

Synthesis of some new 2-mercaptobenzoxazole and study their biological activity against some plant pathogenic fungi

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Abstract:

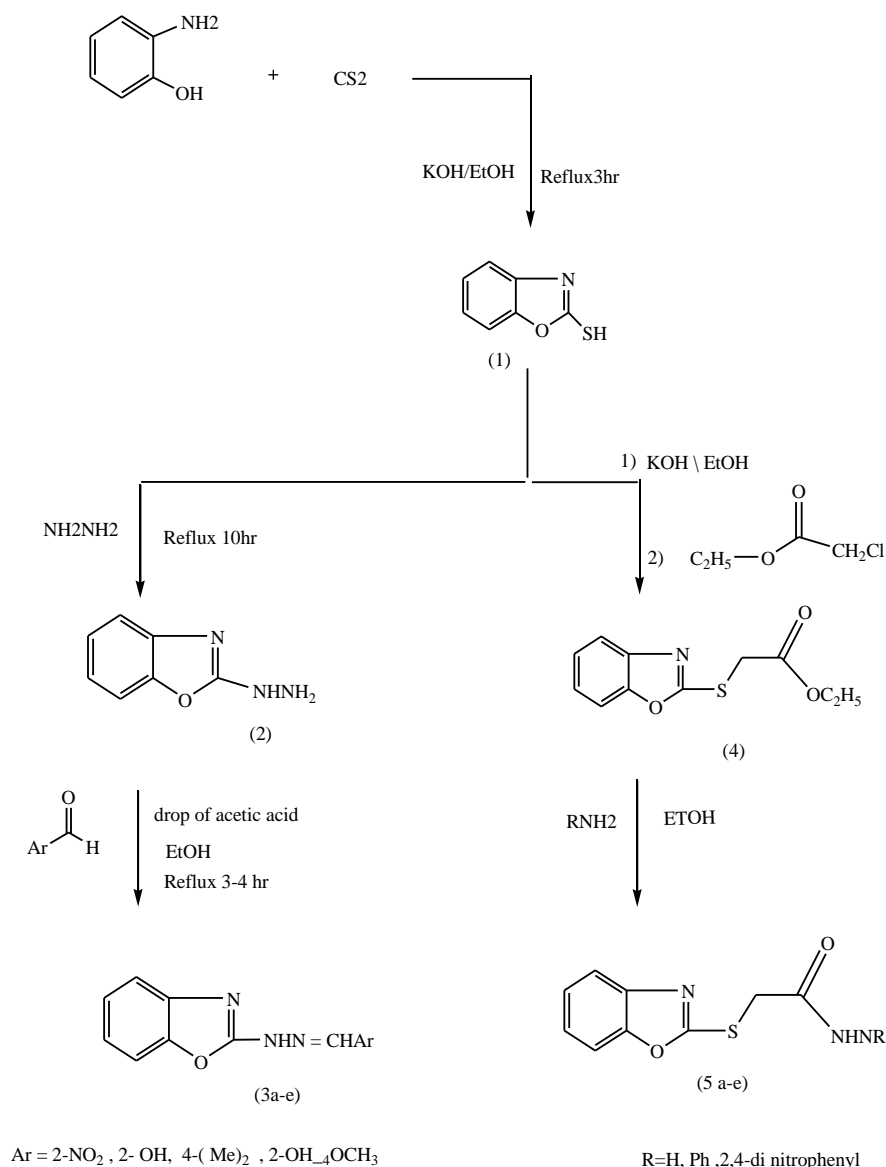
The research included synthesis of 2-mercapto benzoxazole (MBO) (1) from the reaction of ortho hydroxyl aniline with carbon disulfide in ethanolic potassium hydroxide. The hydrazine benzoxazole HMBA2 (2) was synthesized from the reaction of compound MBO (1) with hydrazine hydrate in presence of alcohol. Compounds (3_(a-e)) were synthesized by condensate on of substituted Benzaldehydes with 2-Hydrazino benzoxazole HMBA2. The Ethyl2-(benzoxazolylthio) acetate EMBA1 (4) obtained from the reaction of compound MBO (1) with solution of ethyl chloro acetate using KOH alcoholic. Finally the compound hydrazide HMBA(5_(a-e)) was synthesized from the reaction of compound (4) with hydrazine hydrate in presence of alcohol. All these synthesized compounds were characterized on the basis of their ¹H-NMR, IR. The study is Showed biological activity for chemical compounds, at three concentration 100, 200, 300 ppm in toxic potato Dextrose Agar (PDA) medium method against phytopathogenic fungi three species *Fusariumgraminarium*, *Sclerotiniasclerotium* and *Rhizoctoniasolani*, its isolation on nutritious PDA medium from root plants wheat, eggplant and cotton continually, diameter measure of fungi growth colony result showed all compound growth inhibition barring MMBA compound non effective inhibition its, appear MBO moral superiority after bring HMBA2 both induce inhibition amount 49.69 and 34.22% continually. Compound concentration its average effect result reveal third significant superior on first and second concentration, interference effect concentration and species chemical compound notice higher inhibition amount 100% with third concentration MBO compound all test its fungi.

Key word : 2-mercapto benzoxazole ,2- hydrazinobenzoxazole

Introduction:

Benzoxazole, a physiologically active nucleus, has attracted the attention of many researchers from the point of its chemistry and biological activity. Hoebrekerin1872 prepared Benzoxazole and since then thousands of Benzoxazole derivatives which are having the thiazolidinone moiety have been synthesized and tested with their biological activities. A few of them are of the rapetic importance Parent. benzoxazole itself possesses antibacterial, antifungal and antamoebic activity, Literature survey reveals that in recent years several benzoxazole derivatives have been synthesized and reported to possess varied biological and pharmacological properties. some¹ scientists found to be useful as antitubercular^{2,8}, depressant³ anticonvulsant^{4,9}, antimicrobial & antifungal cardiovascular activity^{5,6}, anesthetic & hypnotic agents¹¹. A good number of them have been also marked as drugs, albendazole (anthelmintic), carbenadazim (fungicide), emedastine

(antihistamine), omeprazole (proton pump inhibitor), Droperidol and pimozide (psycho pharmacological agent),etc. Also quite large number of benzoxazole is at various stages of screening in different laboratories throughout the world with an aim to develop them as future drugs. Some benzoxazole derivatives were found to be associated with anticonvulsant, tranquilizing and paralyzing properties. In view of pharmacological significance of benzoxazole derivatives and thiazolidinone derivatives specially CNS activities it is planned to synthesize some new benzoxazole derivatives containing thiazolidinone moiety and these compounds will be screened for their CNS activity. Keeping in view an array of applications, it has been felt worthwhile to synthesize some new 3-[1H- benzoxazole-2-yl-amino]-2-phenyl-1,3-thiazolidin-4-one (V) as such reactions are not reported so far and also to screen for the central nervous system activity. The synthesis of title compounds could be achieved by the Scheme-I



1) CS₂/Alcoholic KOH
2)Hydrazine hydrate(99%)
3) substituted benzaldehydes /methanol

Scheme 1

Materials & methods:

Experimental:-

All the chemicals and solvents used were of Aldrich and Fluka products and were used without further purification. Melting point were determined using an electro thermal 9300 digital melting point apparatus and are un corrected FT-IR spectra were recorded on 85005 shimadzu FTIR Japan spectrophotometer on potassium bromide pellets .

Synthesis of 2-Mercapto benzoxazole (1) MBO

A mixture of 10.9 gm (0.1 mole) of ortho hydroxy aniline, 5.65 gm (0.1 mole) of potassium hydroxide and 7.67gm(0.1 mole, 6.19 ml) carbon disulphide, 100 ml of 95% ethanol and 15 ml of water in 500 ml

of round bottom flask were heated under reflux for 3 hr. Then added 1.15 gm of charcoal cautiously and then mixture was further heated at the reflux for 10 minutes, the charcoal was removed by filtration. The filtrate was heated to 60-70⁰C, 100 ml of warm water was added and acidified with dilute acetic acid with good stirring. The product separated as glistens white crystals, and the mixture was placed in a refrigerator for 3hr to complete crystallization. The product was collected on a Buchner funnel and dried over night at 40⁰ C. The dried product was recrystallized ethanol, the yield was 94 % and melting point is 185-188⁰C.lit. Anal Calculate for C₇H₅NSO (M.wt. 151), IR: 3020, 1597, 1035 cm⁻¹(C=C in aryl ring), 1625

cm⁻¹ (C=N), 1225 cm⁻¹ (C-O-C); 2572 cm⁻¹ (-SH), in addition 3114, 3159 cm⁻¹ (C-H).

Synthesis of 2-hydrazinobenzoxazole (2) HMBA2

A mixture of 2- mercaptobenzoxazole (0.04mole ,6.04g) was dissolved (20 ml) and hydrazine hydrate NH₂NH₂.H₂O (0.05 mole) (90 %) in methanol (100 ml) with stirring, than the reaction mixture was refluxed on water bath for 10 hrs. it was cooled, filtered and solvent was distilled off and the sold was collected and recrystallized from methanol, yield 85 % , m.p.168-171°C(lit 171 °C)¹⁰. Anal Calculate for C₇H₇N₃S (M .wt. 218), IR, Cm⁻¹: 3392, 3276, (-NH₂), 3355(-NH), 3020, 1597, 1035 (aryl ring), 1650 (C=N), 1192, 1078, 669(C-S-C);

Synthesis of (2-benzylidene) hydrazinobenzoxazole 3(a-e)(MMBA)

A mixture of 2-Hydrazinobenzoxazole (0.001mol) and an appropriate aromatic aldehyde (0.002mol) in methanol (50ml) containing 3-4 drops of glacial acetic acid was refluxed on water bath for 30 min. and cooled. The crystalline solid which separated out during reaction, was filtered and recrystallized from suitable solvent. The structure of synthesis compounds (3_{a-e}) were confirmed by melting -point, and I-R ,the spectral characterization data are given in described below table (1) and the physical properties of the synthesized are given in Table (2).

Preparation of Ethyl 2-(benzoxazolylthio)acetate (4) EMBA1

A stirred mixture containing (3.48g ,0.03mole) of 2-Mercapto benzoxazole 50 ml of ethanol and 1.69 gm., 0.03 mole of potassium hydroxide was added and heated the mixture was refluxed for 10 minute than ethyl chloroacetate (3.66 ml ,0.03 mole) was added in one potion, The resulted mixture was refluxed for 2 hours and the reaction mixture poured into 100gm ice cold water and with good stirring for 30 hrs. And the mixture was placed in a refrigerator for 3hr to complete crystallization. The product was collected on a Buchner funnel and dried. The dried product was recrystallized water, the yield was 70 % and melting point is 105-108°C. Anal Calculate for C₇H₇N₃S (M.wt. 227), IR, cm⁻¹: 3020, 1597, 1035 (C-H benzene ring), 1635 cm⁻¹ (C=N), 1192 cm⁻¹ (C-S-C), 1070, 1150 cm⁻¹ (C-O) , 1730 cm⁻¹ (C=O ester).

Synthesis of 2-Hydrazinobenzoxazole (5) (MMBA)

A mixture of Ethyl 2-(benzoxazolyl thio)acetate (0.04mole,9.08g) was dissolved (20ml) and hydrazine hydrate NH₂NH₂.H₂O (0.04mole) (90%) in methanol (100 ml) with stirring, than the reaction mixture was refluxed on water bath for 10 hrs. it was cooled, filtered and solvent was distilled off and the sold was collected and recrystallized from ethanol, M.P 202-204 °C, M.P 203-205 °C, lit. 202-204¹²³ yield 80% Anal Calculated for C₉H₉N₃O₂S (M.wt.196), IR: 3392,3276 (-NHNH₂), 3020,1597, 1035 (sub.aryl ring), 1650 (C=N), 1192,1078, 669(C-S-C);

Results & discussion :

The compound 2-mercaptobenzoxazole (1) was prepared by reaction of ortho hydroxy aniline with carbon disulfide in ethanolic potassium hydroxide in yield 94% 185-188°C, as described by^[1], 2-Hydrazinobenzoxazole(2) was synthesized by reaction of 2-mercapto benzoxazole with hydrazine hydrate. Also the thiol group of 2-mercaptobenzoxazole converted into hydrazino derivative by reflux with an ethanolic solution of hydrazine hydrate. The melting point of compound (2) (202- 204°C), limit⁽²³⁾ , and the infrared , (IR) spectra of this compound (2) showed band at (3260 cm⁻¹) due to stretching (N-H) group, and disappear band stretching 2570 due to (SH) band at (1620 cm⁻¹) for (C=N) group, band at (1150 cm⁻¹) for (C-O-C) group. The 2-benzylidene) hydrazinobenzoxazole (3_{a-e}) were prepared by condensation various substituted benzaldehydes. with 2-hydrazinobenzoxazole (2).IR spectrum of the compound 2-[2-(4-chlorobenzylidene) hydrazinebenzoxazole(2) (inKBr) exhibited characteristic absorption bands (in cm⁻¹) at 3457 (N-H), 2956 (=C-H) and 1641(C=N), 1561(C=C), and I-R, the spectral characterization data are given in table (1). The Ethyl-2-(benzoxazolylthio) acetate EMBA1(4) obtained from the reaction of compound MBO (1) with solution of ethyl chloroacetate using KOH alcoholic the infrared,(IR) spectra of this compound (4) showed band at (3271-3323 cm⁻¹) sym. and asym. due to stretching (-NH-NH₂) group, and disappear band stretching 2570 due to (SH), band at (1150, 1210cm⁻¹) for sym. and asym. due to stretching (C-O-C)) group,1192 cm⁻¹ (C-S-C), 1750 cm⁻¹ (C=O ester) group, 3020, 1597, 1035 (C-H benzene ring). 2-Hydrazined (5) was synthesized by reaction of 2-mercapto benzoxazole with hydrazine hydrate. showed in figure (1) cm⁻¹ stretching bands at (3271-3323cm⁻¹) due to stretching (NH-NH₂) group, band at (1635-1667 cm⁻¹) for (C=O) group, 1640-1630 (C=N),The structure of synthesis compounds were confirmed by melting-point, and I-R, the spectral characterization data are given in table, (3)

Test the biological activity against some plant pathogenic fungi

The fungi *Fusariumgraminarium*, *Sclerotiniasclerotium* and *Rhizoctoniasolani* caused root rot disease many economic important plants its soil inhabitant fungi *Fusarium graminarium* cause root rot and head blight disease on wheat plant ,*Sclerotiniasclerotium* fungus its rot white disease on eggplant,*Rhizoctoniasolani* cause damping-off cotton plant. Agrios, (2005). Isolated fungi from plants root aggregate than infection fields and occur of isolation on potato dextrose agar (PDA) nutrition medium in plant disease laboratory, Agriculture collage, Tikrit University. The fungi diagnosis and depend on classification key indicate, Wetanabe et al, (2002). The biological activity chemical compound, EMBA1,

HMBA2, MBO and MMB to three concentration 100, 200, 300 ppm test in toxic (PDA medium method on petry dish diameter 9 cm., Robert etl.(2006), some petry dish nontoxic to control sample. Inoculated petry dish center colony disc 0.5 mm. diameter from fungi youthfully life 72 h. colony border and incubated 28 ± 2 C ,all treatments at three replicate , after 5 days at growth complete in control treatment measured all colony diameter and inhibition percent count following equation :Inhibition % = growth colony diameter on control - growth colony diameter on treatment / growth colony diameter on control $\times 100$.The data statistical

analysis use SAS program and its moderate control according to LSD test at potentiality level to 0.0., Showed the study biological activity of chemical compounds (1), (2), (4) and (5a) against three pathogenic fungi species indicate in table (4).

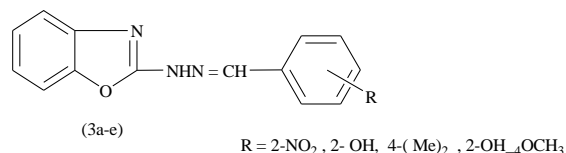


Table:-(1) melting points, crystallization solvent, percent yield and molecular formulae for compounds (3 (a- e))

Comp. No.	Ar	Yield (%)	M.P (°C)	crystallization solvent	Molecular formula
a	2-NO ₂	80	227	EtOH	282
b	4-OH	77	216	EtOH	280
C	3-OH-4-OCH ₃	85	125	EtOH	283
d	4-N(CH ₃) ₂	75	223	MeOH	253
e	-4-Cl	70	214	EtOH	272

Table (2):-The Physical and (I.R) spectroscopy properties of compounds (3 (a- e))

Comp. No	Characteristic bands of IR. spectra		IR (KBr) ν cm ⁻¹				Others
	Ar	C \equiv C ν	C=N ν	(C=C) ν	C-H ν	ν N- H	
a	C ₆ H ₄ -2-NO ₂	1463 1612	1673	3114 3153	3114 3153	3390	3492 (OH)
b	C ₆ H ₄ -4-OH	1460 1602	1650	3043 3102	3043 3102	3442	817 (Br)
c	C ₆ H ₃ -3-OH-4-OCH ₃	1461 1564	1643	3043 3155	3043 3155	3415	1382 (NO ₂)
d	C ₆ H ₄ -4-N(CH ₃) ₂	1460 1611	1650	3101 3150	3101 3150	3395	3490 (OH)
e	C ₆ H ₅ -4-Cl	1465 1604	1652	3045 3104	3045 3104	3419	

Table (3):-The Physical and (I.R) spectroscopy properties of compounds (5 (a- e)):

Comp. No	IR (KBr) ν cm ⁻¹				ν Ar- H	Others
	R	C \equiv C ν	C=N ν	C-H ν		
a	2-NO ₂	1450,1556	1621	2885	3052	2998 C-H
b	4-OH	1456,1558	1620	2878	3092	3350 OH
c	3-OH-4-OCH ₃	1456-1556	1620	2960	3090	
d	4-N(CH ₃) ₂	1456-1552	1620	2960	3090	
e	4-Cl	1450-1552	1610	2890	3100	

Table (4) biological activity to chemical compound MBO (1) ,MMBA (2) EMBA1 (4) ,HMBA2, (5) , with three species plant pathogenic fungi

F*S	Chemical compound (C)				Concentration (S)	Fungi (F)	
	HMBA2 _{COMP.} (5)	MBO _{COMP.} (1)	MMBA _{COMP.} (2)	EMBA1 _{COMP.} (4)			
8.33	22,22	*11.11	0.00	0.00	100	Fusariumgraminarium F1	
21.11	40.00	31.11	0.00	13.33	200		
43.33	55.56	100.00	0.00	17.78	300		
13.23	27.45	23.53	0.00	1.96	100	Sclerotiniasclerotium F2	
27.45	50.48	43.14	0.00	15.69	200		
52.45	70.59	100.00	11.77	27.45	300		
2.94	0.00	11.77	0.00	0.00	100	Rhizoctoniasolani F3	
10.07	13.73	26.53	0.00	0.00	200		
36.76	27.45	100.00	0.00	19.61	300		
Fungi effect							
24.26	39.36	47.40	0.00	10.37	F1	F*C	
31.05	49.67	55.56	3.92	15.03	F2		
16.59	13.73	46.10	0.00	6.54	F3		
Concentration effect							
8.17	16.56	15.47	0.00	0.65	S1	S*C	
19.54	34.90	33.59	0.00	9.67	S2		
44.18	51.20	100.00	3.92	21.61	S3		
	34.22	49.69	1.31	10.65	Chemical compound		
LSD	F	S	C	F*S	F*C	S*C	F*S*C
	1.67	1.67	1.93	2.90	3.35	3.35	5.80

*= moderate inhibition percent to three replicate

C*S=chemical compound and concentration intergrade

F*C = chemical compound and fungi intergrade

F*S*C= interference among chemical compound, concentration its and fungi

LSD = intangible difference less

chemical moderate effect (C) investigate all compound morale inhibited bating MMBA compound its lack effect inhibition in fungi growth ,MBO surpass and after HMBA2 two its inhibition percent investigate amount 49.69 and 34.22%

continually. Compound concentration effect (S) 300 ppm. Surpass on 200, 100 ppm, interaction between chemical compound and concentration (S×C) inhibition upper amount 100 % investigate with 300 ppm to MBO compound all fungi its test.

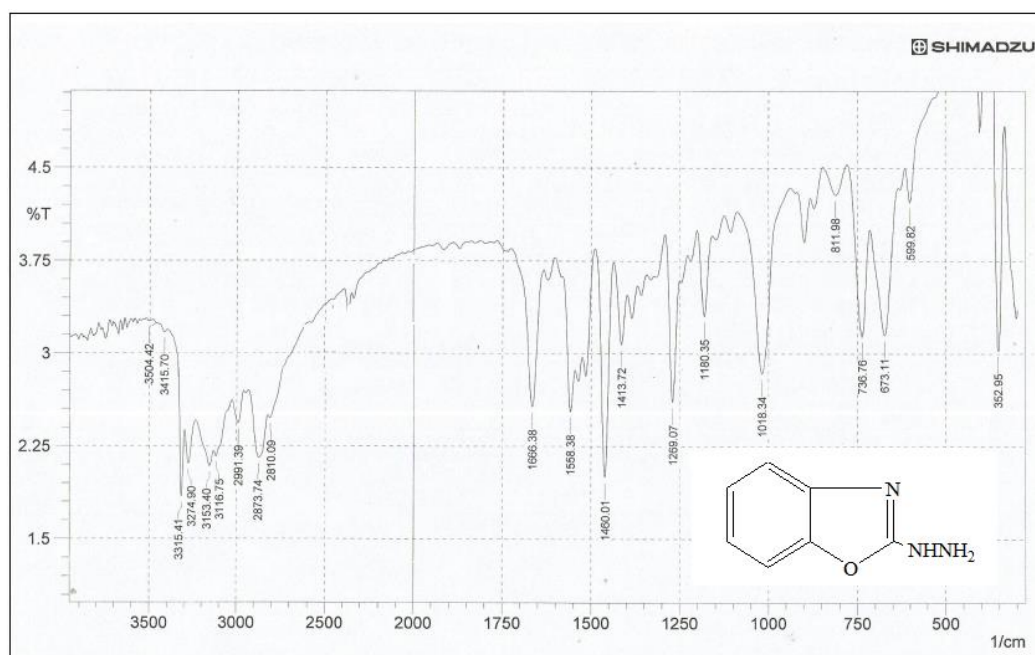


fig.(1)IR for compound (2)

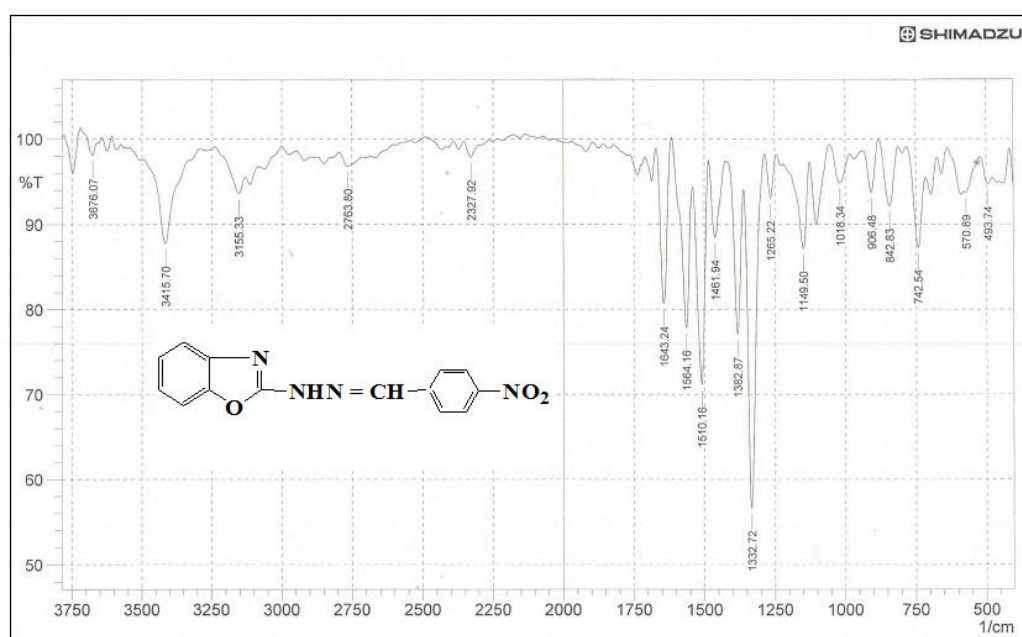
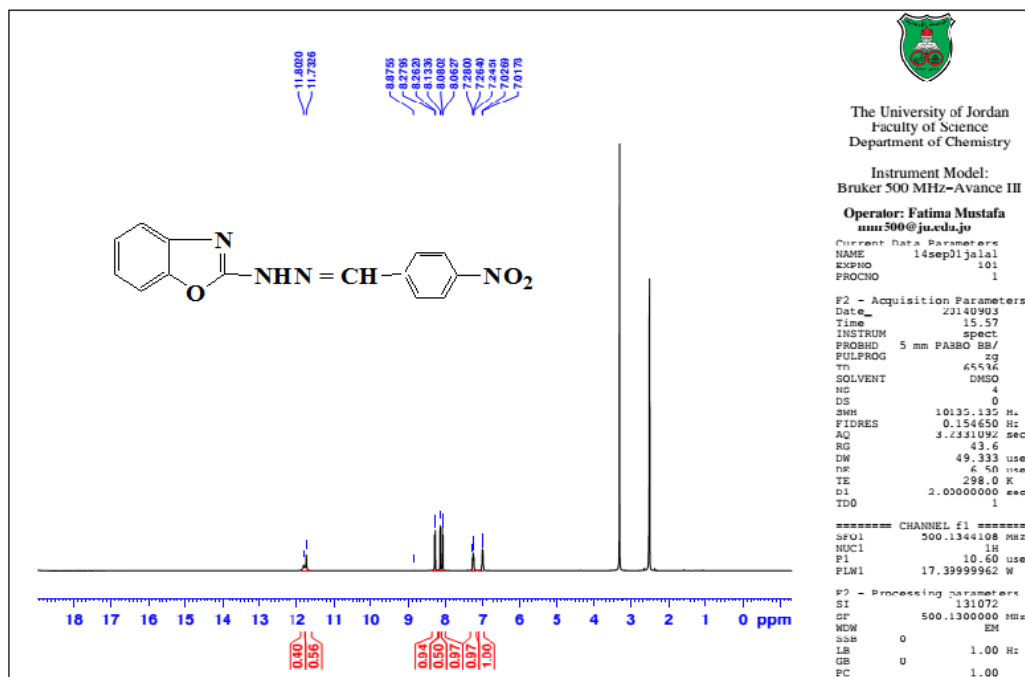
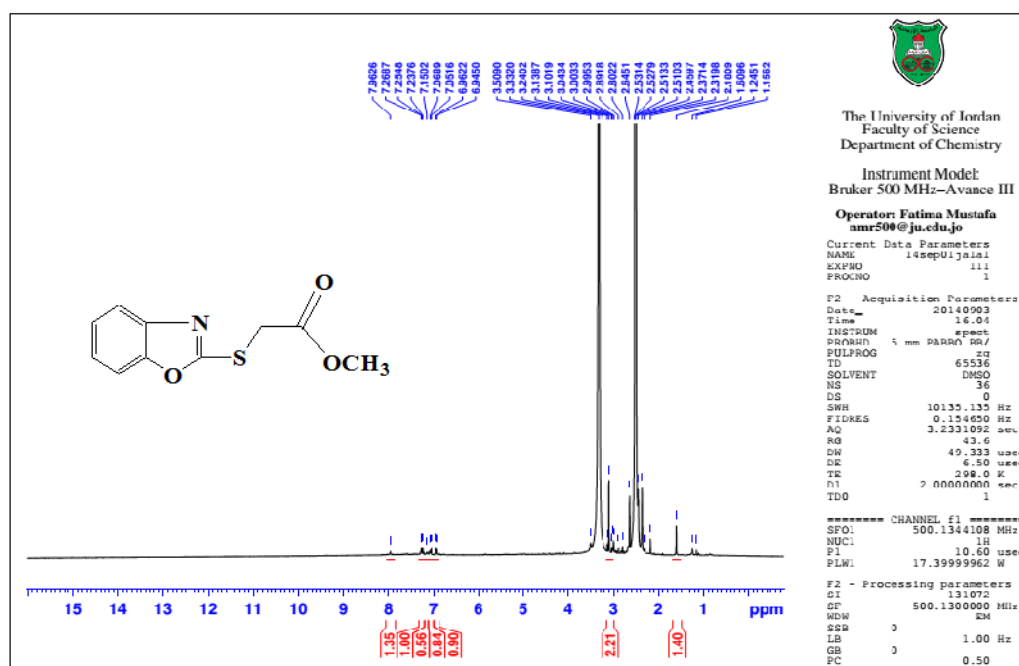


fig.(2)IR for compound (3b)

fig.(3) ¹HNM.R for compound (3b)fig.(4) ¹HNM.R for compound (4)

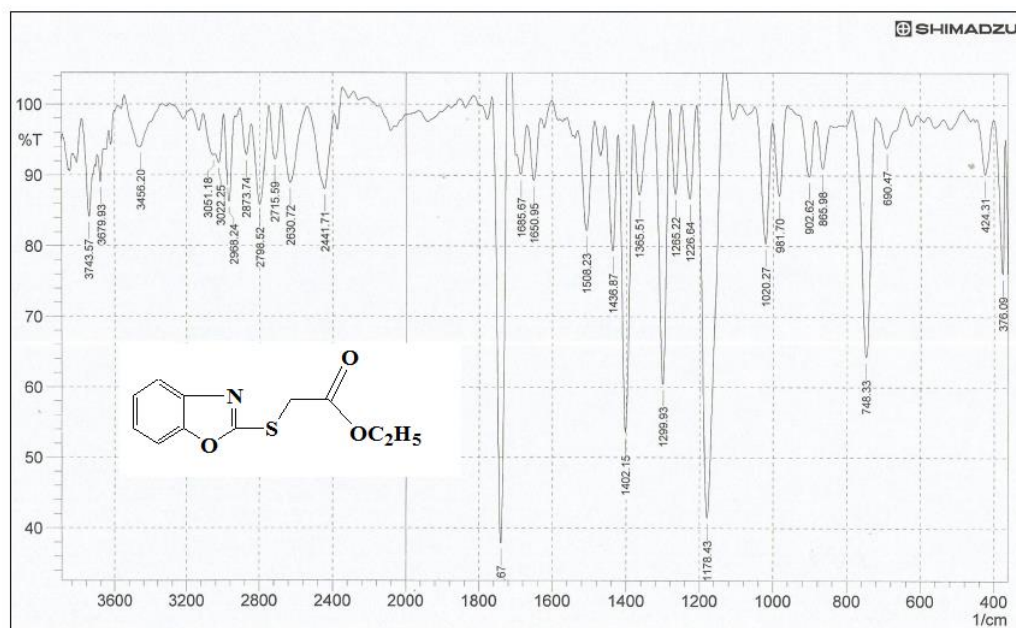


fig.(5)IR for compound (4)

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تحضير بعض المشتقات الجديدة 2- مركبتو بنزواوكسازول ودراسة فعاليتها البايولوجية ضد بعض الفطريات الممرضة للنبات

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الملخص

يتضمن هذا البحث تحضير المركب 2-مركبتو بنزواوكسازول (1) من تفاعل المركب أورثوهيدروكسي أنيلين مع ثنائي كبريتيد الكاربون في محلول هيدروكسيد البوتاسيوم الكحولي ، وحضر المركب 2-هيدرازينو أوكسازول (2) من تفاعل المركب 2-مركبتو بنزواوكسازول (1) مع الهيدرازين المائي في ألأيثانول، كما حضرت الهيدرازونات (3a-b) من التكايف لمعوضات البنزولديهايد مع 2-هايدرازينو في ألأيثانول، بعد ذلك تم تحضير ائيل-2-(بنزوكسازوليل ثايو) استيت (4) من تفاعل 2-مركبتو بنزواوكسازول مع أئيل كلوروأستيت في محلول هيدروكسيد البوتاسيوم الكحولي .وأخيرا حضر المركب الهيدرازيد (5a-e) من تفاعل ائيل-2-(بنزوكسازوليل ثايو) استيت (4) مع الهيدرازين المائي بوجود الكحول. وكل هذه المركبات شخصت بواسطة طيف بواسطة (IR). اظهرت نتائج اختبار تقييم الفعالية البايولوجية للمركبات التالية (MMBA, MBO, EMBA2) بطريقة تسميم الوسط الغذائي (PDA) potato Dextrose Agare (PDA) وبثلاث تراكيز 100, 200, 300 ملغم / لتر ضد ثلاثة انواع فطرية ممرضة للنبات ومنها الفطر Fusariumgraminarium المسبب لمرض تعفن الجذور ولفحة سنابل الحنطة head blight والفطر Sclerotiniasclerotium المسبب لمرض العفن الابيض على نبات الباذنجان والفطر Rhizoctoniasolani المسبب لمرض موت البادرات damping- off لعدد من النباتات ومنها نبات القطن والتي تم عزلها من عوائلها النباتية على الوسط الغذائي PDA وبقياس قطر مستعمرة نمو تلك الفطريات اظهرت النتائج تثبيط معنوي لنموها باستثناء مركب MMBA الذي انعدم تأثيره التثبيطي في نمو مستعمرة تلك الفطريات ، وقد تفوق معنويا مركب MBO ويأتي بعده المركب EMBA2 وكلاهما حققا معدل تثبيط بلغ 49,69 و 34,22 % على التوالي . ولتأثير متوسط تراكيز تلك المركبات اظهرت النتائج تفوق معنوي للتركيز الثالث 300 ppm على التركيزين الاول والثاني ، ومن الملاحظ لتأثير تداخل تركيز المادة الكيميائية ونوعها يلاحظ اعلى تثبيط بلغ 100 % تحقق مع التركيز الثالث لمركب MBO ومع جميع الفطريات التي تم اختبارها .