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Synthesis, Characterization and Biological Activity Evaluation of Some Pyrazoles, Thiazoles and Oxazoles Derived from 2-Mercaptoaniline

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Abstract

Synthesis of 2-mercaptobenzothiazole (A_1) is performed from the reaction of *o*-aminothiophenol and carbon disulfide CS_2 in ethanol under basic condition. Compound (A_1) is reacted with chloro acetyl chloride to give compound (A_2). Hydrazide acid compound (A_3) is obtained from the reaction of compound (A_2) with hydrazine hydrate in ethanol under reflux in the presence of glacial acetic acid .The reaction of hydrazide acid compound (A_3) with ethyl acetoacetate gives pyrazole compound (A_4). The new hydrazone compound (A_5) was prepared from the reaction of compound (A_3) with benzaldehyde. Reaction of compound (A_3) with thiourea dissolved in ethanol gave 2-amino thiazole compounds(A_6) which was used the reaction with 4–N,N-dimethyl benzaldehyde to yield compound hydrazone (A_7).While, the reaction of compound (A_2) with urea in the presence of ethanol gave 2-amino oxazole compounds (A_8) which was used in the reaction with 3-hydroxy – 4 -methoxy benzaldehyde to yield hydrazone (A_9). The structures of the prepared compounds were established by spectral (^{1}H-NMR,Elemental analysis (C.H.N-),and FT-IR. In addition to systematic characterization of some active functional groups in these compounds, antibacterial activity (*Esheriechia coli*, *Bacillus subtilis*) for some of the synthesized compounds were evaluated against two types of fugal (*Candida albicans*) , the synthesized compounds.

Key words: Antibacterial activity, Antifungal 2- amino thiazole,pyrazole, 2-mercaptoaniline, Schiff bases, activity**.**

Introduction:

Heterocyclic compounds contain nitrogen and sulfr. They play an important role, not only for life sciences, but also in many other industrial fields. Benzoxazole contains a benzene fused to an oxazole ring. (1). Heterocyclic compounds, particularly five and six member heterocyclic, brought the attention of pharmaceutical community over the years because of their therapeutic importance .Benzothiazole and its derivatives nucleus are important heterocyclic compounds and because of their synthetic utility and broad range of biological applications , such as antitumor (2) antimicrobial (3) anthelmintic (4) antileshmanial, (5) anticonvulsant (6) anti-inflammatory (7) and antihumane rhinovirus (HRV) activities(8) antibiotic (9) antifungal (10) anticancer (11) antiparkinson(12) anti-HIV (13) antioxidant(14), trypanocidal agent (15), hypoglycemic (16), antidiabetic (17) antituberculosis ,anti-urease (18) and inhibitor of α-glucosidase .They have also been used as ligands for asymmetric transformations(19). Moreover, some derivatives have anti-oxidant and radioprotective effects (20). Farhan reported the preparation and fungicidal activity of 2-mercaptobenzothiazole tyrosine methyl ester derivative of 2- Mercaptobenzothiazole which is found to have an excellent antifungal activity most of all against *Candida albicans* (21)

This research including preparation new derivatives for heterocyclic compounds are 2-mercaptobenzothiazole derivatives.Studying the biological activities of the prepared compounds as antibacterial , antifungal activities .The structure of these newly synthesized compounds were established on the basis of elemental analysis, FT-IR,^{1}HNMR.

Materials and Methods:

Preparation of 2-Mercaptobenzothiazole (A1) (22)

2-Mercptoaniline (1.6 g, 0.01mol), KOH (0.5 g, 0.01 mol) and CS_2 (7.6 g,0.1 mol) were dissolved in a mixture of EtOH (30 mL) and water (15 mL). The mixture was refluxed for 3 hrs. Then charcoal (2.0 g) of was added. The mixture was heated for another 10 min then filtered to remove the charcoal and washed with warm water (75 mL) . The filtrate was acidified with diluted acetic acid (99 %). The yellow precipitate was collected, then recrystallized from aqueous ethanol (10%) to give compound **A1** ,*(1.63g. 73%), m.p. 180-182 °C* .

Synthesis of 2-[(benzothiazol-2-yl)thio] acetyl chloride (A2)

A mixture of 2-mercaptobenzothiazole **(A1)** (1.67 g, 0.01 mol) was dissolved in DMF (15 mL), then chloro acetyl chloride (9 mL, 0.01 mol) was added drop by drop. The reaction mixture was stirred at 0 - 5 ^oC , for 7 hrs. in the presence of the equimolar amount of TEA. Then the reaction was poured onto crashed ice. The precipitate was filtered and recrystallized from ethanol to give dusty crystals the yield compound **(A2)** , (*1.3 g. 62%), m.p.* 164-166 ^oC .

Synthesis of 2-(benzothiazol-2-ylthio)acetohydrazide (A3)

Compound A_2 (1.96 g ,0.007 mol) was dissolved in absolute ethanol (20 mL), followed by the addition of hydrazine hydrate 99 % , (0.014 mol) drop by drop with stirring. The stirring continued for 10hrs at 25 ^oC , then concentrated and cooled and the precipitate, then it was filtered and recrystallized from aqueous ethanol to afford compound A_2 ,(*1.62 g. 86 %), m.p* m.p .184-186 ^0C.

Synthesis of 2-(benzothiazol-2-ylthio)-5-methyl-2,5-dihydro-1H-pyrazol-3-ol (A4)

A mixture of compound **(A3),** (1.18 g , 0.004mol) and acetoethyl acetate (0.52 g, 0.004mol) was dissolved in abs. ethanol (15 mL).The mixture was refluxed for 7 hrs then cooled and concentrated to a light red precipitates which was recrystallized from ethanol**,** compound A_3 , *(0.9 g.77 %), m.p . 176-178 ^oC.*

General Method of Synthesis Hydrazones (A5) (23)

A mixture of compound **A3** (1.31 g , 0.004 mol) with benzaldehyde (0.43 g , 0.45mL, 0.004 mol) were dissolved in absolute ethanol (10 mL) few drops of acetic acid was added. The reaction mixture was refluxed for 4 hrs then it was concentrated to a brown solid (*g , 63 %), m.p.* = 141- 143 ^oC ,*;* (IR (KBr) ν max cm^{-1} : 3298 (NH), 3055 (Ar-H); 1635 (N=CH); ^{1}H-NMR (400 MHz,DMSO-d_6) ,δ ppm) 9.23-11.45 (s,1H, NH),7.88 (s, 1H, N=CH), 7.87- 7.32 (m, Ar-H).

Synthesis 2-amine [4-(benzothiazol-2-ylthio)]-2,3-dihydrooxazole (thiazole) (A6 - A8) (24)

To a solution of 2-[(benzothiazol-2-yl)thio] acetyl chloride (**A_2**) (0.945 g , 0.004 mol) in absolute ethanol (10 mL) , urea (0.24 g , 0.004 mol) or thiourea, (0.3 g , 0.004 mol) was added. The mixture was refluxed for 1hr. After cooling the mixture , it was neutralized to pH (7 to 8) with 10% sodium hydroxide. The precipitate collected and recrystallized from ethanol.

2-Amine [4-(benzothiazol-2-ylthio)]-2,3-dihydrooxazole (thiazole) (A6)

It is a brown solid (0.8 g , 85%); m.p.: 178-180 ^{o} C; IR (KBr) ν max cm^{-1} : 3267 (NH_2),3050 (Ar-H) , 1650 (C=C); ^{1}H-NMR (400 MHz,DMSO-d_6), (δ , ppm): 7.58 - 7.34 (m , Ar-H), 5.62 - 4.21 (s,2H, NH_2) .

2-Amine [4-(benzothiazol-2-ylthio)]-2,3-dihydrooxazole (thiazole) (A8)

It is a red solid (0.64 g , 68 %); m.p.:164-166 ^{o}C ; IR (KBr) ν max cm^{-1} :3267 (NH), 3055(Ar-H) ,1670 (C=C); ^{1}H-NMR (400 MHz,DMSO-d_6) , (δ ppm):8.09 (s, 1H, N=CH), 7.66 - 7.25 (m, Ar-H), 5.70 - 4.21 (s,1H, NH) .

Synthesis of Hydrazones(A7, A9) [23]

A mixture of compound **A_6**or **A_8** (0.004 mol) withsubstituted benzaldehyde (0.004 mol) was dissolved in absolute ethanol (15 mL) of few drops of acetic acid were added .The reaction mixture was refluxed for about 4 hrs, then reaction was concentrated to a brown precipitates which was filtered and recrystallized from ethanol **.**

2-Amine [4-(benzothiazol-2-ylthio)]-2,3-dihydroxazole (thiazole) (A7)

It is a black solid (0.72 g , 76 %); m.p.: 70-72 ^{o}C ; IR (KBr) ν max cm^{-1} :, 3267 (NH), 3043 (Ar-H) 1645 (N=CH); ^{1}H-NMR (400 MHz,DMSO-d_6), (δ ppm):8.09 (s, 1H, N=CH), 7.58 - 7.34 (m, Ar-H), 11.62 - 9.21 (s,1H, NH) , 2.3 ($N(CH_3)_2$) (s,6H, CH_3).

2-amine [4-(benzothiazol-2-ylthio)]-2,3-dihydroxazole (thiazole) (A9)

It is a coffee solid (0.69 g , 70 %); m.p.: 105-108 ^{o}C ; IR (KBr) ν max cm^{-1} ; 3450(O-H), 3267 (NH), 3043 (Ar-H), 1645 (N=CH),; ^{1}H-NMR (400 MHz,DMSO-d_6), (δ ppm):8.09 (s, 1H, N=CH), 7.58 - 7.34 (m, Ar-H), 11.62 - 9.21 (s,1H, NH), 3.50 (s,3H, OCH_3) , 3.10 (s,1H, OH).

Result and Discussions

All the compounds (A1-A9) were synthesized shown of the following scheme 1.

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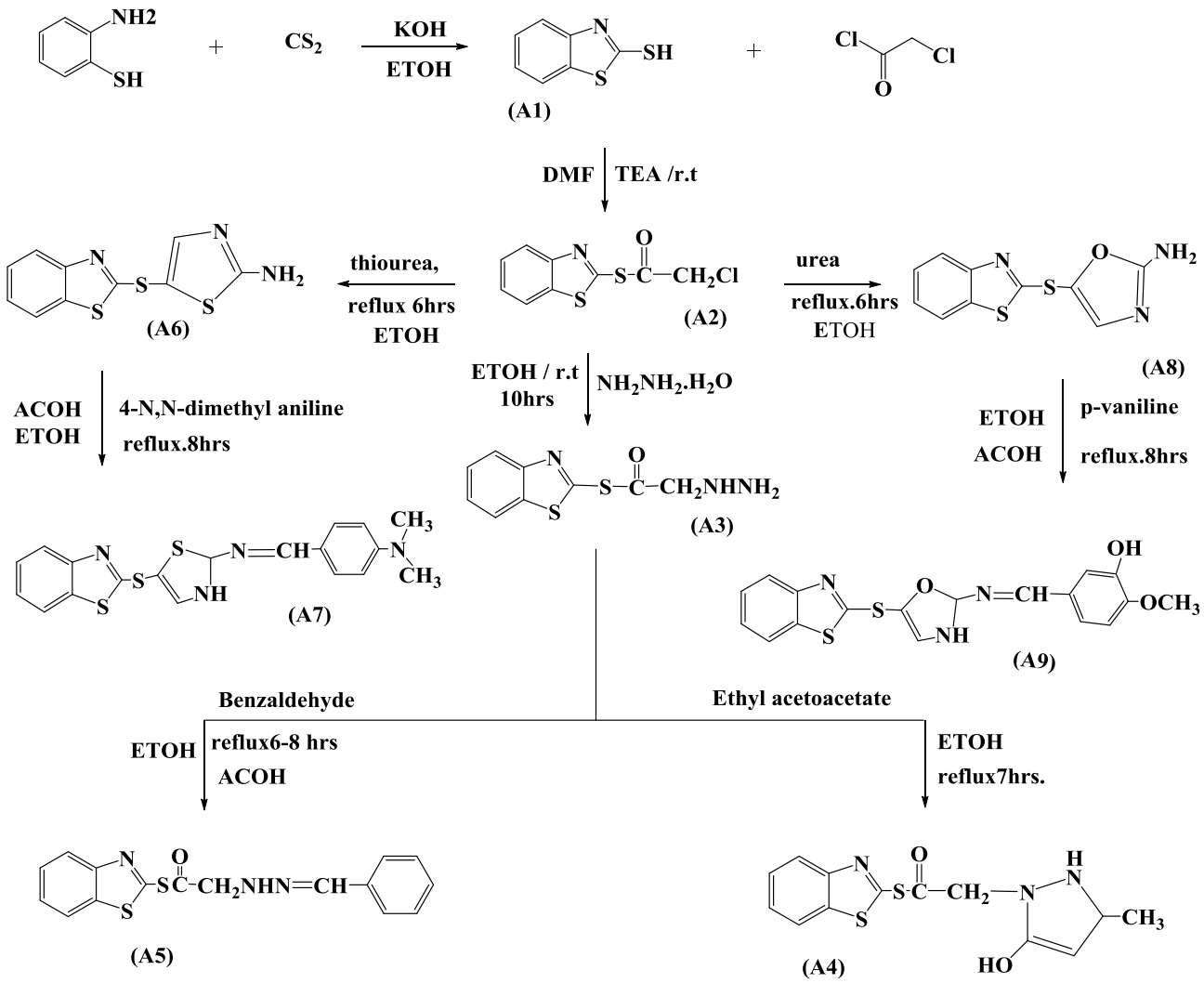


Scheme 1. Synthesis of Compounds(A1- A9)

Preparation of 2-Mercptobenzothiazole (A1)

The compound 2-MBT was prepared according to the reaction of 2-Mercptoaniline with the carbon disulfide (CS_2). The reaction was followed up by using lead acetate paper which changes its color to black paper because of H_2S liberation when the reaction takes place. The FT- IR spectrum of compound (A1) showed an absorption band at υ(2539) cm^{-1} due to (S-H) stretching. other bands shows at υ (3113) cm^{-1} was attributed to C-H stretching of aromatic ring , υ (1593) cm^{-1} due to (C-H) aliphatic. stretching; (1496) cm^{-1} due to (C=N) stretching and υ (752) cm^{-1} due to (C-S-C) stretching. The ^{1}H-NMR spectrum of compound (A1)showed the following characteristic chemical shift ,the (S-H) proton was resonated at (11.96) ppm, in additional to signals at δ= (7.20-7.50) ppm due to aromatic protons

Synthesis of 2-[(benzothiazol-2-yl)thio] Acetyl Chloride (A2)

The compound(A2) was synthesized by the treatment of 2-MBT with the chloroacetyl chloride, the success of the reaction was proved by the changes in the physical properties .The silver nitrate test confirmed the presence of chlorine group. The FT-IR, Fig. 1 spectrum absorption bands that showed disappearance of υ (2550)cm^{-1} due to(-SH) and the appearance strong bands at υ (1643) cm^{-1}.which was attributed to (C=O)group stretching, υ (848) cm^{-1} due to (C-Cl) stretching. The ^{1}HNMR spectrum of (A2)which is depicted in Fig.2, supported the expected structure by presenting chemical shifts δ (7.2 -7.4) ppm due to aromatic ring hydrogen ,peak at δ 4.7 ppm (2H,s) which was attributed to (CH_2).

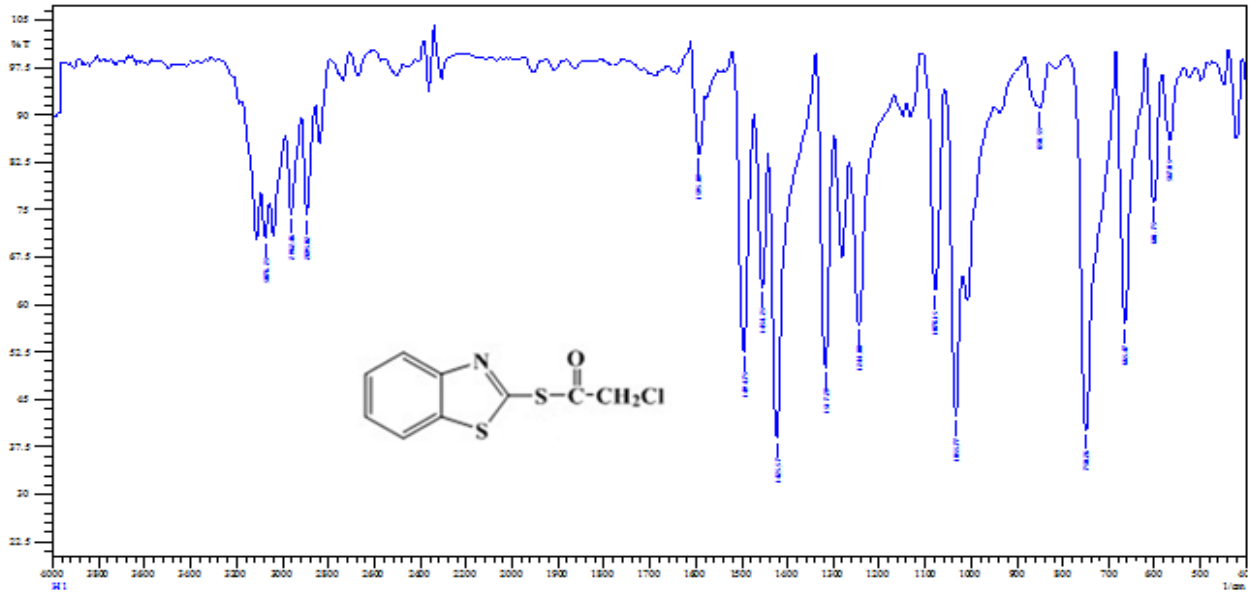


Figure 1. FT-IR spectrum of compound (A2)

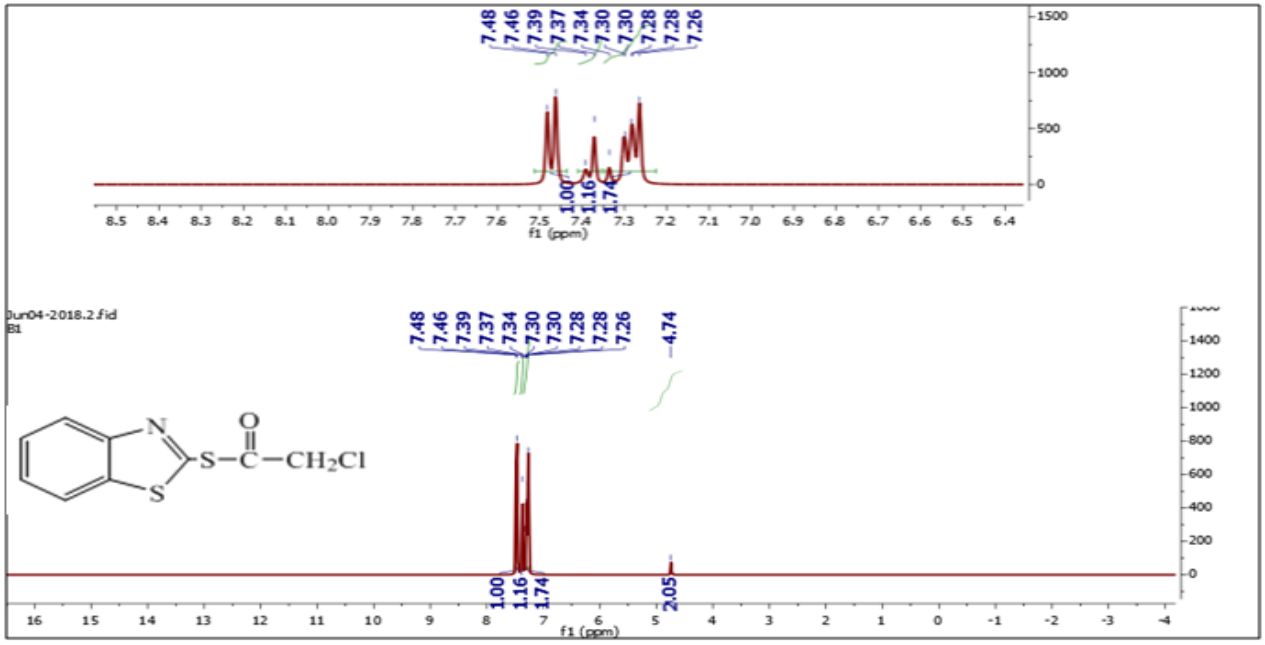


Figure 2. ^{1}HNMR spectrum of compound (A2)

Synthesis of 2-[(benzothiazol-2-yl)thio] Acetyl Hydrazide (A3)

The compound(A3)was synthesized by treating 2-[(benzothiazol-2-yl)thio] acetyl chloride with hydrazine hydrate .The FT-IR characterization shows Fig. 3. Spectrum absorption band at 3250 cm^{-1}, 3332 cm^{-1} sym. and asym, of (NH_2) str. is an excellent evidence on formation the compound. Additional to the other bands showed at (3109) cm^{-1} C-H Ar. Str.; υ (2840) cm^{-1} (C-H) alf. str.; υ(1643) cm^{-1} (C=O) str.; 1595 cm^{-1} (C=C) str.; υ (1496) cm^{-1} (C=N) str; ^{1}H-NMR spectrum of compound (A_3, Fig. 4) showed a signal at δ 3.8 ppm (2H, singlet) which was due to (-NH_2) group protons also showed a peak at 4.5 ppm (H, singlet) which was due to (-NH) proton, and the signal between δ 7.3-8.1 ppm(4H, m) which was attributed to (Ar-H) protons ,also showed a signals between δ 3.6 ppm for (CH_2).

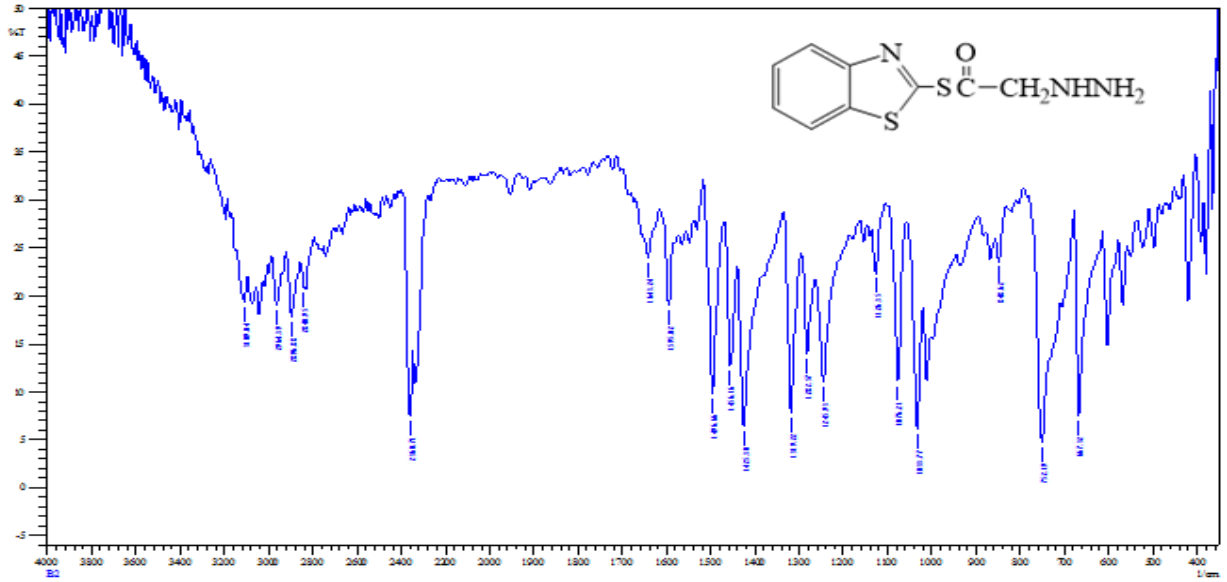


Figure (3) FT-IR spectrum of compound (A3)

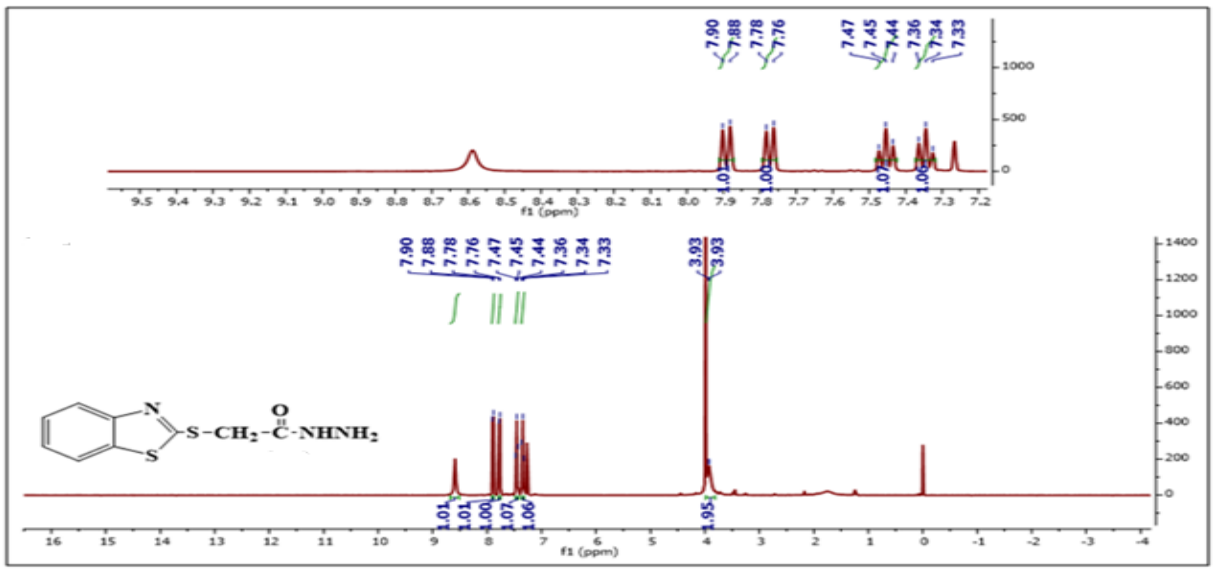


Figure 4. 1HNMR spectrum of compound (A3)

Synthesis of 2-(benzothiazol-2-ylthio)-5-methyl-2,5-dihydro-1H-pyrazol-3-ol (A4)

The compound (A4) was synthesized according to the treatment of compound (A3) with ethyl acetoacetate. The IR spectrum absorption bands prove the success of the reaction, its showed absorption band at υ (3400) cm^{-1} was attributed to (OH) str. which is good sign of the reaction success, other bands at (3114) cm^{-1} NH str., υ (3039) cm^{-1} were attributed to (Ar-H) str., protons.;(2894) cm^{-1} C-H alph.; υ (1650) cm^{-1} were attributed to C=O str.; υ (1595) cm^{-1} due to (C=C) str.

Synthesise of 2-amine[4-(benzothiazol-2-ylthio)]-2,3-dihydrooxazole(thiazole) (A_6,A_8)

Compounds (A6,A8) were synthesized by the reaction of 2-amine[4-(benzothiazol-2-ylthio)]-2,3-dihydrooxazole(thiazole) once with thiourea. The FT-IR spectra are evidences for success of the reactions. The FT-IR characterization compound A6 in Fig.5. showed disappearance of υ (1643) cm^{-1} due to (C=O) , υ (848) cm^{-1} due to (C-Cl) bands and appearance of bands at υ (3314) cm^{-1} , υ (3274) cm^{-1} sym. and asym. of NH_2 stretching; υ (3337) cm^{-1} due to (NH) stretching. Overlapped with (C-H) Ar. 1658 cm^{-1} was attributed to (C=C) Ar stretching. (1494) cm^{-1} was due to (C=N) stretching. υ (1033) cm^{-1} was attributed to (C-O) stretching, the ^{1}H-NMR spectrum of compound A6 in Fig. 6, showed a signal at δ 4.1 ppm (2 H ,singlet) was due to (-NH_2) protons and a signal between δ (7.1-7.4) ppm for four aromatic hydrogen , while the signal at δ 6.3 ppm was (CH,=CH) protons.

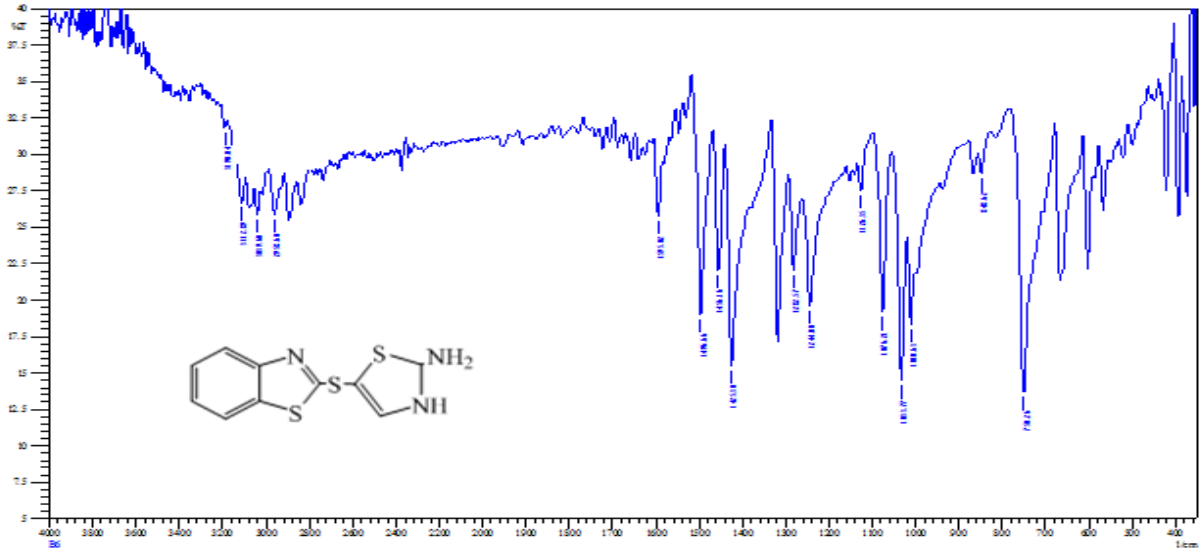


Figure 5. FT-IR spectrum of **compound (A6)**

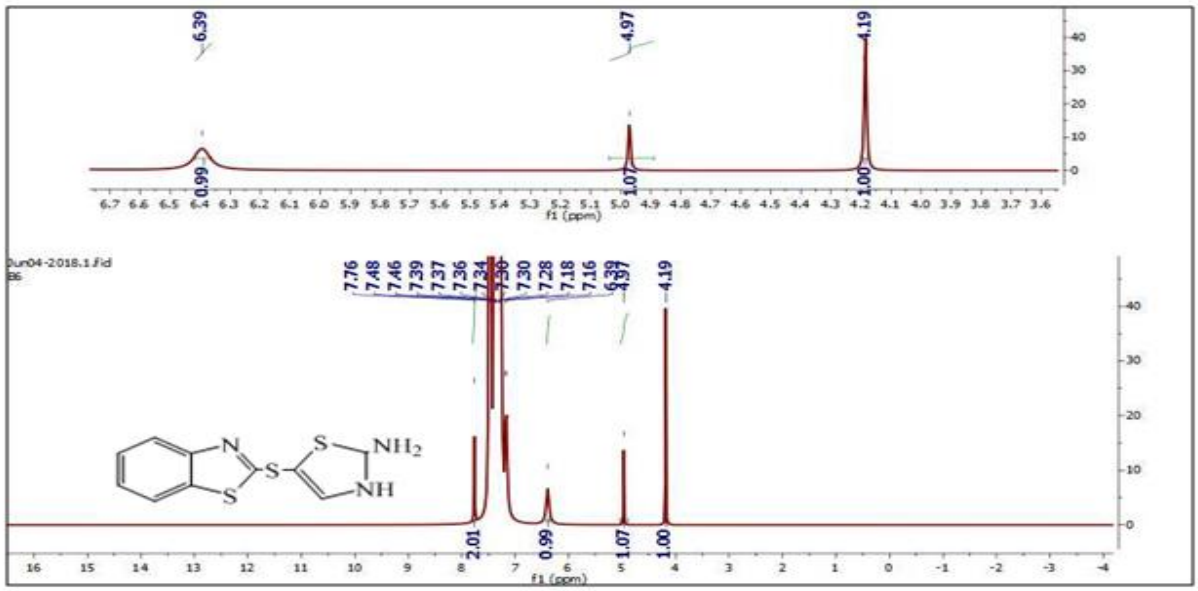


Figure 6. ^{1}HNMR spectrum of **compound (A6)**

Synthesis of Hydrozones (A5,A7and A9)

The final step of this work deals with the reactions of compounds (A5, A7 and A9) by condensation reaction with substituted benzaldehyde to come up with the required benzothiazole linked to Schiff-base through amino group. The first stage in the condensation reaction between aromatic amine compound and various aromatic aldehydes consists nucleophile ,adding compounds containing amine (NH_2) group to carbonyl (C=O)group producing hydrazones which exclude (H_2O)water molecular to afford Schiff's base compounds. So the changes in physical properties and the FT-IR characterization showed disappearance of NH_2 group which is good sign that the reaction took place. The FT-IR spectrum for compound A5 in Fig. 7 was υ (3112) cm^{-1} due to NH stretching , υ (3076) cm^{-1} was attributed to C-H aromatic rings stretching ,2893 cm^{-1} due to C-H aliphatic was due to stretching ,1681cm^{-1}due to C=O stretching , υ (1627) cm^{-1} was attributed to C=C stretching, and υ (1575) cm^{-1} was due to C=N stretching of compound (A7).The ^{1}HNMR spectrum of (A7)which is depicted in Fig. 8, supported the expected structure by presenting chemical shifts δ 6.7-7.7ppm for aromatic hydrogen the singlet also appeared at 6.52ppm attributed to one proton of C=CH. ,signal at δ 9.7ppm for NH hydrogen(1H)and signal at δ 3.0ppm.(6H,singlet) was attributed to (NMe_2) protons.

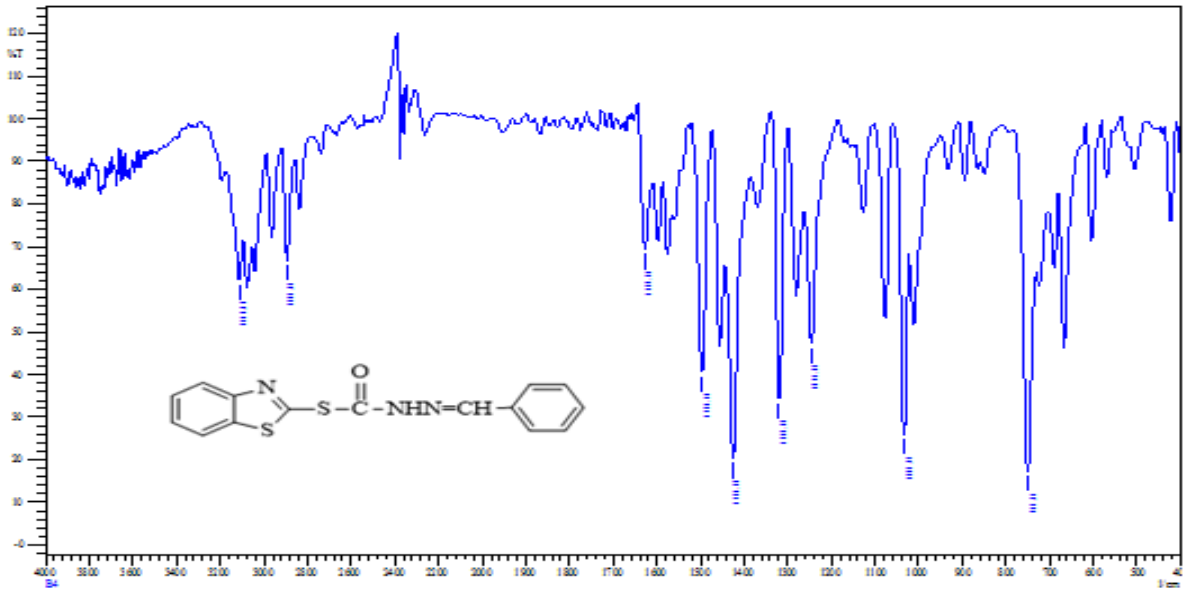


Figure 7. FT-IR spectrum of **compound (A5)**

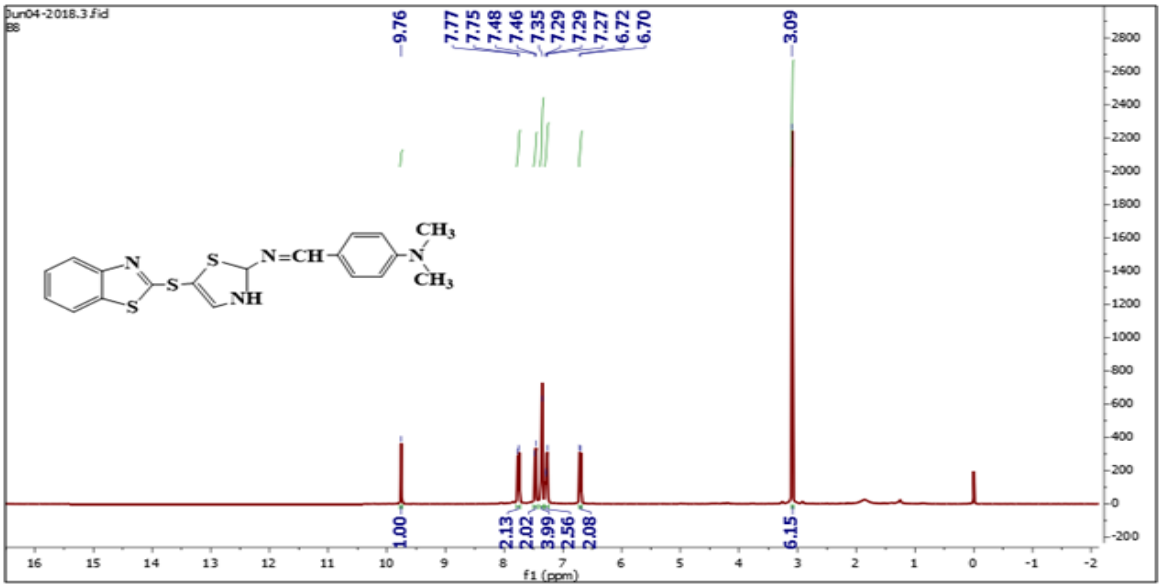


Figure 8. ^{1}HNMR spectrum of **compound (A7)**

Synthesis of 5-((benzothiazol-2-ylthio) methyl)-1,3-oxazol-2-amine (A8)

The compound A8 in Fig.9 was synthesized according to the reaction between compounds (A_2) with pyridine. The FT-IR characterization spectrum bands were good evidence on success the reaction. The ^{1}H-NMR spectra of compound A8 in Fig.10 showed a signals at reign (7.1-7.9) ppm of four aromatic ring protons and the peak at δ 7.3 ppm (2H), which was due to (NH_2) protons, as well as peak at δ 4.63 ppm (s, 2H) was due to ($-CH_2$).

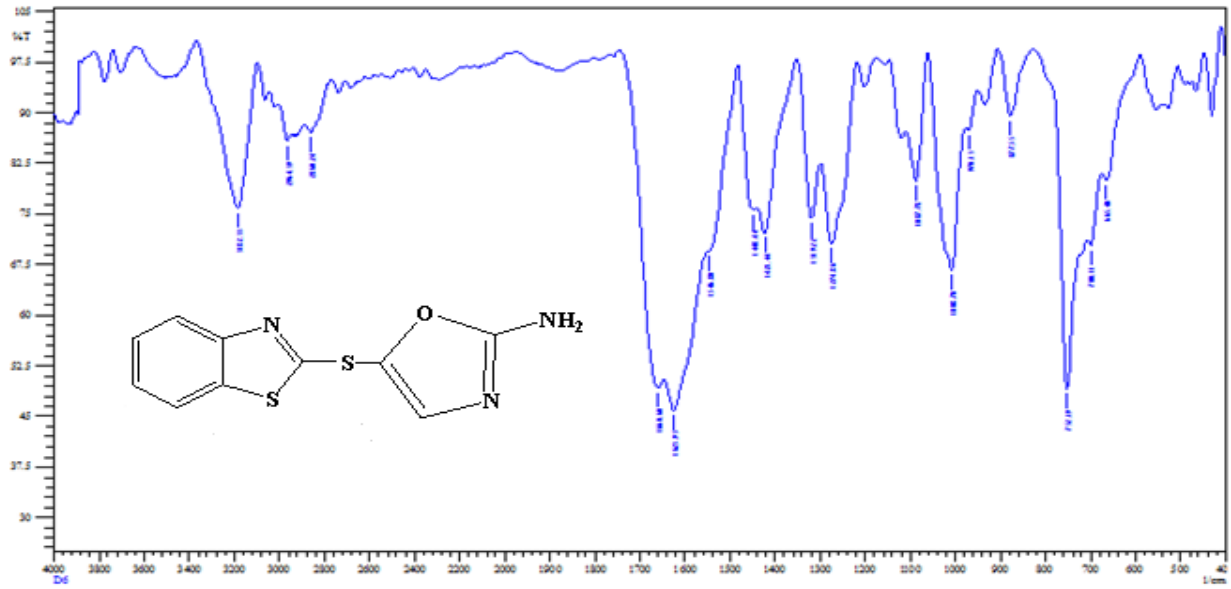


Figure 9. FT-IR spectrum of **compound (A8)**

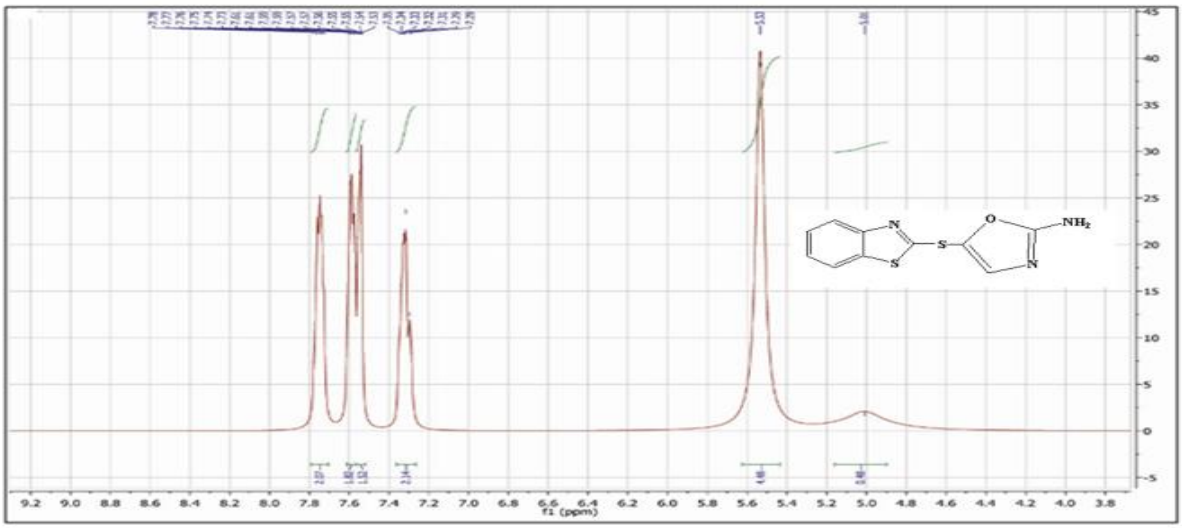


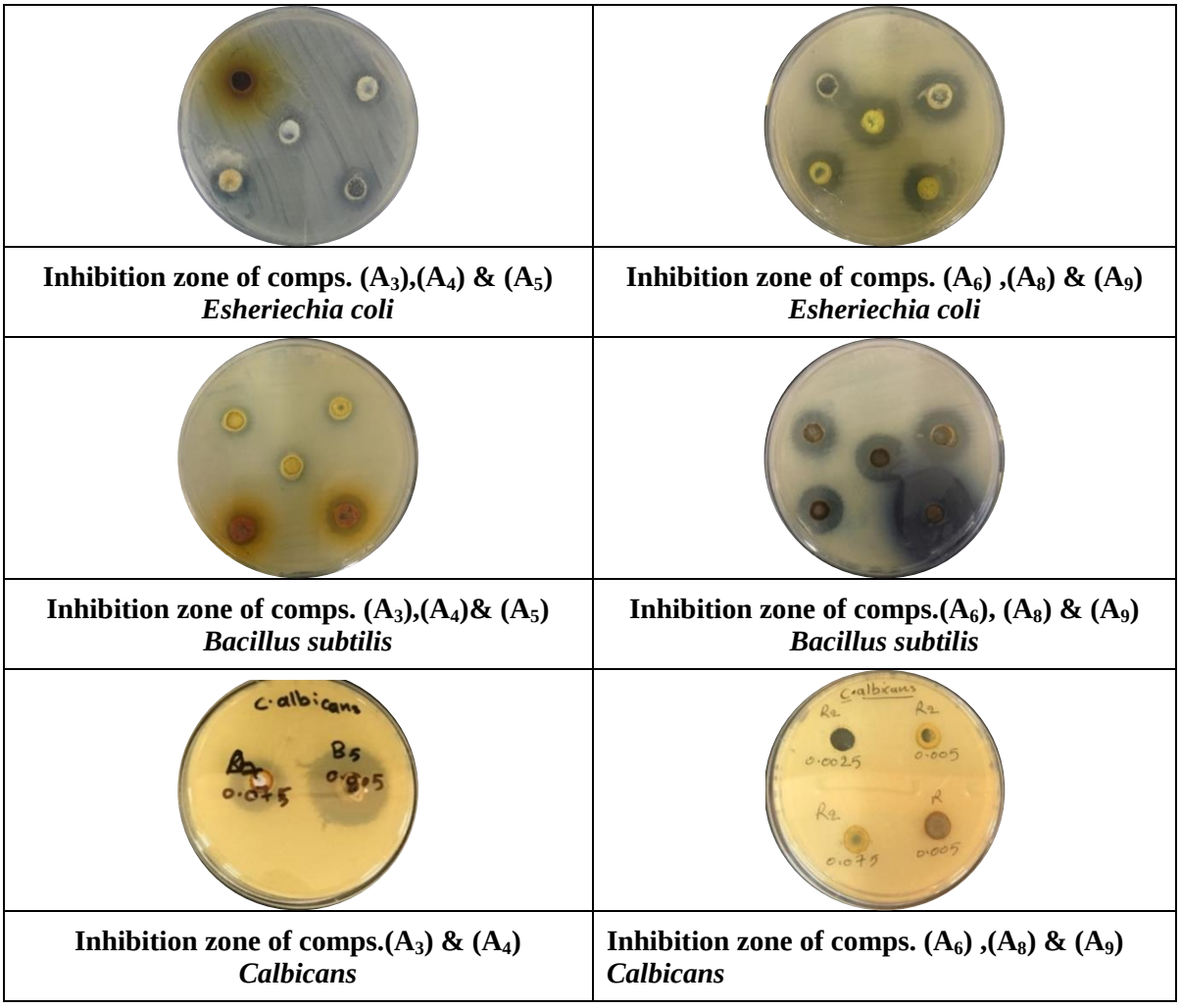
Figure 10. ^{1}HNMR spectrum of compound (A8)

Biological Activity of Some of the Synthesized Compounds

The synthesized compounds in this work were expected to show biological activity since they have active groups in their molecules all of the tested compounds were studied at different concentration of using DMSO as a solvent (0.05, 0.001, 0.075, 0.005, 0.0025 mg/mL). Thus a preliminary evaluation of antibacterial and anti-fungal activity for some of the new 2-MBT compounds were tested against types of bacteria like *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) and against *Candida albicans* fungus. The results showed that most of the tested compounds have good antibacterial and antifungal activity those kinds of bacteria and fungus have been chosen because of their wide importance in the clinical field so they cause many diseases in addition to their various resistance of the antibiotic and chemical drugs. So their biological activity illustrated in Table 1 which shows antifungal activity and antibacterial activity. The result in Table 1 shows that the synthesized compounds have biological activity against the chosen fungus and bacteria because they have ability of inhibing the chosen bacteria and fungi by choosing different concentrations of the compounds, the inhibition zone is from (16 mm the lowest inhibition zone to 36 mm the highest inhibition zone of Fungus), but for bacteria it is about (10 mm the lowest inhibition zone to 32 mm the highest inhibition zone of bacteria). *From the outcome it is also clear that the tested compounds(*A3-A6) and (A8,A9) *showed difference toxicity against different* fungus and one of type *bacteria.This difference in toxicity may be* due to change *in functional group or structures.as shown in picture 1.*

Table (1) Biological activity of compounds(A_3- A_9) against *Candida albicans*, and (*Bacillus* and *E.coli*).

Sample Code	*Antibacterial activity* (zone of inhibition in mm)		*Antifungal* activity (zone of inhibition in mm)	
	Conc.	*Candida albicans*	Gram positive bacteria *Bacillus g/mL*	Gram negative bacteria *.E.col μ g/mL*
	0.050	**20**	**20**	**-**
A3	**0.010**	**17**	**15**	**-**
	0.075	**25**	**19**	**-**
	0.075	**36**	**14**	**14**
A4	**0.010**	**29**	**13**	**-**
	0.025	**35**	**13**	**13**
	0.075	**17**	**22**	**16**
A5	**0.005**	**-**	**22**	**14**
	0.025	**27**	**19**	**14**
A6	**0.075**	**-**	**25**	**16**
	0.005	**-**	**19**	**17**
	0.0025	**-**	**20**	**18**
	0.0025	**-**	**20**	**16**
A8	**0.075**	**-**	**17**	**15**
	0.005	**-**	**31**	**25**
	0.001	**29**	**20**	**23**
A9	**0.05**	**26**	**21**	**24**
	0.005	**22**	**19**	**17**



Inhibition zone of comps. (A_3),(A_4) & (A_5) *Esheriechia coli*	**Inhibition zone of comps. (A_6) ,(A_8) & (A_9) *Esheriechia coli***
Inhibition zone of comps. (A_3),(A_4)& (A_5) *Bacillus subtilis*	**Inhibition zone of comps.(A_6), (A_8) & (A_9) *Bacillus subtilis***
Inhibition zone of comps.(A_3) & (A_4) *Calbicans*	**Inhibition zone of comps. (A_6) ,(A_8) & (A_9) *Calbicans***

Picture 1. Inhibition zone of biological activity of compounds (A3-A6), (A8,A9)

Conclusion:

The present work deals with the synthesis of some benzothiazole derivatives that was achieved with substituted aromatic aldehydes in presence of ethanol to obtained Schiff bases (A_5,A_7 and A_9) . All the derivatives prepared by this method are analyzed by ^{1}HNMR and IR . The data in the table indicate that the synthesized compounds A_6 and A_8 showed moderate antibacterial activity while $A_5$and A_9 showed good biological activity. From the results of various biological activity it is clear that these compounds would be of better use in drug development.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in Tikrit University.

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تحضير وتشخيص وتقييم الفعالية البايولوجية لبعض من البايرازولات الاوكسازولات والثايازولات المشتقة من المركب 2-مركبتوانيلين

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الخلاصة:

تحضير 2-مركبتوبنزوثايازول(A1) من تفاعل المركب 2-مركبتوانيلين مع ثنائي كبريتيد الكاربون بوجود هيدروكسيد البوتاسيوم كعامل مساعد.حضر المركب (A2) من تفاعل المركب 2-مركبتوبنزوثايازول مع المركب كلورواسيتايل كلورايد ثم مفاعلة المركب الناتج مع الهيدرازين المائي في الإيثانول ليعطي الهيدرازيد (A3) .تم مفاعلة المركب (A3) مع الايثل اسيتو اسيتيت ليعطي مركب البايروزول) (A4 بينما عند تفاعل المركب (A3) مع البنزالديهايد بوجود حامض الخليك والايثانول اعطى الهيدرازون (A5) اما عند تفاعله مع الثايوبوريا بوجود الايثانول اعطى 2- امينو ثايازول (A6) والذي بدوره فوعل مع المركب N,N-4-ثنائي مثيل بنزالديهايد ليعطي الهيدرازون (A7) . بينما المركب (A2) عند تفاعله مع اليويا بوجود الايثانول اعطى المركب 2- امينواوكسازول (A8) والذي بدوره فوعل مع المركب4 -ميثوكسي-3-هيدروكسي بنزالديهايد ليعطي الهيدرازون (A9)تم التأكد من المركبات الكيميائية المحضرة باستعمال الطرائق الفيزياوية والطيفية مثل طيف الرنين النووي المغناطيسي البروتوني(^{1}H-NMR) ، وطيف الأشعة تحت الحمراء (FT-IR) وكذلك طيف الأشعة فوق البنفسجية(UV) لبعض المركبات المحضرة، فضلاً عن استعمال عدد من الطرائق للكشف والتشخيص لقسم من المجاميع الفعالة (كشف العناصر CHN) للمركبات المحضرة. كما تم تقييم الفعالية البيولوجية لبعضها ضد نوع واحد من البكتيريا و نوعين من الفطريات.

الكلمات المفتاحية : قواعد شف، 2-امينو ثايازول، بايرازول، 2-مركبتو انيلين