630(C=N str.), 1462 (C-N str.), ^{1}H NMR (400 MHz, DMSO−d6, d ppm), 6.6-7.8(8H, m,Ar- H), 9.5(1H,s,NH).

3.2.3. 2-(4-hydroxyphenyl) benzimidazole (a3)

$C_{13}H_{10}N_2O$, 90% yield, m.p. (166-168) °C, m.w. 210, R_f value 0.28, IR (KBr, υ cm^{-1}), 3460(O-H str.), 3278(N-H str.), 3050(Ar-H str.), 1650 (C=N str.), 1465(C-N str.).

3.2.4. N, N-dimethyl-1-phenyl-1-(2-phenyl-1H-benzo[d]imidazol-1-yl) methanamine (b1)

$C_{22}H_{21}N_3$, 80% yield, m.p. (185-186) °C, m.w. 327, R_f value 0.29, IR (KBr, υ cm $^{-1}$), 3140 (Ar-H str.), 1615 (C=N str.), 1430 (C-N str.).

3.2.5. 1-(2-(4-bromophenyl)-1H-benzo[d]imidazol-1-yl)-N, N-dimethyl-1-henylmethan amine (b2)

$C_{22}H_{20}N_3Br$, 80% yield, m.p. (196-198) °C, m.w. 406, R_f value 0.16, IR (KBr, υ cm $^{-1}$), 3140 (Ar-H str.), 1615 (C=N str.), 1430 (C-N str.).

3.2.6. 1-(2-(4-bromophenyl)-1H-benzo[d]imidazol-1-yl)-N, N-dimethyl-1 henylmethan amine (b3)

$C_{22}H_{21}N_3O$, 68% yield, m.p. (203-204) °C, m.w. 343, R_f value 0.24, IR (KBr, υ cm $^{-1}$), 11.9 (1H, s, OH) , 7.1-7.9 (13H,m,Ar- H),6.13(1H,s,C-H) , 2.27($2CH_3$) 3440 (O-H str.), 3050 (Ar-H str.), 1655 (C=N str.), 1468 (C-N str.).

3.2.7. Dimethylglycine (c)

$C_4H_9O_2N$, 90% yield, m.p. (158-160) °C, m.w. 103, R_f value 0.25, IR (KBr, υ cm $^{-1}$), 3450-3125 (Broad, O-H str.), 2939(C-H Asy. str., CH_2), 2833(C-H Sym. str., CH_2) ,1740 (C=O str.) ,1473(C-N str.).

3.2.8. 1-(1H-benzo[d]imidazol-2-yl)-N, N-dimethylmethanamine (d)

$C_{10}H_{13}N_3$, 82% yield, m.p. (269-270) °C, m.w. 175, R_f value 0.28, IR (KBr, υ cm $^{-1}$), 3260(N-H str.), 3147(Ar-H str.), 2941(C-H Asy. str., CH_2), 2838(C-H Sym. str., CH_2)' 1645(C=Nstr.) ,1445 (C-N str.), 6.6 - 7.2(4H, m, Ar- H), 9.6 (1H, s,NH) , 4.5(2H,s,CH_2) , 2.24($2CH_3$).

3.2.9.1-(2-((dimethylamino)methyl)-1H-benzo[d]imidazol-1-yl)-N, N-dimethyl-1phenyl methanamine (e1)

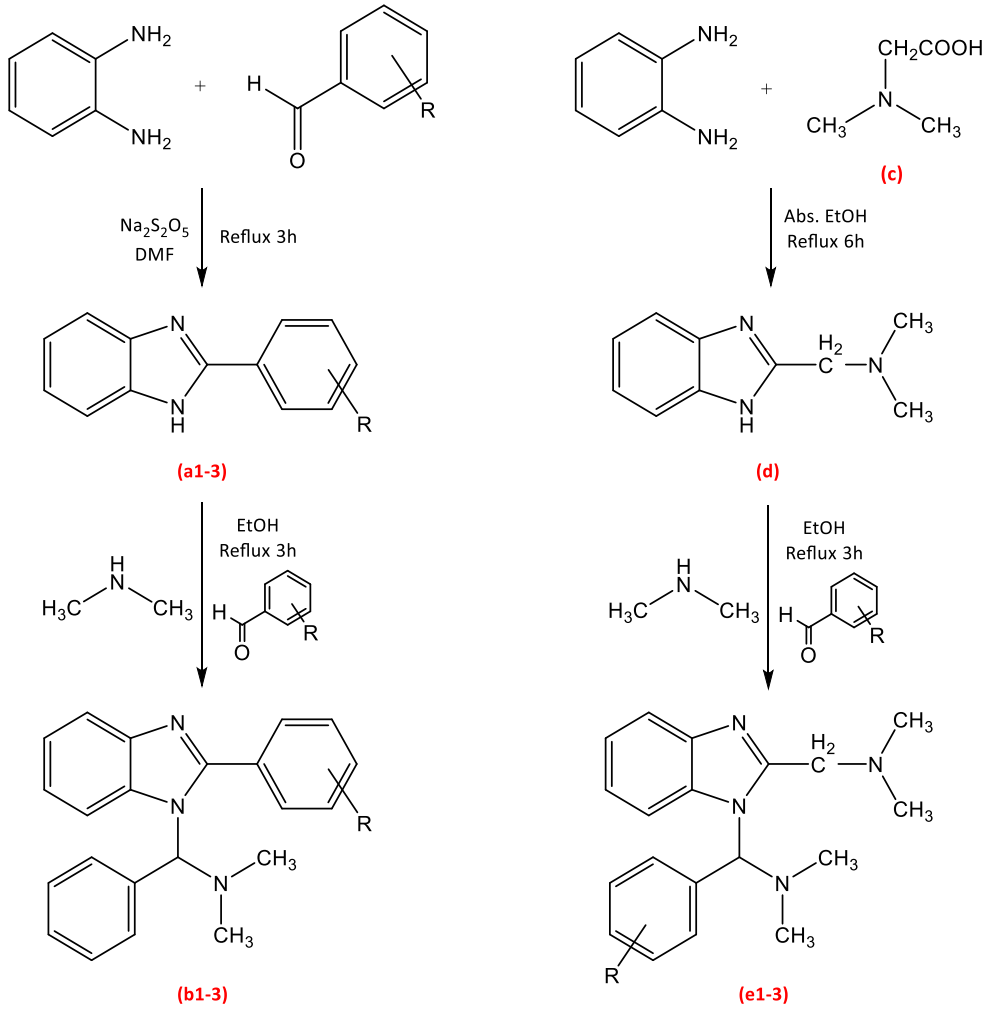
$C_{19}H_{24}N_4$, 87% yield, m.p. (220-222) °C, m.w. 308, R_f value 0.22, IR (KBr, υ cm $^{-1}$), 3151(Ar-H str.), 2960(C-H Asy.str., CH_2), 2812 Sym.str. CH_2), 1604(C=N str.), 1444 (C-N str.).

3.2.10.1-(4-bromophenyl)-1-(2-((dimethylamino)methyl)-1H-benzo[d]imidazol-1-yl)-N, N-dimethylmethanamine (e2)

$C_{19}H_{23}N_4Br$, 75% yield, m.p. (300d) ℃, m.w. 387, R_f value 0.29, IR (KBr, υ cm^{-1}), 3014(Ar-H str.), 2939(C-H Asy.str., CH_2), 2833 Sym.str., CH_2),1645(C=N str.),1473 (C-N str.).

3.2.11.4-((dimethylamino)(2-((dimethylamino)methyl)-1H-benzo[d]imidazol-1-yl) methyl) phenol (e3)

$C_{19}H_{24}N_4O$, 70% yield, m.p. (271-273) ℃, m.w. 324, R_f value 0.38, IR (KBr, υ cm $^{-1}$), 3350(O-H str.), 3045(Ar-H str.), 2945(C-H Asy.str. CH_2), 2830 Sym.str., CH_2),1645(C=N str.),1473(C-N str.), 11.22 (1H, s, OH),7.0-7.5 (8H, m,Ar),6.11 (1H,s,C- H) 4.7 (2H,s,CH_2) ,2.23(4CH_3).



Compounds	Benzaldehydes	Substituents (R)
a1, b1, e1	Benzaldehyde	
a2, b2, e2	p-Bromobenzaldehyde	
a3, b3, e3	p-Hydroxybenzaldehyde	

Scheme 1: Synthesize Mannich bases (b1-3), (e1-3) in the presence of benzaldehydes p-substituted and dimethylamine (DMA)

Table 2: Data on the produced chemicals' spectra

Comp.	FT-IR (KBr, υ cm^{-1})	^{1}H-NMR (DMSO - d_6, δ ppm)
a1	3276(N-H str.), 3145(Ar-H str.),1600(C=N str.), 1460 (C-N str.)	
a2	3270(N-H str.), 3015(Ar-H str.), 1630(C=N str.), 1462(C-N str.)	6.6-7.8(8H, m,Ar- H), 9.5(1H,s,NH)
a3	3460(O-H str.), 3278(N-H str.), 3050(Ar-H str.), 1650 (C=N str.), 1465(C-N str.)	
b1	3140(Ar-H str.), 1615(C=N str.), 1430 (C-N str.)	
b2	3142(Ar-H str.), 1635(C=N str.), 1455 (C- N str.)	
b3	3440(O-H str.), 3050(Ar-H str.), 1655 (C=N str.), 1468(C-N str.)	11.9(1H, s,OH) , 7.1-7.9 (13H,m,Ar-H),6.13(1H,s,C-H) , 2.27(2CH_3)
c	Asy. str., CH_2), 3450-3125 (Broad, O-H str.), 2939(C-H 2833(C-H Sym.str., CH_2) ,1740 (C=O str.) ,1473(C-N str.)	
d	3260(N-H str.), 3147(Ar-H str.), 2941(C-H Asy.str., CH_2), 2838(C-H Sym.str., CH_2)· 1645(C=Nstr.) ,1445 (C-N str.)	6.6 -7.2(4H, m,Ar- H), 9.6 (1H,s,NH) , 4.5(2H,s,CH_2) , 2.24(2CH_3)
e1	3151(Ar-H str.), 2960(C-H Asy.str., CH_2), 2812 Sym.str. CH_2), 1604(C=N str.), 1444 (C-N str.)	
e2	3014(Ar-H str.), 2939(C-H Asy.str., CH_2), 2833 Sym.str., CH_2),1645(C=N str.),1473 (C-N str.)	
e3	3350(O-H str.), 3045(Ar-H str.), 2945(C-H Asy.str. CH_2), 2830 Sym.str., CH_2),1645(C=N str.),1473(C-N str.)	11.22 (1H, s, OH),7.0-7.5 (8H, m,Ar),6.11 (1H,s,C- H) 4.7 (2H,s,CH_2) ,2.23(4CH_3)

Table 3: Antimicrobial activities index of Mannich bases (b1-3), (e1-3).

Comp.	Concentration (µg/mL)	Zone of inhibition in mm diameter against bacteria	
		Staphylococcus aureus	*Escherichia coli*
b1	100	+	++
b2	100	+++	+
b3	100	-	+
e1	100	+++	++
e2	100	++	++
e3	100	+++	+++
Amikacin (Std.)	10	+++	+++
Ketoconazole (Std.)	10	-	-
Solvent control (DMSO)	-	-	-

Key to symbols:
Inactive = - (inhibition zone < 6mm), **Slightly active** = + (inhibition zone 6 - 9mm), Moderately **active** = ++ (inhibition zone 9 - 12mm), **Highly active** = +++ (inhibition zone >12mm).

Conclusions

Through the use of 2-substituted benzimidazoles (a1-3) and (d), a number of novel Mannich bases have been obtained (b1-3) and (e1-3). In the presence of compounds with secondary amine and p-substituted benzaldehydes, these synthetic compounds were created via the Mannich process. Retardation factor (R_f values) and melting point (m.p.) measurements were used to confirm the creation of novel chemical analogs. Data from FT-IR and ^{1}H-NMR spectra validated the structure of the produced compounds. Gram-positive bacteria (*S. aureus*) and gram-negative bacteria (*E. coli*) were used to evaluate the anti-microbial activity of certain newly synthesized compounds in vitro using the disc diffusion method. Against all of the examined species, compounds e1, e2, e3, and b2 at a concentration of (100 µg/mL) shown strong antibacterial activity. The reference standards for antibacterial activity were, respectively, *amikacin* and *ketoconazole* (10 µg/mL).

Declaration of conflicting interests

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تحضير ودراسة الفعالية البايولوجية لبعض قواعد مانخ المحملة لمعوض 2،1–بنزاميدازول

الملخص

الهدف الرئيسي من هذه الدراسة هو تحضير مشتقات قاعدة مانخ التي تحتوي على معوض 2،1–بنزاميدازول والتي من المتوقع أن تكون فعالة كعوامل مضادة للميكروبات مع ميزات واعدة لتطوير الأدوية. يشتمل إطار البحث في هذه الدراسة على نهجين مستخدمين في تصميم أسلوب البحث. أولاً ، تحضير سلسلة من 2− (فينيل معوض) بنزيميدازول (a1-3) بتفاعل بنزالديهايدات معوضة بموقع بارا مع أورثو فينيلين ثنائي أمين (OPDA)، ثم تم استخدامه في تحضير قواعد مانخ (b1-3) وبوجود البنزالديهايد وثنائي ميثيل أمين (DMA).

ثانيًا ، تم تحضير 2− (N- [Bis (dimethylamino) methylene]) benzimidazole (d) عن طريق تفاعل (N,N-Dimethylglycine (DMG) (c)) مع ortho-phenylene Diamine (OPDA) ، والذي تم استخدامه بعد ذلك من أجل تحضير قواعد مانخ (e1-3) في وجود البنزالديهايدات وثنائي ميثيل أمين (DMA) والمعوضة في الموقع بارا. شخصت المركبات المحضرة بواسطة تحديد درجة الانصهار، كروموتوكرافيا الطبقة الرقيقة، R_f ، مطيافية الأشعة تحت الحمراء FTIR، وطيف الرنين النووي المغناطيسي للبروتون. درست الفعالية البايلوجية مختبريا باستخدام قواعد مانخ التي تم الحصول عليها على نوعين من البكتيريا هما موجبة الجرام (*S. aureus*) والبكتيريا سالبة الجرام (*E. coli*) وفقًا لطريقة cup-plate.