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Preparation and characterization of thiazines compounds derived from sulfamethoxazole, and evaluation of some of their antibacterial properties

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Abstract

The 2-Aminobenzothiazol (A) was prepared by reacting Sulfamethoxazole with potassium thiocyanate in the presence of bromine as a catalyst. The Schiff's base derivatives (H1-H3) were also prepared by reacting 2-Amino benzothiazol (A) with benzaldehyde derivatives in the presence of glacial acetic acid as a catalyst and ethanol as a solvent. Preparation of thiazines were derived from Schiff's base derivatives (H1-H3) with the appropriate solvent. The effectiveness of some compounds against four types of bacteria (E. coli, S. aureus, S. pyogenes, K. pneumonia) was tested and the results showed that these prepared compounds have good to moderate activity against the bacteria used in the experiment at different concentrations (0.1, 1, and 10 mg/mL) compared to the standard antibiotic (Fluconazole) at a concentration of 5 mg/ml.

Introduction:

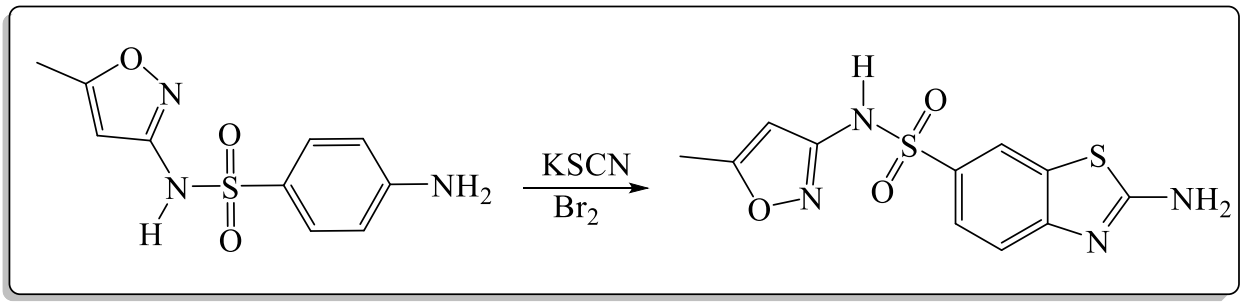
Sulfamethoxazole (SMZ or SMX) IUPAC, also known as 4-Amino -N-(5-methylisoxazol-3-yl) benzenesulfonamide, is a broad-spectrum antibiotic, it was first certified in the United States in 1961. It is currently most commonly used in conjunction with trimethoprim (abbreviated SMX-TMP). Sulfamethalazole, sulfisomezole, and sulfamethazole are other names for it. It is used to treat a variety of bacterial infections and is effective against both positive and negative microorganisms [1]. 2-Aminobenzothiazole is a phenyl ring fused thiazole ring aromatic chemical compound with the molecular formula $C_7H_6N_2S$ [2]. Because of their synthetic usefulness and broad range of biological actions, several 2-aminobenzothiazole derivatives play an important role in medical and pharmaceutical chemistry, they showed different synthetic derivatives of 2- Aminobenzothiazole and their derivatives have different biological activities and pharmacological [3, 4]. Thiazine is a six-membered heterocyclic with two heteroatoms (N and S) positioned at 1,3 places in the heterocyclic ring, thiazines are particularly useful units in the realm of medical and

pharmaceutical chemistry, and they have been shown to have a wide range of biological functions [5-7]. A vast set of dyes, including methylene blue thiazine, have phenothiazine structures and are employed as dyes, tranquilizers, and insecticides, thiazine can help you lose some of the additional water weight on your stomach, thiazine is a pretty basic diuretic supplement that eliminates water and increases vascularity. It is also used in medicine as an anabolic agent [8-9]. The active core of cephalosporins, which are among the most extensively used β- lactum antibiotics, is the 1,3-thiazine nucleus [10-11]. The ability of thiazine to exhibit antitubercular, antibacterial in which inactivate HIV in biological fluid and used as cannabinoid receptor agonist [12-14].

Practical part:

1. Preparation of 2-Amino benzothiazol (A)

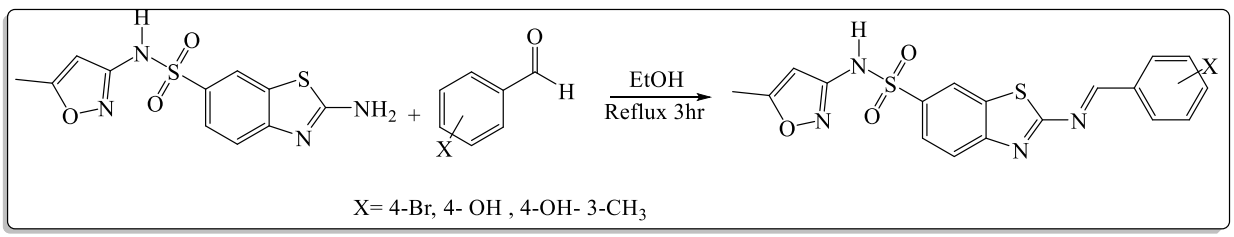
Dissolved 0.002 mol, 0.5 gm of Sulfamethoxazole in glacial acetic acid as a solvent with the addition of 0.002 mol, 0.37 gm potassium thiocyanate in the presence of bromine. The mixture was refluxed for 10 hours, was neutralized with 10% sodium hydroxide, the reaction mixture was left to cool, filtered and the precipitate was collected and recrystallized from ethanol[15]. The product has Molecular Formula $C_{11}H_{10}N_4O_3S_2$, color Orange, mp=134-132 ^oC and yield= 84%.As shown in the following Scheme (1):



Scheme 1: Equation for the preparation 2-Amino benzothiazol (A)

2. General method for Preparing of Schiff's Bases

0.0016 mol, 0.5 gm of 2-Amino benzothiazol (A) was mixed with 0.0016 mol of different benzaldehyde in the presence glacial acetic acid as a catalyst and ethanol as a solvent. The mixture was reflux 3 hours. Leave the mixture to cool, wash with water, filter and collect the precipitate. Table (1) shows some of the physical properties for the prepared compounds (H1-H3), as shown in the following Scheme (2):



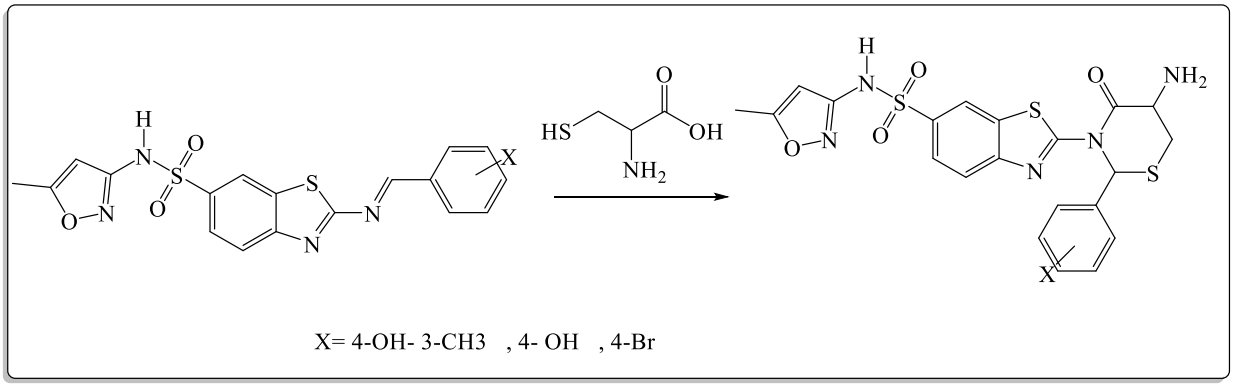
Scheme 2: Equation for the preparation of Schiff's Bases derivatives (H1-H3)

Table 1: Some physical properties of the prepared derivatives (H1-H3).

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P °C	Yield %
H_1	$C_{18}H_{13}BrN_4O_3S_2$	477.35	Dark Yellow	142-144	66
H_2	$C_{18}H_{14}N_4O_4S_2$	414.45	green	138-140	70
H_3	$C_{19}H_{16}N_4O_4S_2$	428.48	Yellow-Green	150-152	75

3. Preparation of Derivatives of Thiazines (H4-H6)

0.001 mol, of Schiff's bases (H1-H3) was mixed with 0.001 mol, 0.5 gm of the amino acid cysteine in the presence of zinc chloride as a catalyst and Dioxane as a solvent. The mixture was refluxed for 10 hours. The mixture was left to cool, wash with water, filter and collect the precipitate. Table (2) shows some of the physical properties of the prepared compounds (H4-H6), as shown in the following Scheme (3):



Scheme 3: Equation for preparing the derivatives of Thiazines (H4-H6)

Table (2) Some physical properties of Thiazines (H4-H6)

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P °C	Yield%
H_4	$C_{21}H_{18}BrN_5O_4S_3$	580.49	Yellow	225-223	32
H_5	$C_{21}H_{19}N_5O_5S_3$	517.59	Yellow	204-202	28
H_6	$C_{22}H_{21}N_5O_5S_3$	531.62	Dark Yellow	227-225	52

Results and discussion:

The infrared spectra of the prepared compound (A1) indicated the appearance of the symmetrical and asymmetrical amine group ($-NH_2$) for 2-Amino benzothiazol (A) at (3361,3467 cm^{-1}). Moreover, the appearance of the (νC-H arom.) at (3072 cm^{-1}). The appearance of absorption bands for (νC-H alip.) at (2975 cm^{-1}). The results were in agreement with the literature [16-18]. Show fig. (1), the FT-IR spectrum of compound (A1)

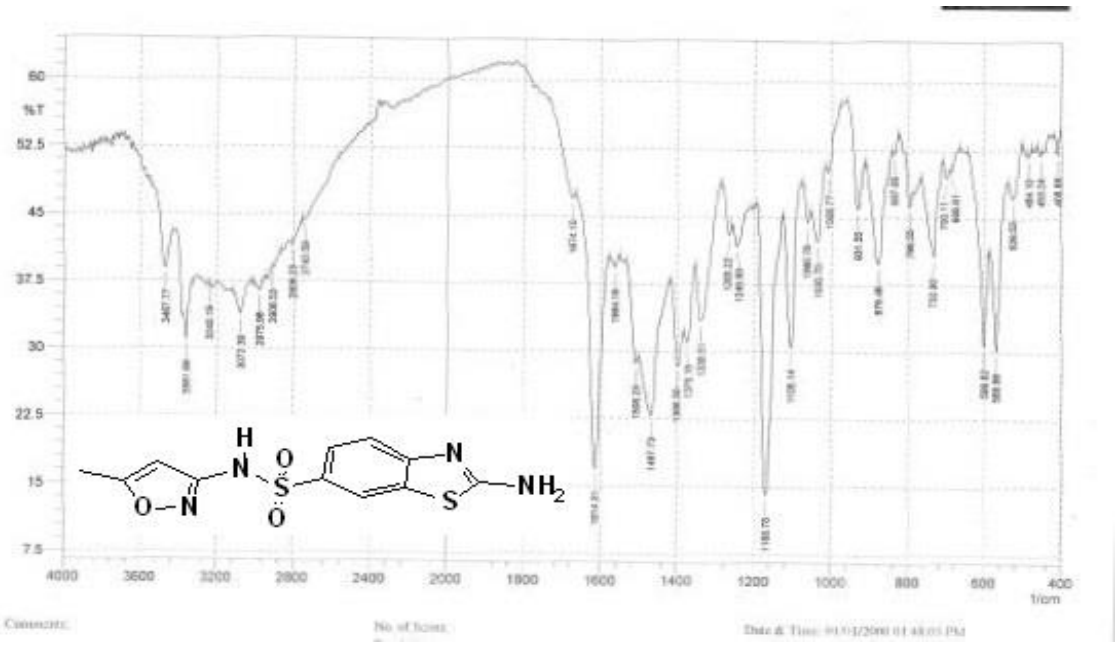


Fig. 1: The FT-IR spectrum of compound (A1)

The structural formula of the compound was confirmed by proton 1H-NMR spectroscopy. The compound (A) showed a Singlet signal at [δ=2.31 ppm (s,3H, CH_3)]. A Singlet signal appeared at [δ=6.14ppm, (s,1H)] refers to a proton isoxazole ring and the singlet signal at [δ=7.07ppm, (s,2H, NH_2)]. While the multiple signals at [δ=7.86-8.42ppm,(m,3H, CH Arom)]. and Singlet signal appeared at [δ =11.27 ppm, (s,1H,NH)][19]. Show fig.(2) ^{1}H-NMR spectrum of compound A

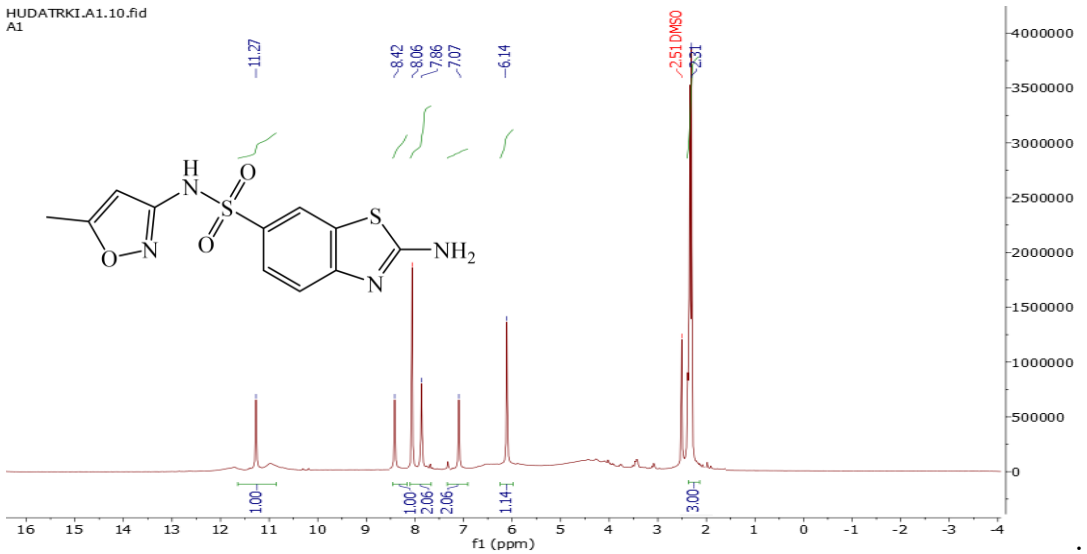


Fig. 2: ^{1}H-NMR spectrum of compound A.

The structures of the synthesized Schiff's bases were confirmed by their FT-IR spectra, which showed the disappearance of the characteristic absorption frequencies of both (C=O) at (1720-1740)cm^{-1} and (-NH_2) at (3300-3500)cm^{-1} of the aldehyde and the primary amine respectively, and the appearance of the stretching absorption bands of azomethine group (C=N) within the range (1695- 1674)cm^{-1}, in addition to the appearance of stretching

absorption of the other groups data are given in table (3) [18-19]. the fig.(3) the FT-IR spectrum of compound H2.

Table 3: FT-IR spectrum data of Schiff's Bases derivatives (H1-H3)

IR (KBr) cm^{-1}									
Comp. No.	NH	C-H arom.	C-H alip.	C=N	C=C		SO_2 Asym	SO_2 Sym	Others
H1	3357	3078	2995	1695	1589	1465	1338	1265	C-Br 597
H2	3357	3020	2927	1674	1598	1458	1338	1217	OH 3418
H3	3360	3087	2966	1674	1598	1463	1332	1267	OH 3427

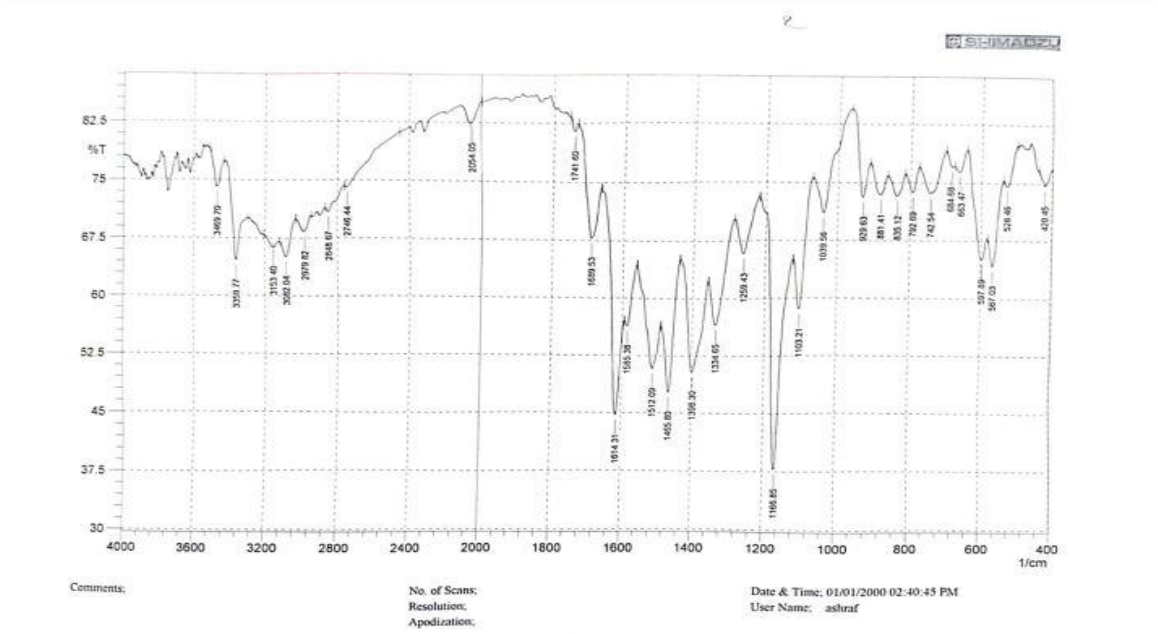


Fig. 3: The FT-IR spectrum of compound H2

^{1}HNMR spectra confirm the structures of synthesized compounds. Fig. (4): ^{1}H NMR spectrum of compound H3 and table (4).. Chemical Shift δ ppm of (H_1-H_3).

Table 4: Chemical Shift δ ppm of (H_1-H_3).

Comp. No.	Alkyl groups	Five ring	CH=N	Ar-H	NH	others
H1	3H s	1H s	1 H s	7H m	1H s	…….
	2.31	6.14	9.09	7.76-8.39	11.27	
H2	3H s	1H s	1 H s	7H m	1H s	OH 1Hs
	2.19	6.15	9.15	6.95-8.41	11.48	9.78
H3	6H s	1H s	1 H s	6H m	1H s	OH 1Hs
	2.13, 2.31	6.15	9.03	6.98-8.46	11.34	9.77

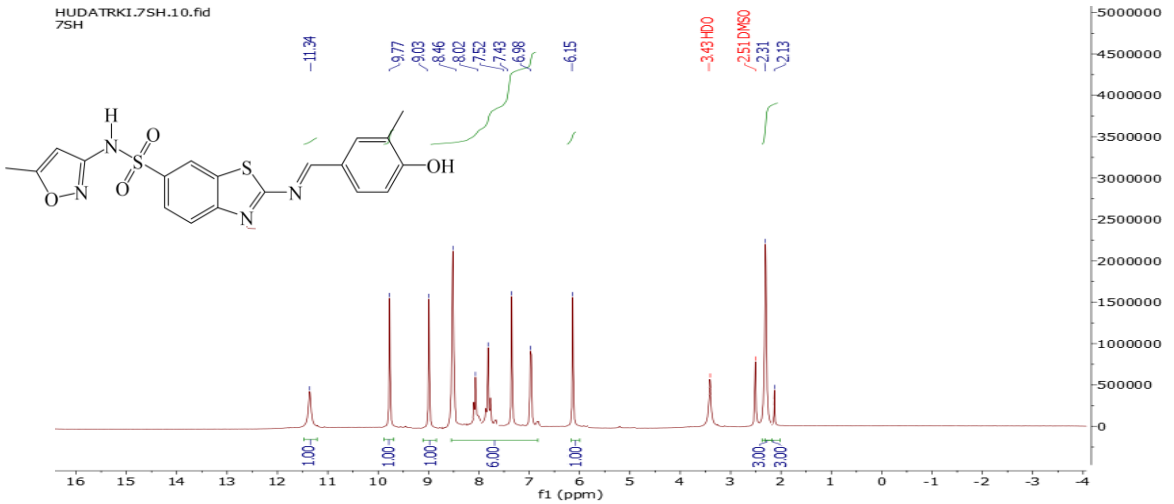


Fig. 4: ^{1}H-NMR spectrum of compound H3.

The prepared of Thiazines (H4-H6) were characterized by FTIR. The spectra indicated the disappearance of the stretch vibration absorption bands of (C=N) in the Schiff's Bases. The appearance of the absorption bands of the amine group (N-H) at (3477- 3413 cm^{-1}) in addition to the appearance of (νC-Harom) absorption bands within the range (3031-3029 cm^{-1}) in the table (5). the fig.(5) the FT-IR spectrum of compound H4.

Table 5: FT-IR spectrum data of Thiazines (H4-H6)

IR (KBr) cm^{-1}										
Comp. No	NH2		NH	C-H arom.	C-H alip.	C=O lactam	C=C		C-S	Others
H 4	3477	3417	3230	3029	2916	1618	1587	1488	675	C-Br 540
H 5	3477	3413	3232	3031	2930	1618	1589	1488	675	OH 3548
H 6	3471	3415	3210	3028	2918	1618	1587	1488	675	OH 3548

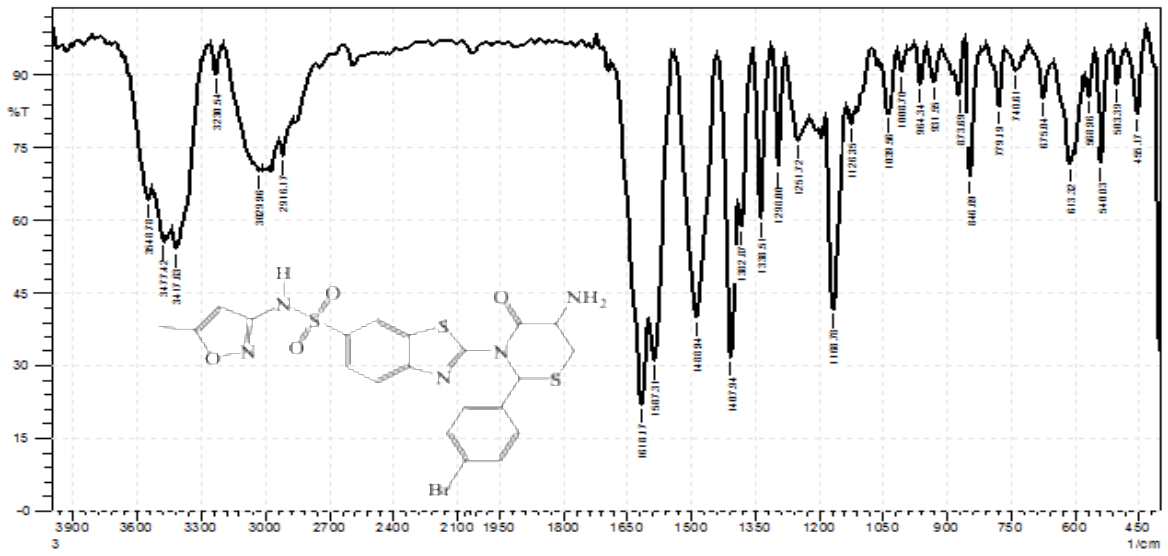


Fig. 5: The FT-IR spectrum of compound H4.

^{1}HNMR spectra confirm the structures of synthesized compounds. Fig.(6): ^{1}H NMR spectrum of compound H5 and and table (6). Chemical Shift δ ppm of (H_5-H_6).

Table 6: Chemical Shift δ ppm of (H_5-H_6).

Comp. No.	Alkyl groups	Thiazines ring	Isoxazole ring	Ar-H	NH2	NH	others
H5	3.32(3H s)	3.06-5.91 (4H s,m)	6.04(1H s)	6.71-8.43 (7H m)	2H s 8.80	11.34 (1H s)	OH 1Hs 9.06
H6	2.32, 2.09 (6H s)	2.93-5.88 (4H s, m)	6.15(1H s)	7.06- 8.46 (6H m)	2H s 8.83	11.28 (1H s)	OH 1Hs 9.78

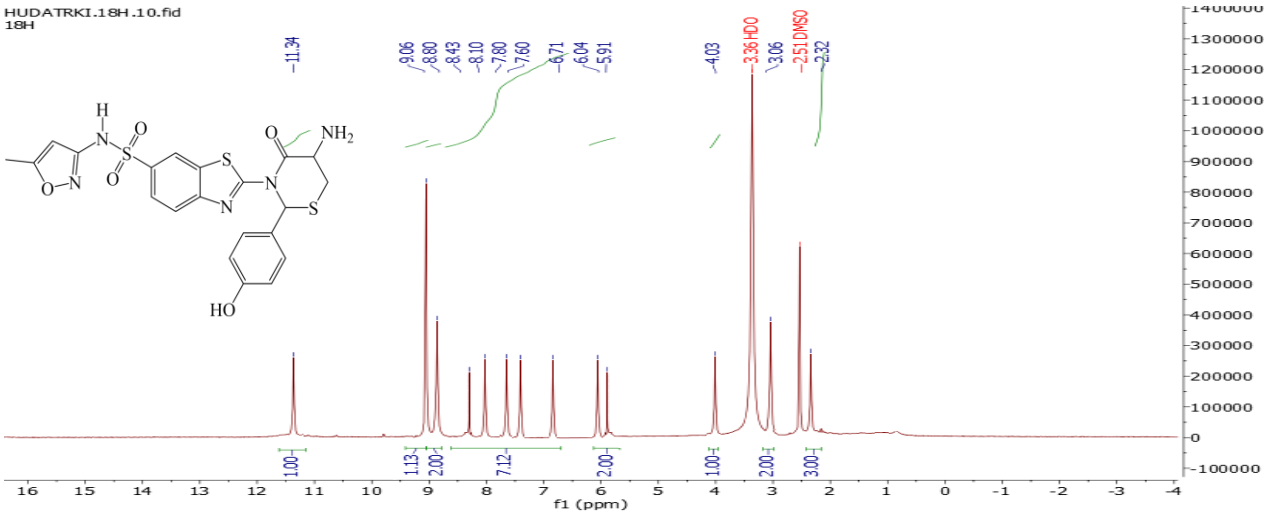


Fig. 6: ^{1}H-NMR spectrum of compound H5

The mass spectrum of the compound (H4) was recorded, which showed a main peak at m/z + = 467 and with a relative abundance (12%) due to the molecular weight of the compound [$C_{18}H_{18}N_4O_5S_3$], Fig. (7). Scheme (4) showed fragments of compound H4

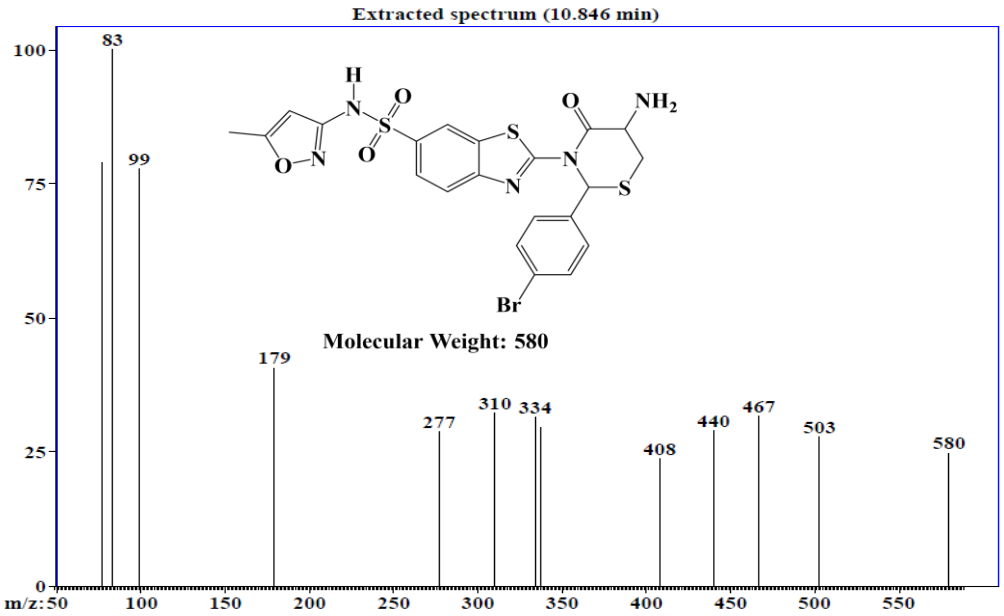
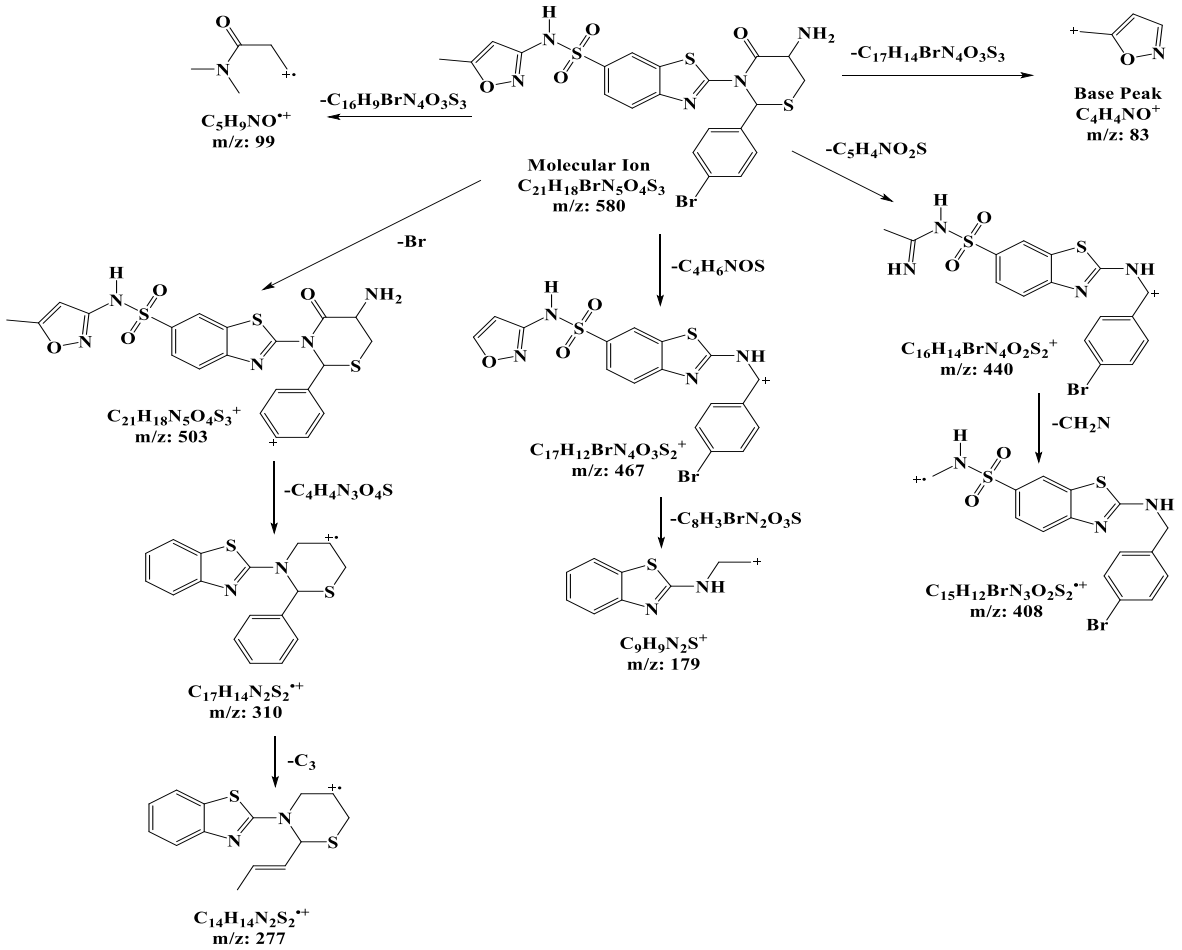


Fig. 7: Mass spectrum of compound H4



Scheme 4: fragments of compound H4

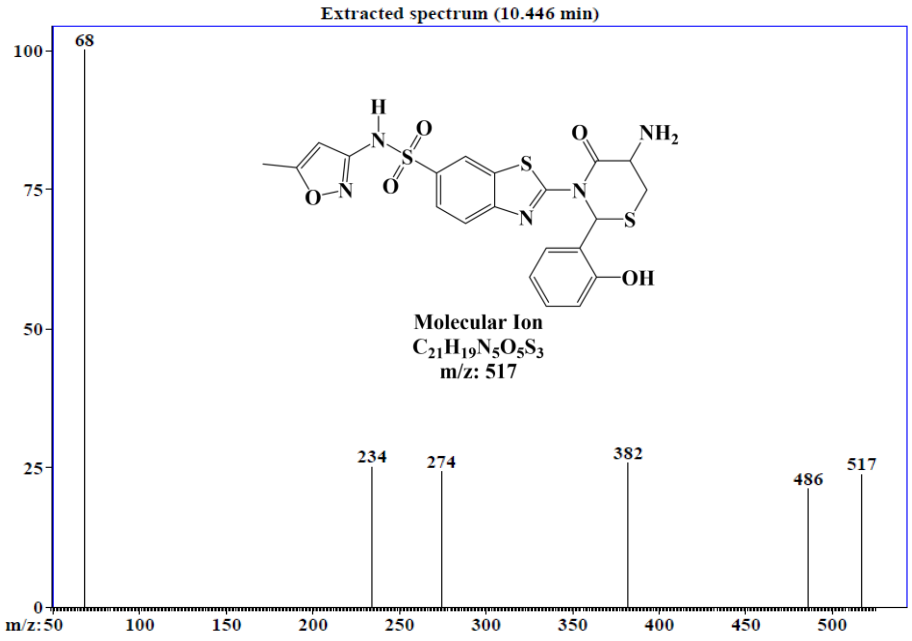
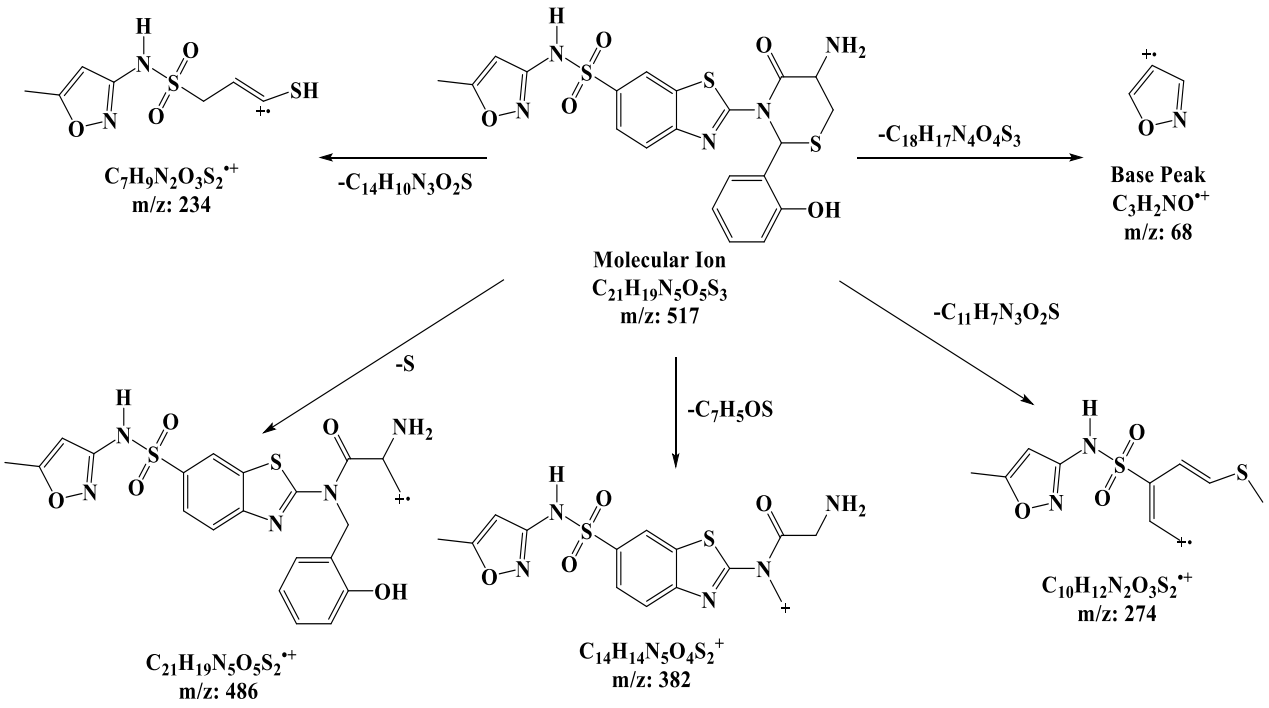


Fig. 8: Mass spectrum of compound H5



Scheme 5: fragments of compound H5

Evaluation of the biological activity of some prepared compounds [20]

The biological activity of some prepared compounds (A1, H3, H6) was evaluated on four types of bacteria isolates (***E. coli***, ***S. aureus***, ***S. pyogenes*** and ***K. pneumonia***). The results were compared with the standard antibacterial (Fluconazole), and showed that these compounds have the ability to Inhibition is good to medium by using different concentrations of compounds (0.1 mg/ml), (1 mg/ml), (10 mg/ml) compared to the inhibition with the standard antibacterial (Fluconazole) with a concentration of 5 mg/ml. Shown in Table (7).

Table (7): Anti-bacterial activity data for compounds (A1, H3, H7) and measured mm

Com No.	*Conc.%*	*E. coli*	*Staphylococcus aureus*	*Streptococcus pyogenes*	*Klebsiella pneumonia*	Control
	0.1	1mm	5mm	--	5mm	--
A1	1	2mm	10mm	--	7mm	--
	10	2mm	25mm	10mm	15mm	--
	0.1	3mm	36mm	3mm	5mm	--
H3	1	3mm	47mm	5mm	10mm	--
	10	3mm	55mm	15mm	15mm	--
	0.1	1mm	3mm	--	--	--
H6	1	2mm	10mm	--	--	--
	10	2mm	25mm	--	--	--

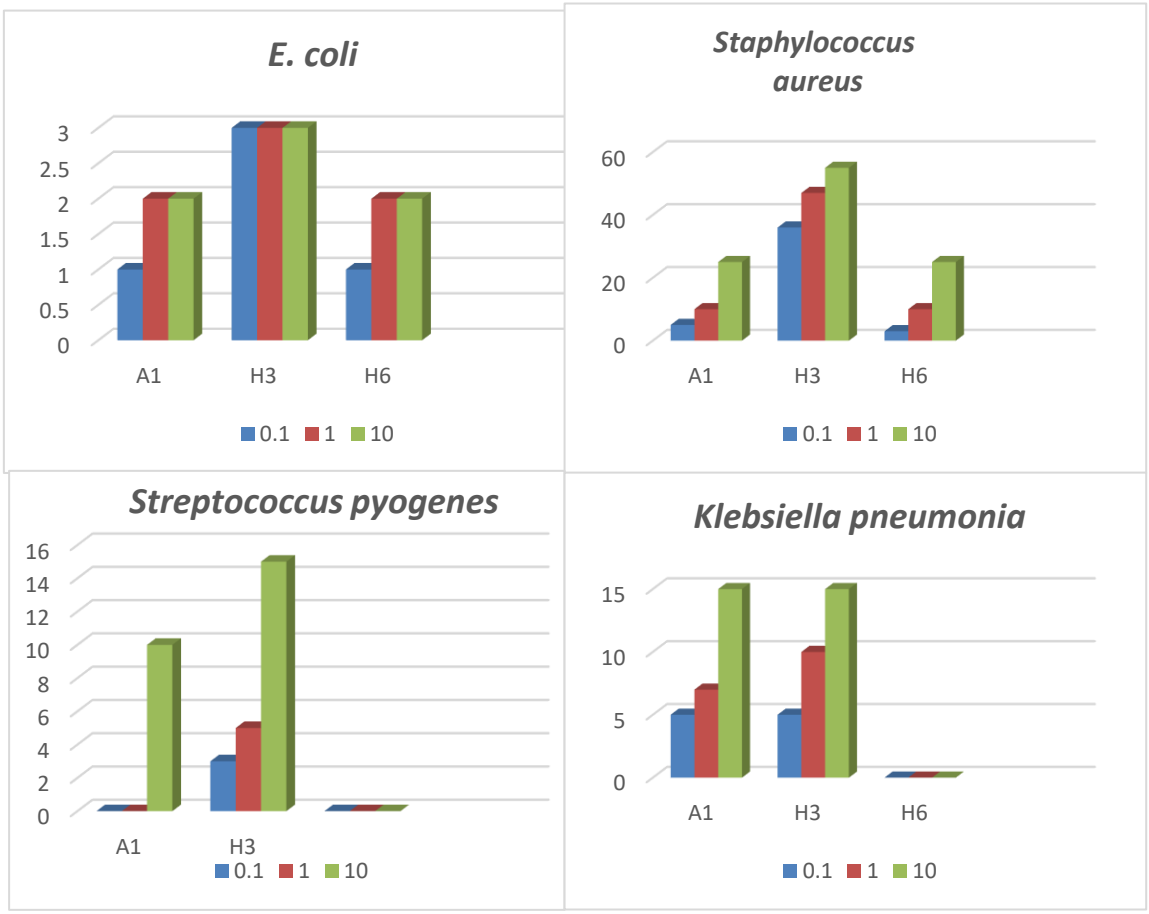


Diagram 1: Inhibitory activity of synthesized compounds (A1, H3, H6) against *E. coli*, *S. aureus*, *S. pyogenes* and *K. pneumonia*

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تحضير وتشخيص مركبات الثيازين المشتقة من سلفاميثوكسازول وتقييم بعض خصائصها المضادة للبكتيريا

هدى تركي مهدي [1]*، ملاذ خلف رشيد[1]
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معلومات البحث:
تأريخ الاستلام:2023/7/9
تاريخ التعديل : 2023/7/12
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الكلمات المفتاحية:
2-أمينو بنزوثيازول, الثيازينات, سلفاميثوكسازول, مضاد البكتريا

معلومات المؤلف

الايميل:
الموبايل:

الخلاصة:
تم تحضير 2-أمينو بنزوثيازول (أ) عن طريق تفاعل سلفاميثوكسازول مع ثايوسيانات البوتاسيوم في وجود البروم كعامل مساعد. كما تم تحضير مشتقات قاعدة شيف (H1-H3) عن طريق تفاعل 2-أمينو بنزوثايزول (أ) مع مشتقات البنزالديهايد في وجود حمض الخليك الثلجي كمحفز والإيثانول كمذيب. تحضير الثيازينات المشتقة من مشتقات قاعدة شيف (H1-H3) بالمذيب المناسب. تم اختبار فعالية بعض المركبات ضد أربعة أنواع من البكتيريا (E. coli، Staphylococcus aureus، Streptococcus pyogenes، Klebsiella pneumonia) وأظهرت النتائج أن هذه المركبات المحضرة كان لها نشاط جيد إلى متوسط ضد البكتيريا المستخدمة في التجربة بتركيزات مختلفة (0.1 ، 1 ، 10 ملغم / مل) مقارنة بالمضاد الحيوي القياسي (فلوكونازول) بتركيز 5 ملغم / مل.