European Science Methodical Journal
ISSN (E): 2938-3641
Volume 3, Issue 1, January- 2025

SYNTHESIS, DESIGN, AND ANTIMICROBIAL EVALUATION OF SCHIFF BASE BASED ON BENZIMIDAZOLE

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Abstract:

This effort involved the design and synthesis of new antibacterial medications that are Schiff base derivatives linked by a methylene bridge to the 1-position of the heterocyclic ring (benzimidazole). By using 1H, 13C NMR, and FTIR spectroscopy, the final chemical structures of the produced tetrazole derivatives were verified. By using the microdilution method, chemicals can fight off Gramp positive bacteria like Bacillus cereus and S. aureus as well as Gram negative bacteria like E. coli and Pseudomonas aeruginosa. Using the broth microdilution technique, the in vitro antibacterial activity of Schiff base compounds (a1-a5) was investigated against two Gram positive and two Gram negative microorganisms. The compounds' minimum inhibitory concentrations (MIC) were contrasted with those of streptomycin, which served as a reference antibiotic. Staphylococcus aureus was more susceptible to the antibacterial activity of compounds (a3 and a5) (MIC 19.8 and 15.5 µg/mL) than streptomycin (MIC 35 µg/mL). Gram-negative microorganisms Compounds (a3 and a5) had a greater effect on Escherichia coli (MIC 33.2 and 24.3 µg/mL).

Keywords: Benzimidazole, Schiff base, Antibacterial activity, Resistance, Oxadiazole.

Introduction

As they continue to undermine the effectiveness of many antimicrobial drugs, parasites, fungi, viruses and bacteria are the main causes of health problems around the world, especially with the high resistance of these microorganisms, so this has become one of the major challenges facing researchers in the field of antibiotic innovation in order to overcome these challenges [1]. Schiff base derivatives are a well-known class of organic molecules which, according to the literature, show interest in industrial sectors such as the manufacture of refractory materials, corrosion resistant materials, catalysts and many other industrial applications. As for biological and medical applications, Schiff base derivatives are important in the pharmaceutical industry and medical treatments. Schiff bases are prepared by reacting one of the carbonyl compounds (aldehydes or ketones) with primary amines, whether aromatic or aliphatic, using absolute alcohol as an organic solvent at a temperature of up to 80°C [2]. Cyclic ring compounds are used because of interest in finding new therapeutic Schiff bases to reduce pathogen invasion linked to microbial resistance. In biological applications, aromatic-based imine compounds

have shown more promise due to an electron's free delocalization with the ring structure [3]. Heterocyclic ring-derived Schiff bases provide several benefits; comprehensive details are available here [4]. In organic compounds, oxygen, nitrogen, and sulfur (O, N, and S) are the most common heteroatoms. Heterocyclic compounds that include nitrogen, such imidazole and benzimidazole, make up a significant family of pharmacophores [5]. Due to the widespread use and commercialization of their derivatives enviroxime, carbendazime, astemizole, and mebendazole, they have drawn the interest of numerous researchers [6, 7]. Benzoimidazole and their derivatives is derived from imidazole moiety that is used in the production of pharmaceutical drugs. Since it constituted the core of nitrogen bases, its fused type of heterocyclic ring structure is essential to the creation of nucleotide derivatives [5]. Because of their easy interaction with biopolymers, benzomidazole and its derivatives show promise in establishing suitable platforms for the synthesis of physiologically active molecules that share structural similarities with derivatives of vitamin B12 [8]. Benzimidazole and its derivatives exhibit fascinating biological action against a variety of human diseases and microbial assaults. These consist of viruses [11], fungi [10], and bacteria [9]. Benzimidazole-modified Schiff bases have also been utilized in DNA binding and cleavage [12, 13], topoisomerase inhibitory [14], antitumor [15], and anticancer [16] applications. As previously reported, their viral and parasitic characteristics cannot be refuted [17]. In pharmaceutical chemistry, benzoimidazole is referred to as a fortunate structure and serves a number of biological purposes. As a heterocyclic aromatic chemical, benzoimidazole features a benzene ring structure, where the benzene ring is joined to a five-member imidazole ring with nitrogen atoms at positions 1 and 3. [18,19] Furthermore, benzimidazole is an extremely valuable therapeutic scaffold with encouraging pharmacological characteristics. Clinically used benzimidazole drugs have well-established safety and effectiveness profiles. Due to their remarkable antiviral, anticancer, antibacterial, antihistamine, anti-inflammatory, antitubercular, antihypertensive, antiulcer, analgesic, and anthelmintic properties, [20-21] benzimidazole derivatives have garnered a lot of interest in the medical sector [22]. Many important drugs that are used therapeutically in the field of research contain the benzimidazole ring. Examples of medications with a benzimidazole structure include Astemizole (antihistamine), Omeprazole (antiulser), Bendamustine (anticancer), and Albendazole (anthelminthic). [23,24] In an attempt to prepare several organic compounds that we expect to have antimicrobial activity and be of relatively high reliability to prevent the invasion of microorganisms that are highly resistant to known and marketed treatments, we prepared new organic compounds, which are new imines, using heterocyclic benzimidazole compound as a starting material for the reaction and reacting it with bromonitrile to prepare oxazole compounds and then evaluating their antibacterial activity against four bacterial strains used in this study.

Experimental

The entire set of chemicals needed for the synthetic process was purchased from Sigma-Aldrich Chemicals (Sigma-Aldrich, Baghdad, Iraq) or Merck Chemicals and commercial sources. The melting point apparatus (MP90 digital) was used to determine the uncorrected melting points

of the compounds. The 1H- and 13C NMR spectra of the compounds generated in DMSO-d6 were recorded using a Bruker digital FT-NMR spectrometer (Bruker Bioscience, Iran) set to 400 and 100 MHz, respectively. The following symbols were used to represent the splitting patterns in the NMR spectra: s for singlet, d for doublet, t for triplet, and m for multiplet. Hertz was the reported unit of coupling constants (J). All reactions were seen using thin-layer chromatography (TLC) with Silica Gel 60 F254 TLC.

Synthesis of 5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-amine [25]

After mixing (0.05 mol) of urea and (0.05 mol) of 2-(1H-benzo[d]imidazol-1-yl)acetonitrile was synthesized in previous study [26] in 20 mL of 100% ethanol, acetic acid was added to the mixture drop by drop. After 12 hours of reflux, the reaction was dumped onto ice, producing a white precipitate. After being cleaned with water, the final product (74%) was recrystallized from ethanol. TLC (4:1, Benzene: Methanol), m. p: 154-156 °C, FT-IR spectra (v max): 2844-2971 cm-1 (Aliphatic CH), 3327 cm-1 (NH_2 sym, asym), 1539 cm-1 (C-N), ^{1}H NMR (DMSO-d_6) δ 8.12 (s, 1H, proton of C2 imidazole ring), 7.67–7.27 (m, 4H of aromatic ring), 5.46 (d, J = 5.8 Hz, 1H, protons of amine group), 5.13 (s, 2H, protons of methylene group), ^{13}C NMR (DMSO-d_6) δ 165.27(C-2 Oxadiazole ring), 156.29(C-5 Oxadiazole ring), 143.10, 141.35, 134.10, 123.42, 122.35, 119.54, 109.69 (carbons of benzimidazole ring), 42.44 (carbon of methylene group).

General Synthesis of Schiff base derivatives (a1-a5) [25,27]

Twenty milliliters of 100% ethanol were combined with a mixture of (0.05 mol) compound (a) and (0.05 mol) of several aromatic aldehydes, including 4-Bromobenzaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde, 4-hydroxybenzaldehyde, 4-nitrobenzaldehyde, and vanillin. Three to four drops of glacial acetic acid were added to the solution of reaction mixture. Then reaction mixture was refluxed and stirred for six hours. After being cleaned with water, the finished products were dried and recrystallized from heated ethanol.

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-1-(4-bromophenyl) methanimine (a1): FT-IR spectra (vmax): 2890-2966 cm-1 (Aliphatic CH), 1647 cm-1 (C=N imine), 1587 cm-1 (C=C aromatic),1548 cm-1 (C-N), ^{1}H NMR data was measured by using (DMSO-d_6) δ 8.62 (s, 1H, CH=N), 8.11(s,1H, proton of C2 imidazole ring), 7.89–7.28 (m, 8H, protons of aromatic ring), 5.21 (s, 2H, protons of methylene group), ^{13}C NMR data was measured by using (DMSO-d_6) δ 169.63(C-2 Oxadiazole ring), 167.13(-CH=N-, carbon of imine group), 156.41(C-5 Oxadiazole ring), 142.97, 141.42, 135.24, 134.32, 131.68, 130.81, 124.35, 123.15, 122.32, 119.54, 109.80(carbons of aromatic rings), 42.64(carbon of methylene group).

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-1-(4-chlorophenyl) methanimine (a2): FT-IR spectra (vmax): 2888-2958cm-1 (Aliphatic CH), 1652 cm-1 (C=N imine), 1581cm-1 (C=C aromatic),1534 cm-1 (C-N), ^{1}H NMR data was measured by using

(DMSO-d_6) δ 8.63(s, 1H, CH=N), 8.14 (s,1H, proton of C2 imidazole ring), 7.89–7.29 (m, 8H, protons of aromatic ring), 5.22 (s, 2H, protons of methylene group), ^{13}C NMR data was measured by using (DMSO-d_6) δ 169.68(C-2 Oxadiazole ring), 167.05(-CH=N-, carbon of imine group), 156.41(C-5 Oxadiazole ring), 143.01, 141.38, 137.12, 135.03, 134.18, 131.17, 129.19, 123.31, 122.37, 120.87, 109.77(carbons of aromatic rings), 42.67(carbon of methylene group).

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-1-(4-hydroxyphenyl) methanimine (a3): FT-IR spectra (vmax): 3374cm-1 (hydroxyl group), 2862-2968cm-1 (Aliphatic CH), 1642 cm-1 (C=N imine), 1577cm-1 (C=C aromatic),1531 cm-1 (C-N),^{1}H NMR data was measured by using (DMSO-d_6) δ 9.19 (s, 1H, phenolic proton),8.65 (s, 1H, CH=N), 8.12 (s,1H, proton of C2 imidazole ring), 7.67–7.24 (m, 8H, protons of aromatic ring), 5.21 (s, 2H, protons of methylene group), ^{13}C NMR data was measured by using (DMSO-d_6) δ 169.63(C-2 Oxadiazole ring), 167.34(-CH=N-, carbon of imine group), 156.41(C-5 Oxadiazole ring), 157.25, 142.57, 141.38, 134.18, 131.84, 128.48, 123.44, 122.37, 119.53, 116.40, 109.65(carbons of aromatic rings), 42.63(carbon of methylene group).

(E)-N-(5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-1-(4-nitrophenyl) methanimine (a4): FT-IR spectra (vmax): 2880-2974cm-1 (Aliphatic CH), 1649 cm-1 (C=N imine), 1565cm-1 (C=C aromatic),1545 cm-1 (C-N), 1358 cm-1 (NO_2),^{1}H NMR data was measured by using (DMSO-d_6) δ 8.74 (s, 1H, CH=N), 8.08 (s,1H, proton of C2 imidazole ring), 8.24-7.32 (m, 8H, protons of aromatic ring), 5.22 (s, 2H, protons of methylene group), ^{13}C NMR data was measured by using (DMSO-d_6) δ 169.69(C-2 Oxadiazole ring), 166.95(-CH=N-, carbon of imine group), 156.41(C-5 Oxadiazole ring), 149.00, 142.96, 141.71, 141.33, 134.13, 130.35, 124.45, 123.11, 122.36, 119.57, 109.75(carbons of aromatic rings), 42.54(carbon of methylene group).

(E)-4-(((5-((1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)imino)methyl)-2-methoxyphenol(a5): FT-IR spectra (vmax): 3394cm-1 (hydroxyl group), 2877-2947cm-1 (Aliphatic CH), 1651 cm-1 (C=N imine), 1571cm-1 (C=C aromatic),1542 cm-1 (C-N),^{1}H NMR data was measured by using (DMSO-d_6) δ 8.31 (s, 1H, phenolic proton),8.65 (s, 1H, CH=N), 8.12 (s,1H, proton of C2 imidazole ring), 8.21-7.25 (m, 7H, protons of aromatic ring), 5.21 (s, 2H, protons of methylene group),3.86 (s, 3H, protons of methoxy group),^{13}C NMR data was measured by using (DMSO-d_6) δ 169.73(C-2 Oxadiazole ring), 165.53(-CH=N-, carbon of imine group),156.41(C-5 Oxadiazole ring), 148.15, 147.46, 142.96, 141.33, 134.13, 128.33, 125.69, 123.11, 122.36, 119.57, 114.70, 111.70, 109.75(carbons of aromatic rings), 56.15(carbon of methoxy group), 42.64(carbon of methylene group).

Biological Activity Antibacterial Test [28]

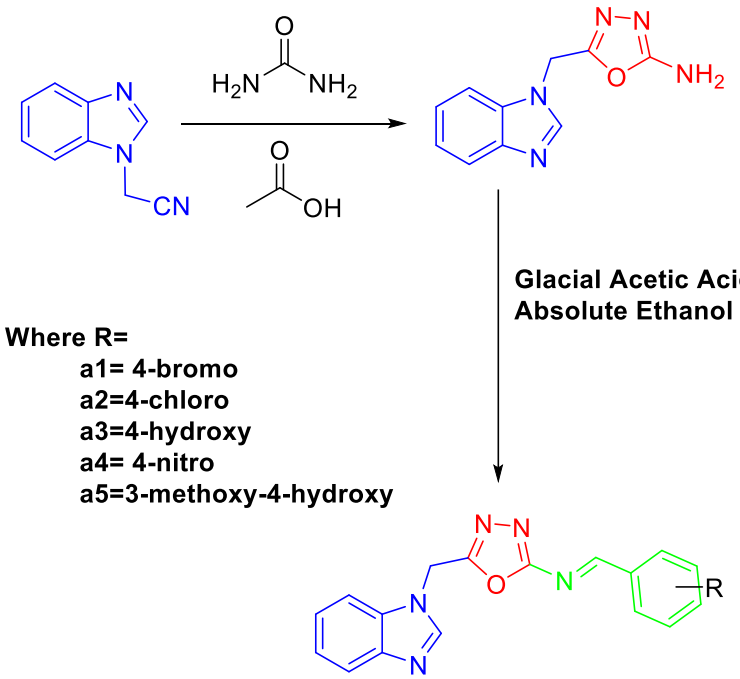
Schiff base compounds attached to heterocyclic rings such as oxazole rings. By using the microdilution method, the produced compounds (a1–a5) were tested in vitro against

representatives Bacillus cereus (BC) (ATCC10876), S. aureus (SA) (ATCC25923) as Gramp positive bacterial whereas using E. coli (EC) (ATCC25922) and Pseudomonas aeruginosa (PA) (ATCC27853) as Gram-negative bacterial species. Using reference method M38-A2, the mini mum inhibitory contractions (MIC) were calculated [29]. Streptomycin served as a positive control for comparison. Fresh bacterial cultures were extracted from an overnight bacterial growth and diluted in nutritional broth to achieve the 0.5 McFarland standards, or 1 × 105 cfu/mL. This suspension (100 µL) was then aseptically seeded into a 96-well plate that contained 100 µL of serially diluted test compound concentrations of 500, 250, 125, 62.5, 31.2, 15.6 and 7.8 µg/mL. The plates were then incubated at laboratory temperature of 37°C for a full day (24 hours). The cells used in this study were tested for viability or possible death by adding resazurin dye (0.02%), which is enzymatically digested to produce a chemical precipitate of resazurin, which is pink in the presence of live cells and blue in dead cells. The minimum inhibitory level for each drug is recorded and provided with standards.

Results and discussion

Chemistry

The synthesis of Schiff base compounds (a1-a5) took the actions specified in Scheme 1. The starting material was 2-(1H-benzo[d]imidazol-1-yl)acetonitrile (Compound 1). The synthesized compounds were characterized and their structure established using spectral measurements such as NMR analysis and FTIR methods. Spectral analyses confirmed the purity of the newly prepared compounds.



Scheme 1 Preparation benzimidazole derivatives (Schiff base a1-a5)

FTIR Data

This Schiff base series' infrared spectra revealed vibration signals at frequencies predicted by the chromophores and functional moieties. The imine (C=N) bond of the ligands is responsible for the stretching frequencies at 1652–1642 cm−1, which are consistent with this result [7]. Low intensity vibration signals characteristic of the aliphatic's C–H stretching band were detected between 2842 and 2890 cm−1. The O–H stretching frequencies of the hydroxyl group are responsible for the sharp bands that are present in the compounds' spectra at 3394 cm-1 for compound (a3) and 3374 cm-1 for compound (a5). The effective synthesis of the Schiff base ligands is implied by the absence of any signal typical of the main amine's -NH2.

NMR Data

The spectra of the Schiff bases that were described showed no imine proton, and the carbonyl that was employed in the reaction was a ketone. These compounds' 1H NMR revealed both aromatic and aliphatic protons (Ar–H). In relation to the phenyl ring, the protons that attached to the aromatic ring resonate at single, doublet, and multiplate chemical shifts δ = 7–8 ppm. Nevertheless, in compounds a3 and a5, other Ar–H protons were detected in excess of δ = 8 ppm due to electron donating groups on the substituted aromatic rings, which raises the proton's chemical shift and produces the deshielding effect. As predicted, phenolic protons are visible for Compound (a3) at chemical shift δ = 9.19 ppm and for Compound (a5) at δ = 9.31 ppm. The methylene group's (-CH2) signals are visible at about 5 ppm of chemical shift. There are no signs of contamination when the protons at position two of the benzimidazole ring emerge as a singlet in the high range chemical shift (8.08–8.14 ppm). As anticipated, the C=N signals of the azomethane of the prepared Schiff bases were detected in the 13C NMR spectra at δ = 165–167 ppm. Along with the C=N signals of the benzimidazole, aromatic carbons may be observed at δ = 109–148 ppm. Meanwhile, the oxadiazole ring's C-5 and C-2 resonate at δ = 169 ppm and 156 ppm, respectively. All aliphatic carbons were detected at δ = 42 ppm, while compound (a5)'s -O–CH3 resonance was observed at δ = 56 ppm.

Pharmacological activity

Antibacterial activity

Using the broth microdilution technique, the in vitro anti microorganism’s activity of Schiff base compounds (a1-a5) was investigated against two Gram positive and two Gram negative microorganisms. Table 1 and Figure 1 show the results of comparing the compounds' minimum inhibitory concentrations (MIC) to streptomycin, which was utilized as a reference antibiotic agent.

Table 1: The Schiff bases' antibacterial properties (a1–a5)

Minimum inhibitory concentration MIC (µg/mL)				
Compounds	Gram negative		Gram positive	
	EC	PA	BC	SA
a1	81	254	187	65.5
a2	95.5	237	168	53
a3	33.2	157.5	87.8	19.8
a4	73.6	214.6	159.5	47.5
a5	24.3	135	57	15.5
STM	48.5	18	35	35

STM, streptomycin; E. coli, (EC); Pseudomonas aeruginosa, (PA); Bacillus cereus, (BC); S. aureus, (SA).

Exposure to the substances caused distinct reactions in the tested species, and their susceptibility varied with concentration. When tested against several bacterial representatives, the test compounds showed good to high antibacterial activity. For example, of the Gram-positive strains under investigation, Staphylococcus epidermidis was the most sensitive, with a MIC ranging from 15.5 to 19.8 µg/mL. Staphylococcus aureus was more susceptible to the antibacterial activity of compounds (a3 and a5) (MIC 19.8 and 15.5 µg/mL) than streptomycin (MIC 35 µg/mL). Gram-negative microorganisms Compounds (a3 and a5) had a greater effect on Escherichia coli (MIC 33.2 and 24.3 µg/mL). Other factors than the imine C=N bond may also contribute to these molecules' increased potency. These consist of the substituted aromatic rings and the benzimidazole ring. Because of the characteristics of their cell membranes, positive Gram strains were more susceptible to test substances than negative Gram bacteria. Poor target engagement or the targeted enzyme/partway's non-essentiality in vivo could possibly be the cause of the lack of action [30]. Most likely, the cause is the fluctuation in the composition of the brane in the cell membrane. Compared to Gram-negative bacteria, which have three extra components outside the peptidoglycan (periplasmic space, lipopolysaccharides, and phospholipids) for defiance, positive Gram bacteria are more vulnerable to external attacks because they lack these protective layers outside the peptidoglycan layer making inhibition easier than for Gram-negative bacteria. [31]. The variation in the brane's composition within the cell membrane is most likely the cause. Because positive Gram bacteria lack these protective layers outside the peptidoglycan layer, they are more susceptible to external attacks than Gram-negative bacteria, which have three additional components outside the (periplasmic space, lipopolysaccharides, and phospholipids) for defiance [32]. These molecules comprise the bilayer membrane that regulates and controls the movement of molecules within cells; in contrast to Gram-positive cells, Gram-negative bacteria's complex lipids may make it more difficult for chemicals to diffuse easily into the cytoplasm of the organism. Compared to Gram-positive bacteria, they are therefore more resistant to chemicals.

European Science Methodical Journal
ISSN (E): 2938-3641
Volume 3, Issue 1, January- 2025

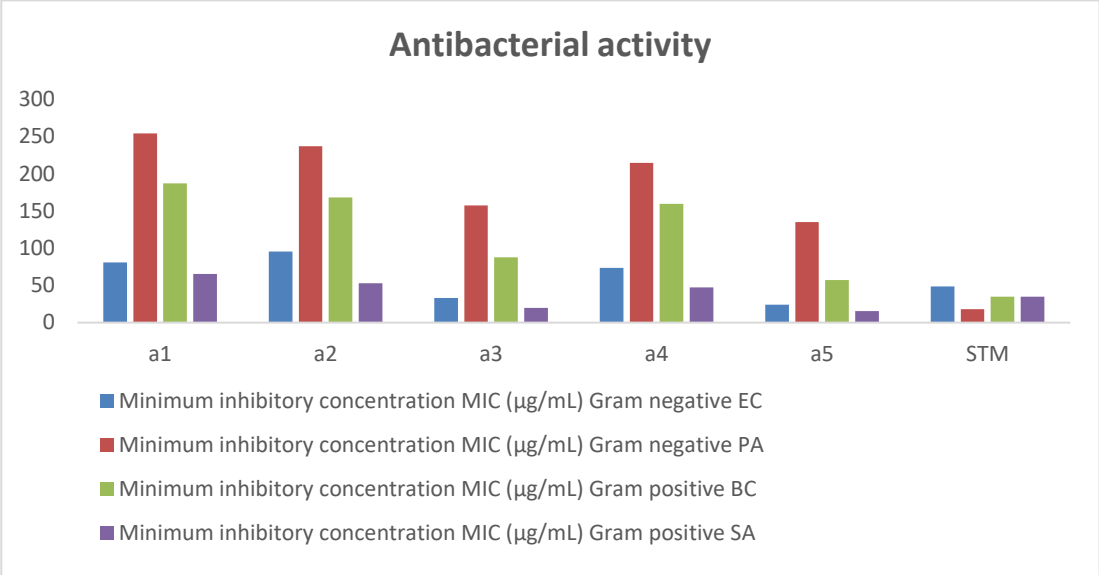


Figure 1: Antibacterial activity of the Schiff bases (a1-a5)

Conclusion

Schiff bases conjugated with oxazole rings are of great importance in biological applications, including antibacterials. Five new Schiff base compounds with benzimidazole scaffolds were successfully synthesized, and FTIR and NMR studies verified their chemical structures. These chemicals' biological uses against four microorganisms were investigated. The chemicals have strong antibacterial activity against the microorganisms under study, changing their respiratory and metabolic processes, which ultimately results in cell death. It is recommended that the recently synthesized Schiff bases be used as lead material for the future development of antibiotic medicines because they do not exhibit any harmful effects on HeLa cell lines.

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