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Synthesis, Characterization, and Preliminary Evaluation of Biological Activity of 6-Mercaptopurine Heterocyclic Derivatives

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Abstract

Bacterial infections are ongoing challenging due to resistance developed by infectious bacteria. So that many researches targeting designing new antibacterial are published annually. Heterocycles are important field in organic synthesis due to their biological activities. Because of their important and considerable pharmacological activities; 1,3-benzothiazole derivatives had received special attention. The purines nucleus are present in several compounds that possess a wide range of biological activities such as antiviral, antifungal, antitumor and antibacterial activities. On the other hand, hydrazide Schiff's base derivatives (hydrazones) are good scaffolds for various pharmaceutical applications, and characterized by the presence of highly reactive group (–CO–NH–N=CH–). Hybridization-combing two pharmacophores to form one molecule-is the important method in designing new drugs. The new compounds [purine-6-thio acetyl amido benzothiazole and purine-6-thio-hydrazones] derivatives were synthesized through a multi-steps procedure starting from reacting 2-amino Benzothiazole derivatives with chloro acetyl chloride to synthesize compounds IIa and IIb, then 6-MP reacted either with compounds IIa and IIb to give targeted compounds IIIa and IIIb or with ethyl chloroacetate to give compound IV which by hydrazinolysis gave compound V which by condensation with 4-hydroxy benzaldehyde gave the targeted compound VI, the targeted compounds characterized by thin layer chromatography and spectroscopically by ATR-FTIR and ^{1}HNMR. Well diffusion method was used to evaluate the antibacterial activities of the new compounds. Compounds IIIa and IIIb showed good activities against gram positive and gram negative bacteria.

Keywords: Bacterial infections, Heterocycles, Benzothiazoles, Purines, Hybridization.

Introduction

Worldwide, a major health problem is the resistance to commercially available antibacterial agents such as β-lactams, quinolones, and macrolides. (1) Increase in morbidity and mortality, prolonged treatment period, and increased healthcare cost are consequences of infections caused by multidrug-resistant microorganisms. (2) Wise use of currently available antibiotics and the development of new anti-ineffective agents with enhanced activity and a novel mechanism of action are ways to counteract the challenge of microbial resistance. (3,4)

In the development of pharmacological active drugs; an essential role was played by heterocyclic chemistry. Many pharmacological active drugs are made up of heterocycles. The presence of heterocyclic fragments responsible for pharmacological activity of most of the pharmaceutical molecules. Numerous heterocyclic moieties five-or six-membered (mostly, nitrogen-containing or combinational set of nitrogen, Sulphur, and oxygen atoms in different positions) can be considered as a beneficial structure. (5)Among these heterocycles, benzothiazole has particular and wide use in experimental drugs.

Because of their powerful and considerable pharmacological activities; 1,3-benzothiazole derivatives had received special focus in synthetic and pharmaceutical chemistry studies. Therapeutic activities of benzothiazole are related to the fused rings of benzothiazole-one six-membered (benzene) and the other five-membered(thiazole). (6)

Purines [conjugated pyrimidine and imidazole rings] are heterocyclic aromatic compounds with most common expression is found in the form of DNA and RNA. The purines nucleus is present in several compounds that possess a wide range of biological activities such as antiviral, antifungal, antitumor and antibacterial activities. These pharmacological properties of purines in synthesizing several new 6-mercaptopurine 6-MP derivatives linked to heterocyclic compounds with expected

pharmacological activity as anticancer and /or antimicrobial. [7].

6-MP, figure 1, is cytotoxic prodrug that interfere with nucleic acid synthesis by either direct substitution of deoxythio GTP, thereby causing further modifications and mismatches upon replication, or by inhibition of de novo purine biosynthesis. They are used, in combination with other drugs, in the treatment of leukemia or in its remission maintenance programs. [8]

6-MP has been one of the most effective antineoplastic prodrugs for the last 45 years. It is widely used as an antileukemic agent in the treatment of childhood acute lymphoblastic leukemia. It also exerts immunosuppressive effects and is used in the treatment of inflammatory diseases such as Crohn's disease and ulcerative colitis. Although various analogs of mercaptopurine have been devised, they suffer major therapeutic disadvantages, particularly dose limiting toxicity. [8]

On the other hand, hydrazones constitute an important class of pharmacologically active drug molecules such as nitrofurantoin which is known to contain the hydrazone group. Hydrazones due to their diverse biological activities such as analgesic, anthelmintic, anticonvulsant, antidepressant, anti-inflammatory, antimalarial, anticancer, antiviral, and antibacterial which had attracted the attention of medicinal chemists. [9-12]

The aim was to synthesize new hybrid molecules combining either 6-MP with benzothiazole derivatives or 6-MP with hydrazone as possible antimicrobial agents.

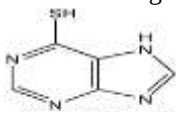


Figure 1. Structure of 6-mercaptopurine.

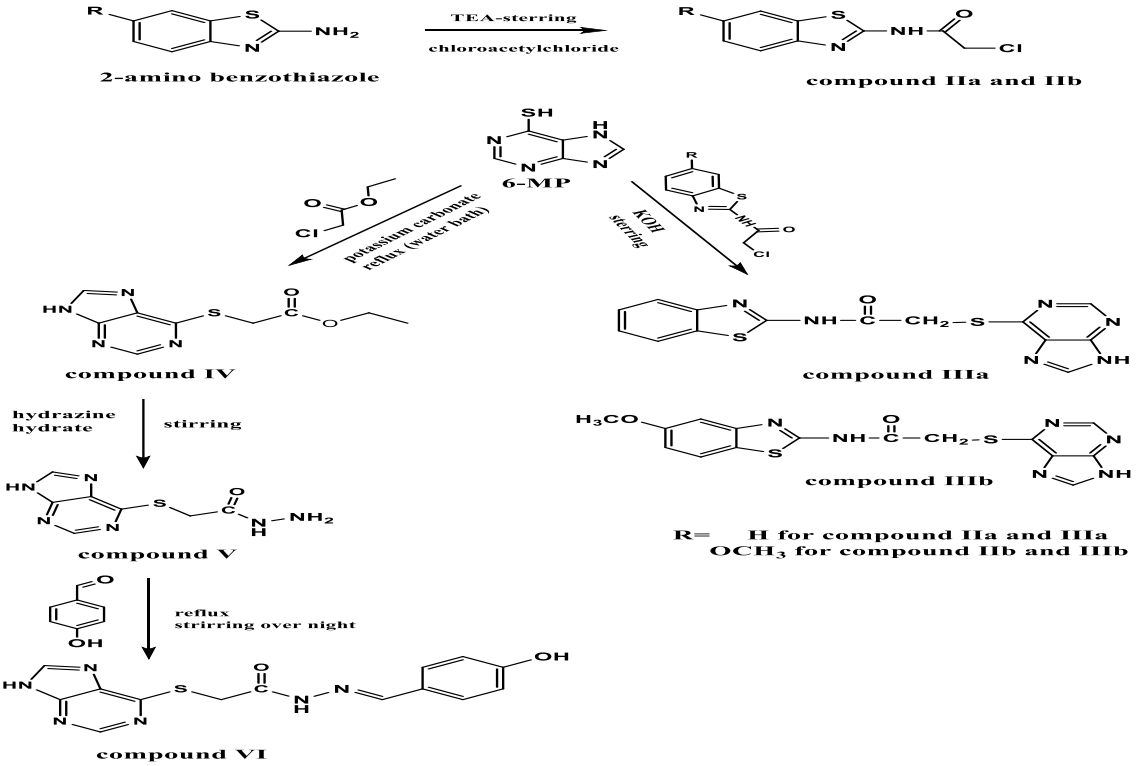
Materials and Methods

China and local commercial sources were chosen to supply the required chemicals. To monitor the progression of reactions, and to evaluate the purity of the synthesized compounds; a type of thin-layer chromatography (TLC) made of aluminum sheets pre-coated with Silica gel GF254 (type 60) was used. Depending on two solvent systems as eluents and exposure of sheets to UV-254nm, the locations of the synthesized compounds were visualized.

All synthesized derivatives were characterized by TLC and spectroscopically either by (Fourier-transformShimadzu Specac GS10800-RIRAffnity-1Spectrometer (Shimadzu, Japan) (FTIR)) which was performed at University of Baghdad/ College of Pharmacy and (Proton nuclear magnetic resonance (1HNMRBruker and Varian model ultra-shield (400) MHz spectrophotometer which was run at Basrah University.

Chemical Synthesis

The synthesis of the targeted **compounds IIIa, IIIb and VI**, scheme 1was proceeding as following



Scheme 1. Stepwise synthesis of the targeted compounds (IIIa, IIIb and VI).

Synthesis of N-(benzo[d]thiazol-2-yl)-2-chloroacetamide; Compound IIa and2-chloro-N-(6-methoxybenzo[d]thiazol-2-yl)ace amide; compound IIb:

Compound IIa and **IIb** were synthesized by dissolving (1gm, 6.6mmole) of 2-aminobenzothiazole derivatives in dry chloroform (10 mL) on an ice bath. Then, 1.85 mL of triethylamine was added drop by drop with continuous stirring and simultaneous dropwise addition of 1.1 mL of chloro-acetyl chloride. The stirring was continued overnight, where the solution's color turned from bright yellow to pink to beige suspension. After that, the mixture's volume was reduced, filtered, washing with hot distilled water and dried.[13,14]

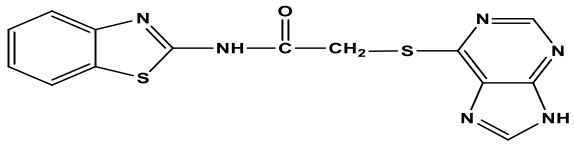
N-(benzo [d]thiazol-2-yl)-2-chloroacetamide ($C_9H_7ClN_2OS$) (IIa): beige powder, yield 75%.**FT-IR**in cm^{-1}: stretching vibration band of NH amide at 3363, stretching vibration band of amide carbonyl group at 1689. **^{1}HNMR**(400MHz, DMSO-d_6) in ppm: signals for -CH_2- protons [2H, s] at 4.50; signals for aromatic protons [4H, m] at 7.33-8.03; signal for amide proton -CONH- [1H, s] at 12.77.

2-chloro-N-(6-methoxybenzo[d]thiazol-2-yl)acetamide ($C_{10}H_9ClN_2O_2S$) (IIb): dark grey powder, yield 80%.**FT-IR**in cm^{-1}: stretching vibration band of NH amide at 3271, stretching vibration band of amide carbonyl group at 1712, stretching vibration band of C-O-CH_3 at 1280.**^{1}HNMR**(400MHz, DMSO-d_6) in ppm: signals for OCH_3 protons at 3.83 [3H,s]; signals for -CH_2- protons [2H, s] at 4.48; signals for aromatic protons [3H, m] at 6.95-7.87; signal for amide proton -CONH- [1H, s] at 12.72.

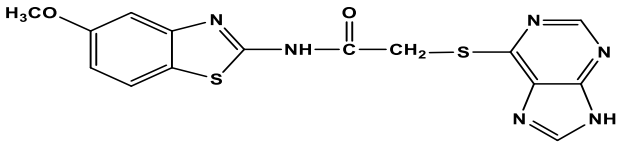
Synthesis of 2-((9H-purin-6-yl)thio)-N-(benzo[d]thiazol-2-yl)ace amide; Compound IIIa and 2-((9H-purin-6-yl)thio)-N-(5-methoxybenzo[d]thiazol-2-yl)acetamide; compound IIIb:

6-mercaptopurine (0.075gm, 0.442mmol) was dissolved in D.W with aid of equimoles of KOH, then (0.1 gm, 0.442mmol) of **compounds IIa and IIb** dissolved in 3ml of dimethylformamide were gradually added to the previous solution; then the mixture allowed to stir overnight. The products were collected by filtration, washed with hot D.W, diethyl ether and finally with chloroform, and dried.[15]

2-((9H-purin-6-yl)thio)-N-(benzo [d] thiazol-2-yl)acetamide ($C_{14}H_{10}N_6OS_2$) (IIIa): bright yellow powder, yield 58%. **FT-IR** in cm^{-1}: stretching vibration band of NH of benzimidazole at 3510, stretching vibration band of NH amide at 3379, stretching vibration band of amide carbonyl group at 1693 and stretching vibration band of C=N of heteroaromatic ring at 1597. **^{1}HNMR** (400MHz, DMSO-d_6) in ppm: signals for -CH_2- protons [2H, s] at 4.51; signals for aromatic protons [6H, m] at 7.29-8.66; signal for amide proton -CONH- [1H, s] at 12.77; signal for benzimidazole NH proton [1H, s] at 13.62.



2-((9H-purin-6-yl)thio)-N-(5-methoxybenzo [d]thiazol-2-yl) acetamide ($C_{15}H_{12}N_6O_2S_2$) (IIIb): grey powder, yield 58%. **FT-IR** in cm^{-1}: stretching vibration band of NH of benzimidazole at 3429, stretching vibration band of NH amide at 3271, stretching vibration band of amide carbonyl group at 1697. **^{1}HNMR** (400MHz, DMSO-d_6) in ppm: signals for OCH_3 protons [3H,s] at 3.84; signals for -CH_2- protons [2H, s] at 4.51; signals for aromatic protons [5H, m] at 6.93-8.69; signal for amide proton -CONH- [1H, s] at 12.74; signal for benzimidazole NH proton [1H, s] at 13.79.



Synthesis of ethyl 2-((9H-purin-6-yl)thio)acetate; Compound IV:

In presence of anhydrous potassium carbonate (1g); equimoles solution of 6-mercaptopurine (1.85g, 0.01mol) and ethyl chloroacetate (1.22 ml, 0.01 mol) in dry acetone (4ml) was refluxed on a water bath for 12hrthe solvent was removed by vacuum distillation and the residue was recrystallized from chloroform.[16]

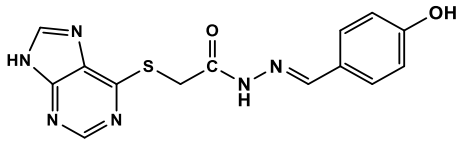
ethyl 2-((9H-purin-6-yl)thio)acetate ($C_9H_{10}N_4O_2S$): pinkish white solid, yield 70%.**FT-IR**in cm^{-1}: ester carbonyl group stretching vibration band at 1732, -CO- stretching vibration band of saturated aliphatic ester 1165 and stretching vibration band of C=N of heteroaromatic ring at 1597.

Synthesis of 2-((9H-purin-6-yl)thio)acetohydrazide; Compound V:

Compound IV (2.36g,0.01mol) and hydrazine hydrate (0.9 mL,0.02 mol) in ethanol (20 mL) were stirred at room temperature for about 12h. The resulting solid was filtered, dried and washed with hot ethanol to obtain **compound V**.[17-19] **2-((9H-purin-6-yl)thio)acetohydrazide ($C_7H_8N_6OS$)**: white solid, yield 75%.**FT-IR**in cm^{-1}:asymmetric stretching vibration band at of NH_2 at 3310, 3290 NH hydrazide stretching vibration band, symmetric stretching vibration band at of NH_2 at 3186, carbonyl stretching vibration band at 1639 (amide I) and bending vibration band of amide NH (amide II) at 1539.

Synthesis of 2-((9H-purin-6-yl)thio)-N'-(4-hydroxybenzylidene)acetohydrazide; Compound VI:

4-hydoxy benzaldehyde(1.22 g, 0.01 mol) was dissolved in 20mI methanol, 3 drops of glacial acetic acid was added; the solution stirred for 10 minutes, then (2.22 g, 0.01 mol) of **compound V**was added. The solution was refluxed for 5h and stirred overnight to allow the reaction to complete which was finished depending on TLC result. The precipitate was filtered, washed by hot ethanol and dried.[20-24] **2-((9H-purin-6-yl)thio)-N'-(4-hydroxybenzylidene)acetohydrazide ($C_{14}H_{12}N_6O_2S$):** pale yellow, yield 65%. **FTIR spectrum in cm^{-1}:** Broad OH stretching vibration band at 3275, NH stretching vibration band at 3213, stretching vibration band of carbonyl group at 1670, stretching vibration band of imine group at 1631 and stretching vibration band of C=N of heteroaromatic ring at 1600.**^{1}HNMR**(400MHz, DMSO-d_6) in ppm: signals for -S-CH_2- protons [2H, 2s] at 5.02&5.44; signals for aromatic protons [6H, m] at 6.81-7.97; signals for imine proton -CH=N [1H, 2s] at 8.26&8.31; signals for OH proton [1H, 2s] at 9.85&9.97; signal for amide hydrazone proton -CONH- [1H, 2s] at 11.54&11.64; and benzimidazole NH [1H, 2s] at 11.73.



Antimicrobial Assay

McFarland turbidity standard **(number 0.5)**-the source of bacterial and fungal suspension of nearly **(1.5×10^8 CFU/ml)**-was used to perform well diffusion assay. Then-by swabbing-the surface of MHA plates was inoculated with the bacterial and fungal suspension. Under a sterile hood, the excess liquid was dried by current of air. **(80µl)** from every concentration **[1000µg/ml]** of the synthesized compounds was poured into four wells which were made in each agar plate of examined bacteria (Gram (+)ve ***S. aureus*** and ***S. pyrogens*** and Gram(-)ve ***E. coli*** and ***P. aeruginosa***) and ***C. albicans*** as fungus. The plates were incubated for **24h** at **37°C**. The diameter of the inhibition zone formed around each well was measured to evaluate the antibacterial activities of the targeted compounds. [25]

Results and Discussion

Chemistry

Compounds I1a and **IIb** are the results of reaction between derivatives of 1,3-benzothiazole-2-amine and chloroacetyl chloride (amino lysis of acid chloride). The mechanism is similar to the one for the hydrolysis of an acid chloride. Mechanism for the amino lysis of an acid chloride involves step 1 which is nucleophilic addition of the amine to produce the tetrahedral intermediate, followed by deprotonation of the positively charged N. Finally, Cl^- is eliminated in Step 3.[13]

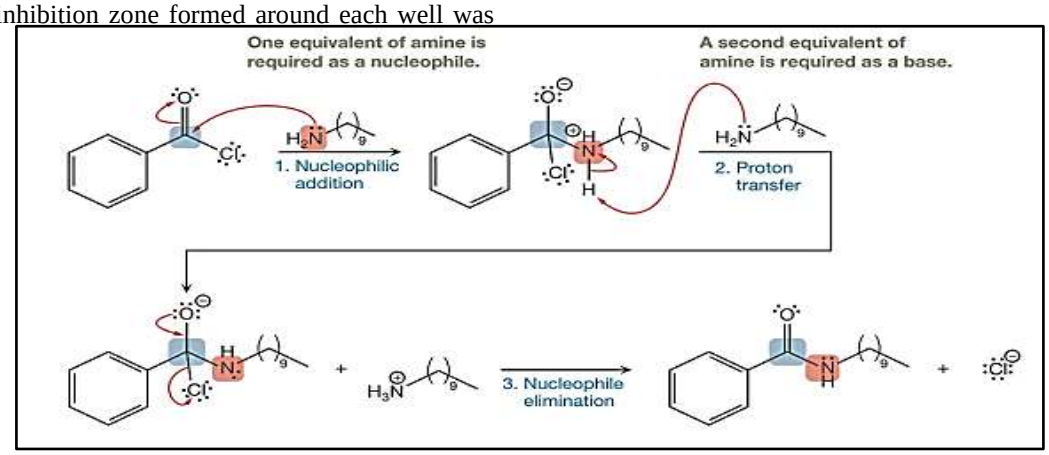


Figure 2. Suspected mechanism of compounds 1Ia and IIb formation.

Characteristics bands in **FT-IR**; for **compound IIa** stretching vibration band of NH amide at 3363, stretching vibration band of amide carbonyl group at 1689while for **compound IIb**

stretching vibration band of **C-O-CH$_3$** at 1280.Characteristics signals in **^{1}HNMR**; for **compound IIa** were signals for -CH_2- protons [2H, s] at 4.50 and signal for amide proton **-CONH-** [1H, s] at 12.77 while for **compound IIb** were signals for **-CH_2-** protons [2H, s] at 4.48 and signal for amide proton **-CONH-** [1H, s] at 12.72.[26-33]

Compounds IIIa, IIIb and IV were the result of a nucleophilic substitution **(SN^2)** reaction between **compounds 1, 2, ethyl chloroacetate** and 6-mercaptopurine in **DMF** either in the presence of potassium hydroxide as a catalyst for **compounds IIIa** and **IIIb** synthesis or in **absolute ethanol** and in the presence of potassium carbonate as catalyst for **compound IV** synthesis.[34] Characteristics bands in **FT-IR** were related to stretching vibration bands of **NH** of benzimidazole at 3510 and 3429 for **compound IIIa and IIIb** respectively, for **compound IV** characteristics bands were stretching vibrations at 1732 for ester carbonyl group and at 1165 for **-CO-** of saturated aliphatic ester. Characteristics signals in **^{1}HNMR**werethe appearance of signals for benzimidazole NH proton [1H, s] at 13.62 and 13.79for **compound IIIa** and **IIIb** respectively.[26-33]

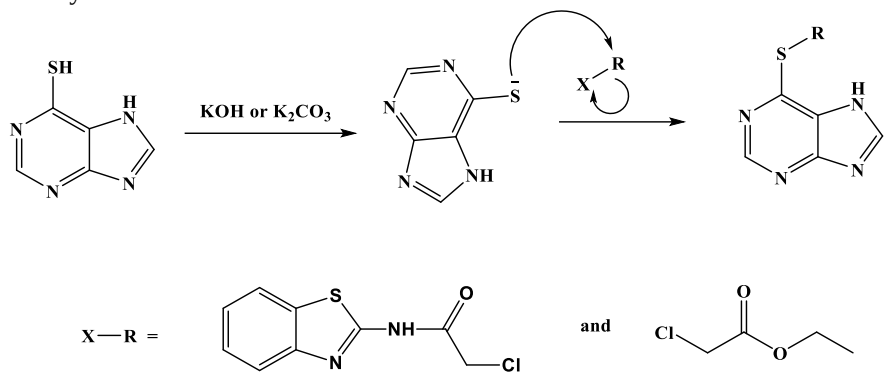


Figure 3. Mechanism of compounds IIIa, IIIb and IV formation.

The synthesis of **compound V (hydrazinolysis of ester)** which is essentially a base catalyzed hydrolysis which was run under normal basic condition. The synthesis its first step involves *two molecules of hydrazine*, in which a proton was being transferred between them and in the second step one hydrazine molecule will be left slowly with one molecule of alcohol. [35] **FT-IR** spectrum was characterized by stretching vibration bands at 3310, 3290, 3186 and 1639 due to hydrazide group -$CONHNH_2$- also strong vibration band of aliphatic ester carbonyl group was absent. [26-28]

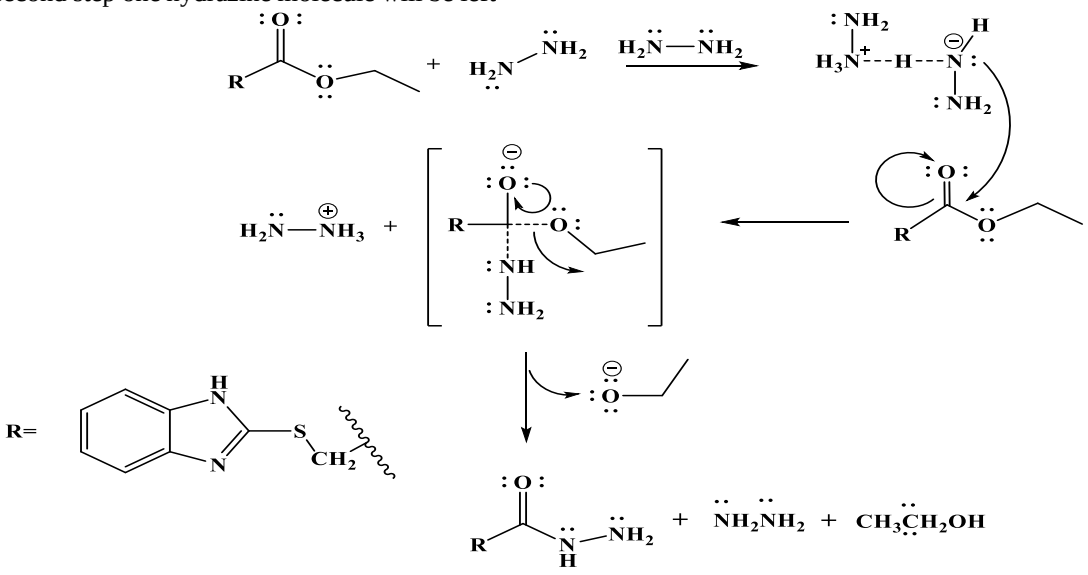


Figure 4. Mechanism of compound V formation.

Compound VI was Schiff base product of hydrazone type; which resulted from reaction between aldehydes with primary amines in mildly acidic conditions and involves six steps; the first three steps produce an intermediate called a *carbinolamine* and the last three steps convert the *carbinolamine into an imine*. [36,37] Its FT-IR spectrum characterized by disappearance of asymmetric and symmetric stretching vibration bands of primary amine and the appearance of new band of OH group (broad) and band related to

imine group at 1631. **^{1}HNMR** were characterized by the appearance of signals for OH proton at 9.85&9.97ppm and signals for imine proton -CH=N at 8.26&8.31ppm due to due to ***syn/anti-syn conformers.*** Signals for amide hydrazone proton -CONH- at 11.54&11.64ppm because of ***E*** and ***Z*** isomers.[26-33]

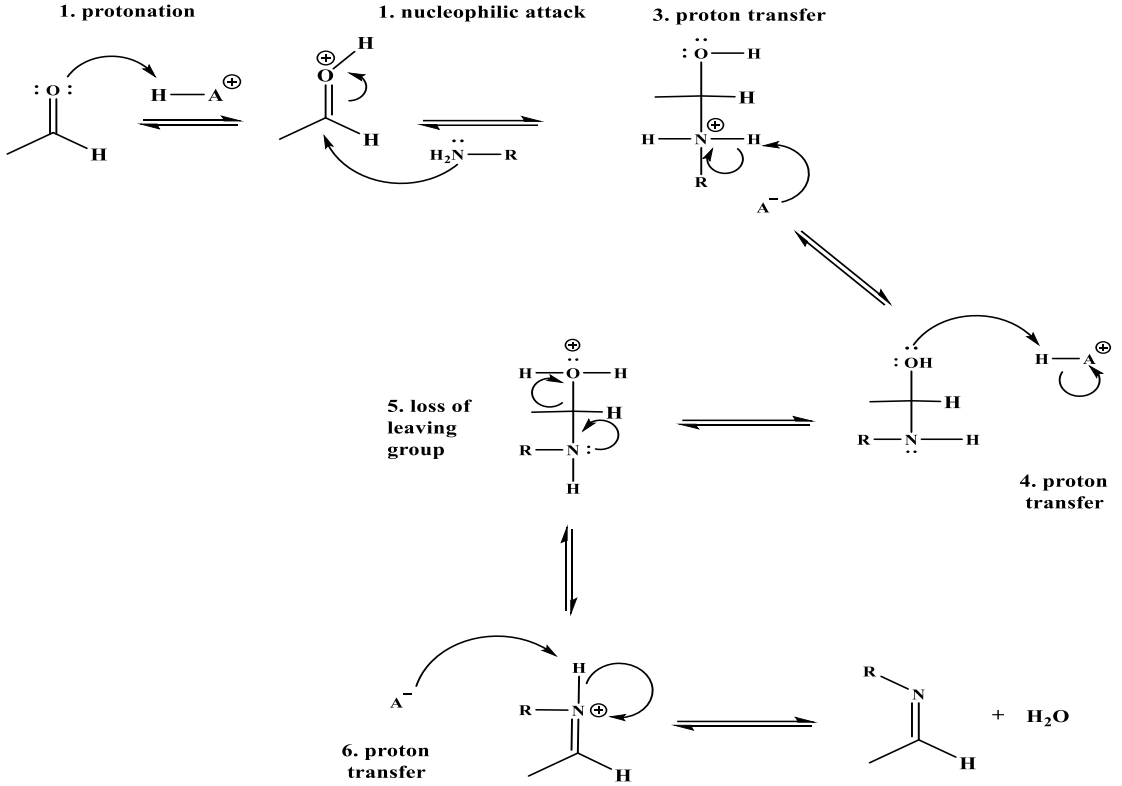


Figure 5. Mechanism of compound VI formation.

Antimicrobial evaluation

The antimicrobial activities of the targeted compounds **(compounds IIIa, IIIb and VI)** were evaluated by well diffusion technique, using gram positive, gram negative bacteria and fungi, in a comparison with amoxicillin, trimethoprim and ciprofloxacin as standard agents while nystatin is the standard for antifungal effect. DMSO was used as a solvent and as a control. **Compound IIIa** showed anti-bacterial activity against ***S. aureus*** comparable to amoxicillin. **Compound IIIa** and **compound IIIb** showed moderate activities against ***P. aeruginosa***, while **compound VI** showed activity against ***E. coli***. **Compound IIIb** was the best one showed activities against three of four bacteria. No derivative was active against ***C. albicans***.

Table 1. Results of the antimicrobial activities of synthesized compounds

Comp. name	Conc. µg/ml	Gram (+)ve		Gram (-)ve		Fungi
		S. aureus	*S. pyrogens*	*E. coli*	*P. aeruginosa*	*C. albicans*
		Zone of inhibition (mm)				
Compound IIIa	10^3	21	11	-	12	-
Compound IIIb	10^3	19	12	-	15	-
Compound VI	10^3	-	-	11	-	-
Amoxicillin	10^3	27	-	40	22	-
Trimethoprim	10^3	41	38	20	14	15
Ciprofloxacin	10^3	44	44	49	38	27
Nystatin	10^3	-	-	-	-	12
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). [38,39]

Conclusion

New 6-mercaptopurine derivatives were successfully synthesized by conventional method. They were characterized and evaluated for their antimicrobial activities which had shown activities against ***S. aureus, S. pyrogens, E. coli*** and ***P.***

aeruginosa. **Compound IIIa** showed best anti-bacterial activity against ***S. aureus*** among all derivatives while **compound IIIb** showed best anti-bacterial activity against ***P. aeruginosa*** among all derivatives. **Compound IIIb** was the best one showed activities against three of four bacteria. No derivative was active against ***C. albicans***.

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 starting materials, study design, supervision on the progress of the reactions, interpretation of **FTIR and ^{1}HNMR**, and interpretation of antibacterial results: Muthanna S. Farhan; synthesis of the compounds, providing essential references and performing **FTIR** analysis: Noor S. Hashim. All authors reviewed the results and approved the final version of the manuscript.

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تخليق، تشخيص وتقييم أولي للفعالية الحيوية لمشتقات حلقية غير متجانسة من ٦-ميركابتو بيورين

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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. تركيز خاص حصلت عليه مشتقات ١،٣-بنزوثيازول بسبب فعالياتها الدوائية المهمة والمعتبرة. نواة البيورينات موجودة في مركبات تمتلك مدى واسع من الفعاليات الحيوية كان تكون مضادات للفيروسات، مضادات للفطريات، مضادات للأورام ومضادات للبكتريا. من ناحية أخرى تعتبر قاعد شف المشتقة من الهيدرازايد (الهيدروزونات) وحدات بناء جيدة في مختلف التطبيقات الصيدلانية وتتميز بوجود مجموعة عالية الفعالية -(CONH-N=CH). التهجين-دمج مركبين لهما فعالية حيوية في جزيئة واحدة-هي طريقة معتادة في تصميم مركبات دوائية جديدة. المركبات الجديدة من مشتقات (بيورين-٦-ثايو أسيتيل اميدو بنزوثيازول و بيورين-٦-ثايو-هايدروزون) تم تصنعيها بعدة خطوات بداية من تفاعل مشتقات ٢-امينو بنزوثيازول مع كلوريد كلورو أسيتيل معطيا المركبات IIaوIIb بعد ذلك ٦-مركابتوبيورين تمت مفاعلته اما مع المركبات IIaوIIb معطيا المركبات الهدف IIIaوIIIb او مع اثيل كلورو الخلات معطيا المركب IV الذي عن طريق التحلل بوجود الهيدرازين هيدرات اعطى المركب V الذي اعطى المركب الهدف VI عن طريق تفاعل تكثيف مع ٤-هيدروكسي بنزالديهايد المركبات الهدف شخصت عن طريق الكروماتوغرافيا (استشراب الطبقة الرقيقة) ومطيافيا باستخدام مطياف الأشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون. طريقة الانتشار استخدمت لتقييم الفاعليات المضادة للبكتريا للمركبات الجديدة. المركبات IIIaوIIIb أظهرت فعالية جيدة ضد البكتيريا الموجبة والسالبة للغرام.

الكلمات المفتاحية: عدوى بكتيرية، حلقات غير متجانسة، بنزوثيازول، بيورينات، تهجين.