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Synthesis and Evaluation of New Hydrazone Derivatives as Antibacterial

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Abstract

Bacterial infections remain a significant challenge because of the increasing resistance developed by pathogenic bacteria. As a result, numerous studies focusing on the development of novel antibacterial agents are published each year. Heterocycles are an important field in organic synthesis due to their biological activities. On the other hand Schiff bases also possessing an important range of pharmacological activities. Hybridization-combing two pharmacophores to form one molecule-is the important method in designing new drugs. The heterocyclic-hydrazone derivatives were synthesized via a multi-step process and their structures were confirmed using thin layer chromatography (TLC) as well as spectroscopic techniques, including ATR-FTIR and ^{1}H NMR analyses. The disk diffusion method was used to evaluate the antibacterial activities of the new compounds. The compounds showed weak activities against *K. pneumoniae*, and good activities against *E. coli* and *S. aureus*.

Keywords: Bacterial infections, Heterocycles, Schiff Base, Hybridization, Antibacterial.

Introduction

Globally, the growing ineffectiveness of widely used antibacterial drugs—including β-lactams, quinolones, and macrolides—has become a serious threat to public health [(1)] Multidrug-resistant infections contribute to longer therapeutic courses, elevated healthcare expenditures, and heightened morbidity and mortality worldwide [(2)] Addressing the challenge of microbial resistance requires both the prudent utilization of existing antibiotics and the discovery of new, more potent agents with innovative mechanisms of action.. [(3, 4)]

Due to their structural resemblance to purines, benzimidazole derivatives can interfere with natural purine functions, disrupting nucleic acid and protein synthesis, which ultimately inhibits bacterial growth and leads to cell death. Recognized as a privileged scaffold in medicinal chemistry, benzimidazole holds significant importance owing to its broad spectrum of biological activities. [(5, 6)]

Among heterocyclic compounds, pyridine stands out as a valuable core structure due to the broad range of pharmacological activities associated with its derivatives, such as antimicrobial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory, antioxidant, anti-Alzheimer's, antiulcer or antidiabetic. The pyridine nucleus is found in many natural products, such as vitamins, alkaloids and coenzymes, as well as in many drugs and pesticides. [(7-9)] Hydrazones represent a versatile class of compounds in medicinal chemistry, with structures like nitrofurantoin exemplifying their pharmaceutical relevance. Their wide-ranging biological properties—including antibacterial, anticancer, antiviral, antimalarial, anti-inflammatory, analgesic, anticonvulsant, antidepressant, and anthelmintic effects—have made them a focal point for drug discovery and development efforts. [(10-13)]The aim was to synthesize new hybrid molecules combining hydrazones with different heterocycles as possible antibacterial agents, Figure (1):

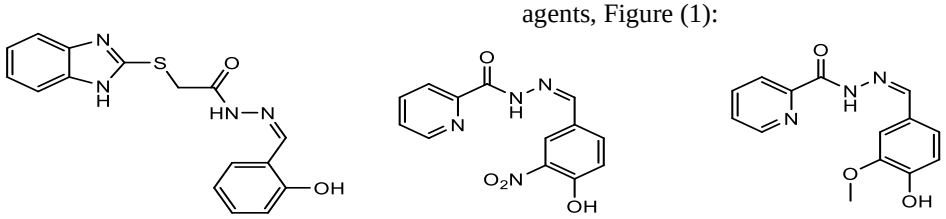


Figure 1. Structures of targeted compounds.

Materials and Methods

All required chemicals were obtained from Hyperchem (China) and other commercial suppliers. The progress of the reactions, determination of Rf values, and assessment of product purity were performed using thin-layer chromatography (TLC) on aluminum plates pre-coated with silica gel GF254 (type 60), visualized under UV light at 254 nm. Two solvent systems were employed as eluents: S1 (toluene: ethyl acetate: ethanol, 3:2:1) and S2 (ethyl acetate: methanol: ammonia, 5:0.5:1.5).

Structural characterization of all synthesized compounds was achieved through TLC alongside spectroscopic analyses. FTIR measurements were performed at Samarra Drugs Industry (SDI), and ^{1}H NMR spectra were recorded at the University of Basrah.

Chemical Synthesis

The synthesis of the targeted compounds (comp. A4, comp. B1, and comp. B2) was proceeding as following:

Synthesis of 1H-benzo[d]imidazole-2-thiol; comp. A1

o-phenylenediamine (3g, 0.028mole) was dissolved in a minimum amount of absolute ethanol then KOH (2.3g, 0.042mole) was added to the above solution, after that the solution was immersed in an ice bath and when the temperature dropped to about 0-1°C, carbon disulfide (CS2), (2.13g, 0.056mole) was added with continuous stirring (ppt. formed which dissolved by adding few mls of D.W). Then the reaction solution refluxed for 5 hours until most hydrogen sulfide (H2S) disappeared. After cooling a reaction mixture was cooled, acidified using conc. HCl, and the precipitate was filtered and dried. [14] **1H-benzo[d]imidazole-2-thiol ($C_7H_6N_2S$)**: brown powder, R_f 0.65, yield 72%. **FTIR spectrum in cm^{-1}:** Stretching vibration bands related to NH of benzimidazole at 3149 and SH at 2571 (weak band).

Synthesis of ethyl 2-((1H-benzo[d]imidazol-2-yl)thio)acetate; comp. A2

Comp. A1 (3g, 0.0199mole) was dissolved in a minimum amount of absolute ethanol with the aid of KOH (1.119g, 0.0199mole); then ethyl chloroacetate (2.44g, 0.0199mole) was added to the above solution and refluxed for 2 hour then stirred overnight; depending on TLC result the reaction was finished. The solvent was evaporated on water bath; then cold water was added to enhance precipitation of the product also ice bath was used to facilitate precipitation which was filtered and dried. [15] **ethyl 2-((1H-benzo[d]imidazol-2-yl)thio)acetate ($C_{11}H_{12}N_2O_2S$)**: brown powder, R_f 0.78, yield 66%. **FTIR spectrum in cm^{-1}:** Strong stretching vibration band at 1750 due to aliphatic ester carbonyl group.

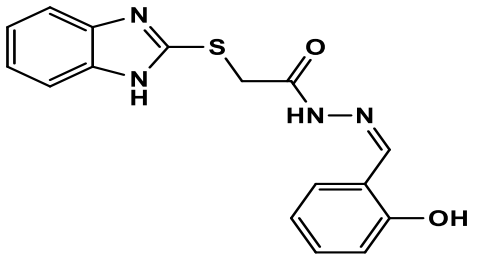
Synthesis of 2-((1H-benzo[d]imidazol-2-yl)thio) acetohydrazide; comp. A3

Comp. A2 (3g, 0.0123mole) was dissolved in a minimum amount of absolute ethanol with gentle heating. Hydrazine hydrate 80% (6.3g, 0.123mole) was added to the above solution with stirring. After few minutes white precipitate began to appear. The reaction mixture left to stir overnight to allow the reaction to complete. Depending on TLC result the reaction was finished. The precipitate was filtered, washed with absolute ethanol and dried. [16]

2-((1H-benzo[d]imidazol-2-yl)thio) acetohydrazide ($C_9H_{10}N_4OS$): white powder, R_f 0.35, yield 63%. **FTIR spectrum in cm^{-1}:** 3314 NH_2 asymmetric stretching vibration band, 3271 NH amide stretching vibration band, 3147 NH_2 symmetric stretching vibration band, 1653 stretching vibration band of carbonyl amide, 1616 NH bending vibration band of hydrazide amine, 1545 NH bending vibration band of hydrazide amide.

Synthesis of 2-((1H-benzo[d]imidazol-2-yl)thio)-N'-(2-hydroxybenzylidene)acetohydrazide; comp. A4

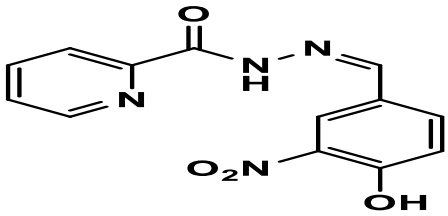
Salicyldehyde (0.55g, 0.0045mole) was dissolved in 5mI methanol, 3 drops of glacial acetic acid was added; the solution stirred for 10 minutes, then (0.5g, 0.00225mole) of **comp. A3** was added. The solution stirring overnight to allow the reaction to complete which was finished depending on TLC result. The precipitate was filtered, washed and dried. [17] **2-((1H-benzo[d]imidazol-2-yl)thio)-N'-(2-hydroxybenzylidene)acetohydrazide ($C_{16}H_{14}N_4O_2S$)**: off-white powder, R_f 0.55, yield 69%. **FTIR spectrum in cm^{-1}:** Broad phenolic OH stretching vibration band at 3400. Stretching vibration band of carbonyl due to **-CO**NH- group at 1659. Stretching vibration band of imine group **HC=N-** at 1610. **^{1}HNMR**(400MHz, DMSO-d_6) in ppm: signals for -S-CH_2- protons [2H, 2s] at 4.41&4.6; signals for aromatic protons [8H, m] at 6.83-7.71; signal for imine proton -CH=N [1H, 2s] at 8.36&8.45; signal for OH proton [1H, 2s] at 10.11&11.03; signal for amide hydrazone proton -CONH- [1H, 2s] at 11.61&12.11; and imidazole NH [1H, 2s] at 12.62&12.69.



Synthesis of N'-(4-hydroxy-3-nitrobenzylidene) picolinohydrazide; comp. B1

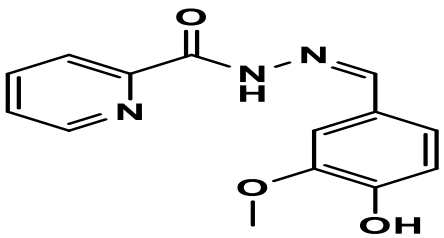
4-hydroxy-3-nitro benzaldehyde (0.5g, 0.003mol) was dissolved in round bottom flask by 10ml of methanol, then 2-3 drops of glacial acetic acid were added with stirring for 10 minutes. After

that (0.3g, 0.0022mol) of picolinic acid hydrazide was added and the reaction mixture was stirred for 48 hours. The formed precipitate was filtered, washed and dried. [17] **N'-(4-hydroxy-3-nitrobenzylidene)picolinohydrazide ($C_{13}H_{10}N_4O_4$)**: dark yellow powder, R_f 0.65, yield 80%. **FTIR spectrum in cm^{-1}:** Broad **OH** stretching vibration band. **NH** stretching vibration band of -CO**NH**- group at 3300. Stretching vibration band of carbonyl due to **-CO**NH- group at 1664. Stretching vibration band of imine group **HC=N-** at 1607. **^{1}HNMR**(400MHz, DMSO-d_6) in ppm: Two signals for **OH** [1H, 2s] proton of at 9.91&11.56; signal of imine proton -C**H**=N- [1H, s] at 8.64ppm; and signal of amide hydrazone proton -CON**H**- [1H, 1s] at 12.22.



Synthesis of N'-(4-hydroxy-3-methoxybenzylidene)picolinohydrazide; comp. B2

4-hydroxy-3-methoxy benzaldehyde (0.6g, 0.0044mol) was dissolved in round bottom flask by 10ml of methanol, then 2-3 drops of glacial acetic acid added with stirring for 10 minutes. After that (0.3g, 0.0022mol) of picolinic acid hydrazide was added and the reaction mixture was stirred for 48 hours. The formed precipitate was filtered, washed and dried. [17] **N'-(4-hydroxy-3-methoxybenzylidene)picolinohydrazide ($C_{14}H_{13}N_3O_3$)**: white powder, R_f 0.62, yield 85%. **FTIR spectrum in cm^{-1}:** Broad OH stretching vibration band. NH stretching vibration band of -CO**NH**- group at 3300. Stretching vibration band of carbonyl due to **-CO**NH- group at 1664. Stretching vibration band of imine group **-HC=N-** at 1604. **^{1}HNMR**(400MHz, DMSO-d_6) in ppm: signal for O**CH$_3$** protons [3H,s,] at 3.86ppm; signal of imine proton -C**H**=N- [1H, s] at [8.54ppm]; signal for **OH** proton [1H,s] at 9.62; and signal of amide hydrazone proton -CON**H**- [1H, 1s] at 11.99.



Antibacterial Assay

Bacterial suspension equivalent to a 0.5 McFarland standard, corresponding to approximately 1.5 × 10^8 CFU/mL, was prepared for use in the well diffusion assay. The surface of Mueller-Hinton agar (MHA) plates was uniformly inoculated by swabbing with this bacterial suspension. Excess moisture was allowed to evaporate under sterile airflow conditions. Subsequently, 80 µL of each synthesized compound solution at a concentration of 1000 µg/mL was carefully dispensed into four wells created in the agar of each plate. The plates were then incubated at 37°C for 24 hours. Following incubation, the diameters of the clear zones surrounding the wells were measured to assess the antibacterial efficacy of the compounds. [18]

Results and Discussion

Chemistry

Stepwise synthesis of the targeted compounds showed in figure 2 A and B at the end of this section. Comp**. A1** is the result of reaction between *o*-phenylene diamine and CS_2 which enhanced in the presence of KOH, potassium salt of **comp. A1** was formed which by addition of HCl gave **comp. A1**. [14] **Comp. A1** characterized by presence of stretching vibration bands related to NH of benzimidazole at 3149 and SH at 2571 (weak band) and absence of asymmetric and symmetric vibration bands of primary amine groups. [19, 20]

Comp. A2 was the result of a nucleophilic substitution **(SN^2)** reaction between **comp. A1** and ethyl 2-chlorooacetate in absolute ethanol and in the presence of potassium hydroxide as a catalyst. [21] **Comp. A2** characterized by strong stretching vibration band at 1750 due to aliphatic ester carbonyl group and the absence of weak band of SH at 2571. [19, 20]

The preparation of Compound A3 primarily involves the base-catalyzed hydrolysis of an ester through hydrazinolysis, conducted under standard basic conditions. This process occurs in two distinct stages: the initial and rate-limiting step features an interaction between two hydrazine molecules, during which a proton transfer takes place. Subsequently, the second stage proceeds with the gradual departure of one hydrazine molecule accompanied by the release of an alcohol molecule. [22] The **FTIR** analysis revealed characteristic absorption peaks corresponding to the primary amine groups of the hydrazide at 3314 cm^{-1} and 3147 cm^{-1}. Additionally, a distinct NH stretching vibration of the amide was observed at 3271 cm^{-1}, while the amide carbonyl (C=O) exhibited a strong band at 1653 cm^{-1}. Notably, the spectrum lacked any significant absorption associated with the carbonyl group of an aliphatic ester, indicating its absence. [19, 20]

The synthesis of compounds **A4**, **B1**, and **B2** involved the formation of hydrazone derivatives, created by the reaction of aldehyde groups with primary amines in an environment with slight acidity. [23] The **FTIR** spectra showed the

disappearance of the asymmetric and symmetric NH_2 stretching vibrations typical of hydrazide groups. Instead, broad absorption bands corresponding to phenolic OH stretching appeared, alongside distinct imine (-HC=N-) stretching vibrations observed at 1610 cm^{-1}, 1607 cm^{-1}, and 1604 cm^{-1} for compounds **A4**, **B1**, and **B2**, respectively**.** [19, 20] The **^{1}H NMR** spectrum of compound **A4** exhibited distinct peaks corresponding to hydroxyl protons appearing at 10.11 and 11.03 ppm, attributed to both free and intramolecular hydrogen-bonded forms. Additionally, two signals at 11.61 and 12.11 ppm were assigned to the **CONH** protons, reflecting the presence of E and Z isomers. Furthermore, the **CONH=CH** protons displayed splitting into two separate signals, indicative of syn and anti-syn conformers at [8.36 and 8.45]ppm. For **comp. B1** signals for OH proton of at 9.91&11.56ppm due to free and intramolecular hydrogen bond; for **comp. B2** signals for OCH_3 protons at 3.86ppm and OH proton at 9.62ppm; and signals of imine protons at 8.64ppm and 8.54ppm for **comp. B1** and **comp. B2** respectively. [24-31]

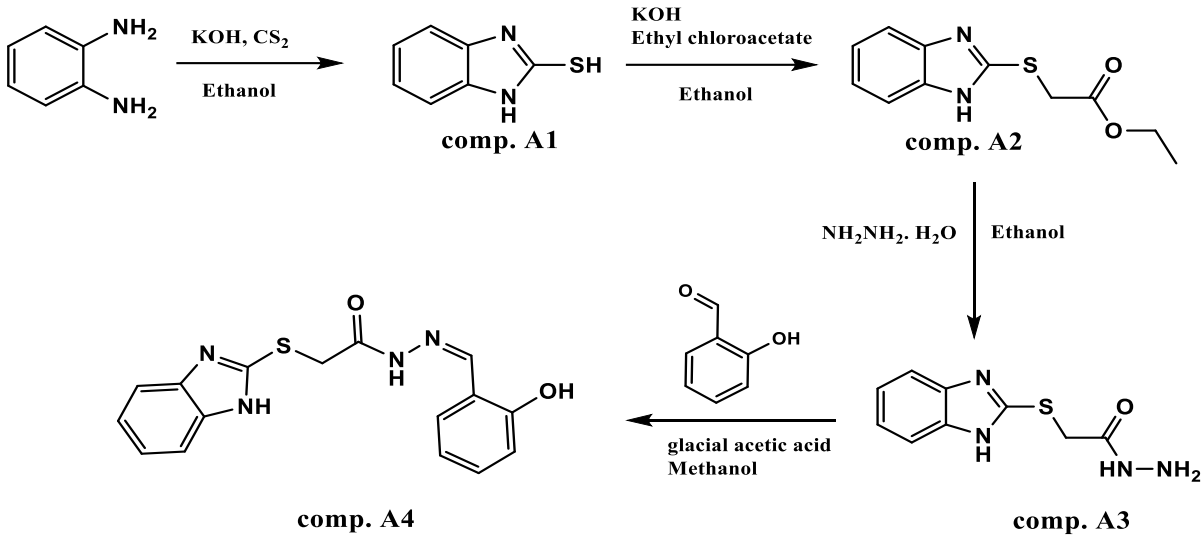


Figure 2 A. scheme for synthesis of targeted compound A4.

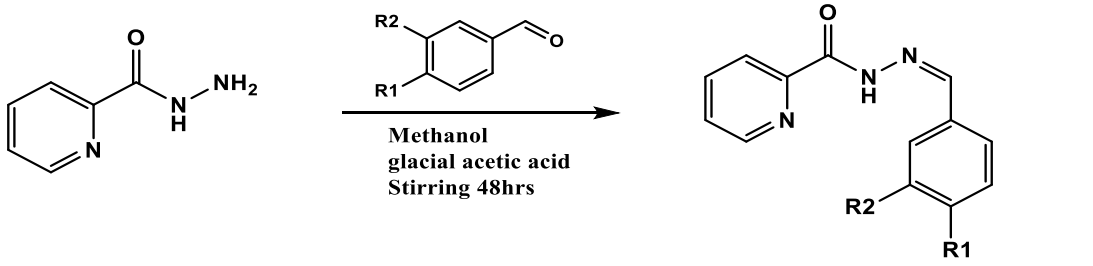


Figure 2 B. scheme for synthesis of targeted compounds B1 and B2.

Antibacterial evaluation

The synthesized compounds are structurally related to compounds synthesized by Saleh *et al*. [which were benzimidazole derivatives] and compounds synthesized by Kamat *et al*. [which were pyridine and thiazole based hydrazones]. These compounds showed activities against ***S. aureus***, ***E. coli***, ***K. pneumoniae*** and ***P. aeruginosa.*** [32, 33]

The antibacterial activities-as shown in table 1-of the targeted compounds **(comp. A4-B2)** were evaluated by well diffusion technique, using gram positive and gram negative bacteria, in a comparison with [amoxicillin and nitrofurantoin] as standard antibacterial agents. DMSO was used as a solvent and as a control. **Comp. A4** at concentration **1000µg/ml** showed antibacterial activity against ***K. pneumoniae*** and ***E. coli.*** The **comp.B1** at concentration **1000µg/ml** showed activity better than that of amoxicillin at **1000µg/ml** against ***S. aureus***, **comp. B2** showed less activity than amoxicillin against ***S. aureus***, this can be explained

on the basis of hydrophobicity [the more hydrophobic compound the more active against gram positive bacteria]. Neither **comp. B1** nor **comp. B2** was showed activity against ***E. coli*** and ***K. Pneumoniae*** [the more polar compound the more active against gram negative bacteria]. [32] The synthesized compounds are structurally related to compounds synthesized by Saleh *et al*. [which were benzimidazole derivatives] and compounds synthesized by Kamat *et al*. [which were pyridine and thiazole based hydrazones]. These compounds showed activities against ***S. aureus***, ***E. coli***, ***K. pneumoniae*** and ***P. aeruginosa.***

Table 1. Results of the antibacterial activities of synthesized compounds

Comp. name	Conc. µg/ml	Gram (+)ve	Gram (-)ve	
		S. aureus	*E. coli*	*K. pneumoniae*
		Zone of inhibition (mm)		
Comp. A4	10^3	-	13	9
Comp. B1	10^3	14	-	-
Comp. B2	10^3	10	-	-
Amoxicillin	10^3	11	10	12
Nitrofurantoin	10^3	21	16	20
DMSO	Solvent and control	-	-	-

(-)= No activity, slightly active (ZI =5-10 mm), moderately active (ZI= 10-15 mm), highly active (ZI= more than 15 mm).[33]

Conclusion

A series of novel hydrazone compounds were prepared using traditional synthesis techniques. These new molecules were thoroughly analyzed and tested for their ability to inhibit bacterial growth, demonstrating effectiveness against ***Escherichia coli***, ***Klebsiella pneumoniae***, and ***Staphylococcus aureus strains***.

Acknowledgment

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Conflicts of Interest

Not found.

Funding

Not found.

Ethics Statements

The study did not need ethical approval from an ethics committee.

Author Contribution

The authors confirm contribution to the paper as follows: supplying of *o*-phenylenediamine, study design, supervision on the progress of the reactions, interpretation of **FTIR and ^{1}HNMR**, and interpretation of antibacterial results: Mostafa F. Tawfeeq; supplying of picolinic acid hydrazide and providing essential references: Ali H. Abbas; synthesis of the compounds and performing **FTIR** analysis: Ahmed Y. Taha. All authors reviewed the results and approved the final version of the manuscript.

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تصنيع وتقييم مشتقات هيدرازون جديدة كمضادات بكتيرية

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[1] فرع الكيمياء الصيدلانية، كلية الصيدلة، جامعة تكريت، صلاح الدين، تكريت، العراق.

الخلاصة

العدوى البكتيرية تمثل تحدٍ مستمر بسبب المقاومة التي تطورها تلك البكتيريا. لذلك العديد من الأبحاث التي تستهدف تصميم مضادات بكتيرية جديدة تصدر سنويا. الحلقات الأروماتية الغير متجانسة تمثل مجالاً مهماً في تصنيع المركبات العضوية بسبب فعالياتها الحيوية. من ناحية أخرى قواعد شفت كذلك تمتلك العديد من الفعاليات الدوائية. التهجين-دمج مركبين لهما فعالية حيوية في جزيئة واحدة-هي طريقة مهمة في تصميم مركبات دوائية جديدة. المركبات الجديدة [مشتقات الحلقات غير المتجانسة-هيدرازونات] تم تصنعيها بعدة خطوات وتم تشخيصها عن طريق الكروماتوغرافيا (استشراب الطبقة الرقيقة) و مطيافيا باستخدام مطياف الأشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون. طريقة الانتشار استخدمت لتقييم الفاعليات المضادة للبكتريا للمركبات الجديدة. اظهرت المركبات فعالية ضعيفة ضد الكلبسيلة الرئوية، وفعالية جيدة ضد البكتريا الاشريكية القولونية والبكتريا العنقودية الذهبية.

الكلمات المفتاحية: عدوى بكتيرية، حلقات غير متجانسة، قاعدة شف، تهجين، مضاد بكتيري.