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Mousa & Jassim

المجلة العراقية لبحوث السوق وحماية المستهلك

SYNTHESIS, CHARACTERIZATION, AND STUDY THE BIOLOGICAL ACTIVITY OF SOME SCHIFF'S BASES, AND 1,3 - OXAZEPINE COMPOUNDS DERIVED FROM SULFAMETHOXAZOLE DRUG

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ABSTRACT

This study including synthesis of some new Schiff bases compounds [1-6] from the reaction of Sulfamethoxazole drug with some aromatic aldehydes in classical Schiff base method then treatment Schiff bases with succinic anhydride to get oxazepines rings [7-11]These derivatives were characterized by melting point,FT-IR,^{1}H NMR and mass spectra. Some of synthesized compounds were evaluated in vitro for their antibacterial activities against three kinds of pathogenic strains *Staphylococcus aureus*,*Escherichia coli* and *Pseudomonas aeruginosa*by agar diffusion disk method, and against the fungal species (*Candida*). The results showed that some of these derivatives have good antibacterial activities compared to biological activity of parent drug.

Keywords: Sulfamethoxazole , Schiff base , 1,3-Oxazepine, antibacterial activity .

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تحضير تشخيص ودراسة الفعالية البايولوجية لبعض مركبات قواعد شف و3,1- اوكسازبين المشتقة من دواء السلفاميثاكسازول

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الخلاصة

تضمنت الدراسة تحضير بعض المركبات الجديدة لقواعد شف (1-6) من تفاعل دواء السلفاميثاكسازول مع بعض الالديهايداتالاروماتية بالطريقة التقليدية لقواعد شف، وبعد ذلك تم مفاعلة قواعد شف المحضرة مع انهيدريدالسكسنيك لتعطي مركبات 3,1-اوكسازبين (7-11)، وشخصت هذه المركبات بقياس درجات الانصهار واطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون والكتلة، وتم تقدير الفعالية الحيوية المضادة للبكتريا لبعض المركبات المحضرة ضد ثلاث أنواع سلالات مرضية لبكتريا *Staphylococcus aureus* و *Escherichia coli* و *Pseudomonas aeruginosa* وضد نوع من الفطريات (*Candida*) بأستخدام طريقة أنتشار القرص في الاكار، وكشفت النتائج بعض هذه المركبات أظهرت فعالية جيدة ضد هذه البكتريا وللفطريات مقارنة بالدواء المشتقة منه.

الكلمات المفتاحية: السلفاميثاكسازول، قواعد شف، 3,1-أوكسازبين،الفعالية الحيوية المضادة للبكتريا.

INTRODUCTION

4-Amino-N-5-methyl-3-isoxazolylbenzenesulfonamide is the common name of Sulfamethoxazole, but N1-5-Methyl-3-isoxazolyl sulfanilamide, is the IUPAC name(Figure 1).This drug was considered by previous working groups **(Lyon, 1980; Lyon, 1987)**.Sulfamethoxazole is an antibiotic that has been used since the 1990s to treat various general injuries in humans and different species. There wasmore usein the treatment of acute infections of the urinary tract. AlsoSulfamethoxazole is used against gonorrhea, meningitis, respiratory infections and prevention of poor meningococcal meningitis. Given the relatively unfavorable, pattern of tissue delivery, antibacterial medication that is widely used to treat various systemic infections worldwide with trimethoprim or pyrimethamine. With methoprim, the mixture is used mainly to treat the device's inflammation. Sulfamethoxazole of chloroquineresistant plasmodium falciparum malaria**(Lyon,1980; Gennaro, 1995; Elggellal& Alshadly, 2014)**.

Researches on complexes of sulfamethoxazole have a lot of physiological and pharmacological due to complexes of sulfa drugs have been discovered to be more bacteriostatic than the medication themselves**(Alias *et al.*, 2015; Al-Khodir, 2015)**.

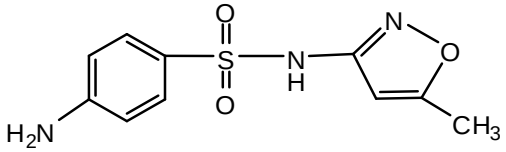


Figure (1): The structure of Sulfamethoxazole.

A heterocyclic compound consisting of an oxygen atom at site 1 and a nitrogen atom at position 3 in addition to five carbon atoms is 1,3- Oxazepinecompound**.** In 1965, the oxazepine derivative was introduced use to relieve psychoneurosis symptoms marked by anxiety and stress**(Kuluod& Hamid, 2013)**. Oxazepine derivatives has been shown to display a broad range of biological activites, including antibacterial, antifungal, hypnotic relaxant, muscle inflammatory and antiepileptic activities**(Taha, 2017)**.

MATERIALS AND METHODE

Materials and measurements of physical

Both reactants and solvents used in this study were reagent grade and are available from companies such as Sigma-Aldrich, BDH and Fluka. Sulfamethoxazole was obtained from Samara, Iraq.

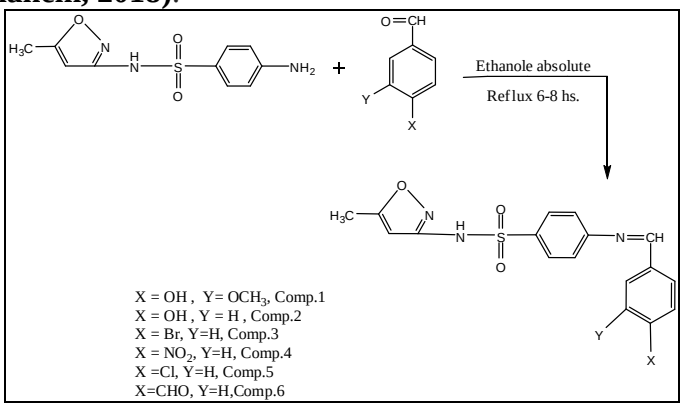
Melting points have been registered and are uncorrected using a hot stage Gallen Kamp melting point apparatus. SHIMADZU model FT-IR-8400S was used to receive the FT-IR spectrum. On the BRUKER model Ultra shield 300MHz spectrophotometer . ^{1}H-NMR spectra were obtained in the DMSO-d6 solution with the TMS as the internal standard. Mass spectra were recorded using Mass Spectrometer, Agilent Technology (HP) at Tehran University, Central Lab, Iran.

Common technique of preparing of Schiff bases (1-6)

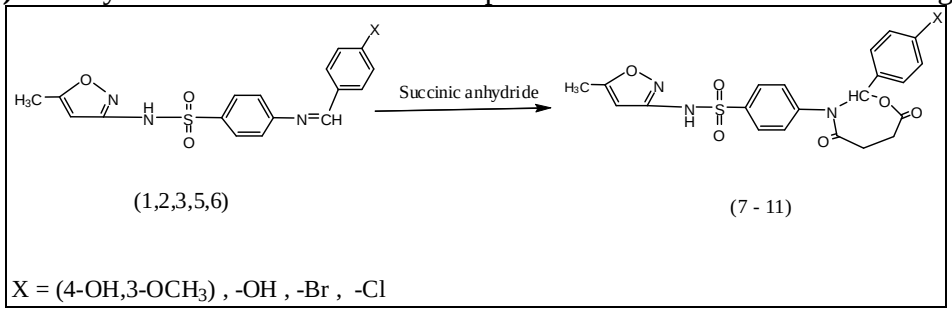
For 6-8 hrs, a mixture of Sulfamethoxazole (0.0039 mole,1 g), and various aromatic aldehydes (0.0039mol) in absolute ethanol (15 mL) and 3 drops of glacial acetic acidwere refluxed**(Jassim & Ali, 2018; Abdullah *et al*., 2013).**The mixture was cooled and the solid was purified after the end of the reaction, checked with TLC ethanol: benzene (1:1),then recrystallized from ethanol and collected by filtration, as shown in (Scheme 1) (Table 1) describes the physical properties of these compounds.

Preparation 1,3-oxazepin-4,7-dione derivatives (7-11)

In 15 mLof dry benzene, Schiff base (1,2,3,5-6) (0.0005 mol) was combined withphthalic anhydride (0.0005 mol) and then refluxed for 18-20 hrs, evaporating the excess solvent. The solid product was washed with distilled waterand then purified and recrystallized, as illustrated in (Scheme 2)(Table 2) lists the physical properties **(Tawfiq*et al*.,2012;Muhsen*et al*., 2017; Sallal&Ghanem, 2018)**.

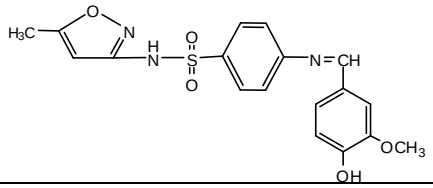
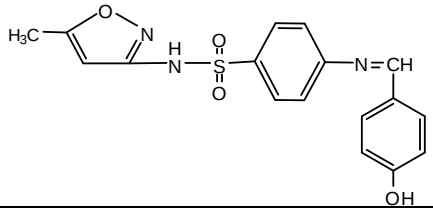
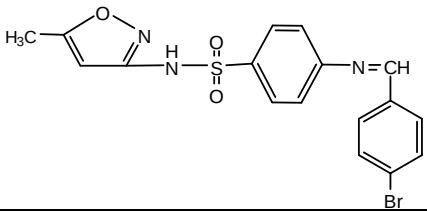
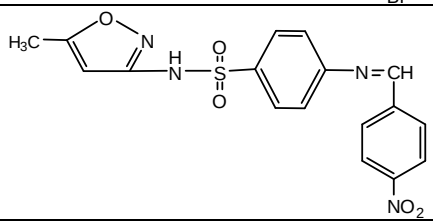
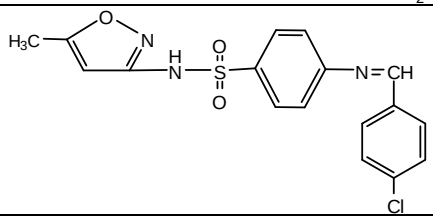
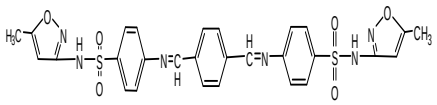


Scheme (1): The synthesis of Schiff's bases compounds from Sulfamethoxazole drug.

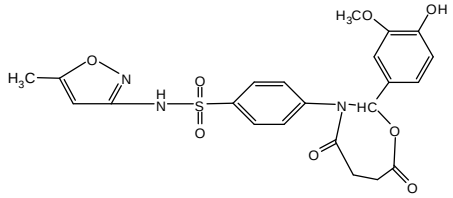
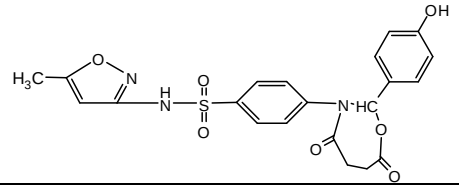
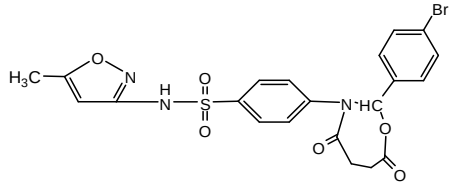
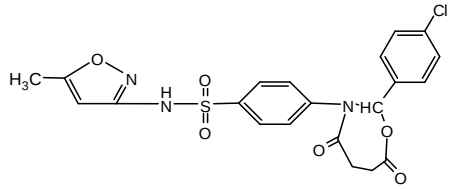
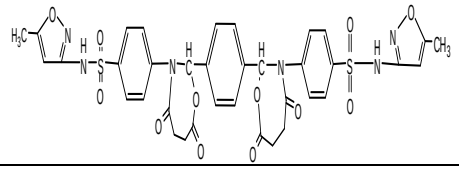


Scheme (2): The synthesis of 1,3-oxazepin-4,7-dione derivatives (7-11) by reaction Schiff's bases compounds with succinic anhydride

Table (1): Physical properties of compounds of the Schiff base(1-6).

Comp. No.	Structure of Compounds	Molecular Formula	Molecular Weight (g/mole)	Yield (%)	M.P. (^{o}C)	Colour	Rf
1		$C_{18}H_{17}N_3O_5S$	387.40	76	172-174	Dark yellow	0.74
2		$C_{17}H_{15}\ N_3O_4S$	420.28	81	192-194	Pale yellow	0.76
3		$C_{17}H_{14}N_3O_3SBr$	420.28	81	196-198	Pale yellow	0.76
4		$C_{18}H_{14}N_4O_5S$	386.28	83	88-90	Yellow	0.77
5		$C_{17}H_{14}N_3O_3SCl$	375.78	86	137-139	Pale Yellow	0.81
6		$C_{28}H_{24}N_6O_6S_2$	604.56	85	> 250(dec)	Orange	0.58

Table(2): The physical properties of 1,3-oxazepin derivatives (7-11).

comp. no.	Structure of Compounds	Molecular Formula	Molecular Weight (g/mole)	Yield (%)	M.P. (^{o}C)	Colour	Rf
7		$C_{22}H_{21}N_3O_8S$	487.98	74	165-167	yellow	0.76
8		$C_{21}H_{19}N_3O_7S$	457.40	75	135-137	Dark yellow	0.90
9		$C_{21}H_{18}N_3O_6SBr$	520.28	73	154 - 156	Orange	0.82
10		$C_{21}H_{18}N_3O_6SCl$	475.78	74	140-142	Yellow	0.94
11		$C_{36}H_{32}N_6O_{12}S_2$	704.56	73	210-212	Orange	0.77

RESULTS AND DISCUSSION

The Schiff's bases compounds of sulfamethoxazole (1-6) were synthesized in good percentage from the reaction ofSulfamethoxazole with different aromatic aldehydes in absolute ethanol as a solvent. These compounds have been synthesized according to the steps described in (Scheme 1).

The physical properties described in (Table1)and spectral methods, such as FT-IRandsome of them by ^{1}H- NMR, verified the structures of (1-6) compounds,spectra of compounds (1-6) displayed, characteristic absorption bands at 1614-1627cm^{-1}, 2976-2993cm^{-1}, 2839-2891cm^{-1}, 3066-3086cm^{-1} and1465-1593cm^{-1}due to stretching vibrations for (C = N)-asymmetrical, (C-H) aliphatic, symmetrical(C-H)aliphatic,(C-H) aromaticand (C=C) aromatic. These and other bands as shown in (Figures 2,3and4).

At 1735-1774cm^{-1}, 2854-2997cm^{-1} and 1265-1267cm^{-1}, 1693-1706cm^{-1}and 1157-1161cm^{-1} to stretch vibrations (C = O)lactone (C=O), lactame, (C-H) aliphatic, (C-N) and (C-O-C) band, the FT- IRspectra of oxazepine compounds (7-11) displayedcharacteristic absorption bands.These and other bands are shown in (Table 4), as shown in (Figure 5).

The ^{1}H-NMR spectra of compounds (1, 3and 6) showed the signal at 2.24, 2.25 and 2.31ppm due to proton of (CH_3) group and the singlet signal at 6.11, 6.05 and 6.08ppm due to proton of isoxazol ring, the multiplet signals at δ[(7.30-7.83) ,(7.33-7.85),(7.44-7.47)]ppm, the singlet signal appeared at δ (8.40, 8.58, 8.73)ppm which could be assigned to proton of (N=CH) group that could be assigned to protons of benzene rings, and the singlet signal at δ (10.92,11.42,10.91)ppm. suggested the attribution of the proton of (NH) group of sulfonamideas shown in (Figures 6,7and 8) .

The ^{1}H-NMR spectra of compounds (7and10) showed the signal at 2.26and2.29ppm due to proton of (CH_3) group,and signal at 2.06-2.79ppm due to the protons of oxazepine ring (CH_2), while the other signals are listed in as shown in (Figures 9 and 10).

The compound 1 mass spectrum (Figure 11), shows the molecular ion at m/z = 387.4,an d the compound 3 mass spectrum,(Figure 12), shows the molecular ion at m/z = 420.28.

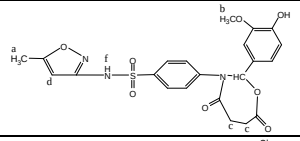
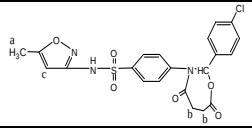
Table (3): The FT-IR distinguishing bands of Derivatives (1-6).

Deriv. No.	Molecular Formula	ν (C-H) Ar.	ν (C-H) Aliph.	ν (C=N)	ν (C=C) Ar.	another bands
1	$C_{18}H_{17}N_3O_5S$	3084	2993,2891	1618	1467-1593	**ν (C-O-C)** (1265,1029) *P-OH(3588)*
2	$C_{17}H_{15}N_3O_4S$	3066	2981,2854	1618	1465-1593	*P-OH(3589)*
3	$C_{17}H_{14}N_3O_3SBr$	3086	2987,2848	1627	1473-1579	*P-Br 684*
4	$C_{18}H_{14}N_4O_5S$	3086	2976,2875	1616	1465-1593	*P-*NO_2(1533 , 1342)
5	$C_{17}H_{14}N_3O_3SCl$	3088	2991,2839	1616	1467-1593	*P-Cl* 786
6	$C_{28}H_{24}N_6O_6S_2$	3086	2991,2879	1614	1469-1581	

Table (4): The FT-IR distinguishing bands of derivatives (7-11).

Comp.No.	Molecular Formula	ν (C-H) aromatic	ν (C-H) aliphatic	ν (C=O) lactone	ν (C=O) lactame	ν (C-N)	ν (C-O-C)	Other Bands
7	$C_{22}H_{21}N_3O_8S$	3078	2987,2893	1745	1701	1161	1267	*p-OH*3550
8	$C_{21}H_{19}N_3O_7S$	3092	2931,2854	Overlap with C=O lactame	1705	1157	1265	*p-OH*3464
9	$C_{21}H_{18}N_3O_6SBr$	3093	2997,2897	Overlap with C=O lactame	1705	1161	1265	*p-Br*686
10	$C_{21}H_{18}N_3O_6SCl$	3093	2926,2854	1735	1693	1157	1265	*p-Cl*792
11	$C_{36}H_{32}N_6O_{12}S_2$	3095	2922	1774	1706	1161	1265	------

Table 5 : ^{1}H-NMR Spectral information for selected derivatives.

Deriv.No.	Derivative Structure	^{1}H-NMR parameters (ppm) δ-H
7		a(2.26)(s,3H,CH_3);b(3.81)(s,3H,CH_3);c(2.06 – 2.39)(t,4H,2CH_2);d(6.07)(s,1H,isoxazol ring); (6.54 - 8.58)(m,8H,for both two benzene ring);f(11.32)(s,1H,NH)
10		a(2.29)(s,3H,CH_3);b(2.54-2.79)(t,4H,2CH_2);c(6.08)(s,1H,isoxazol ring);7.40(s,1H,CH of oxazepin ring);7.44-7.96(m,8H,for both two benzene ring);10.95(s,1H,NH)

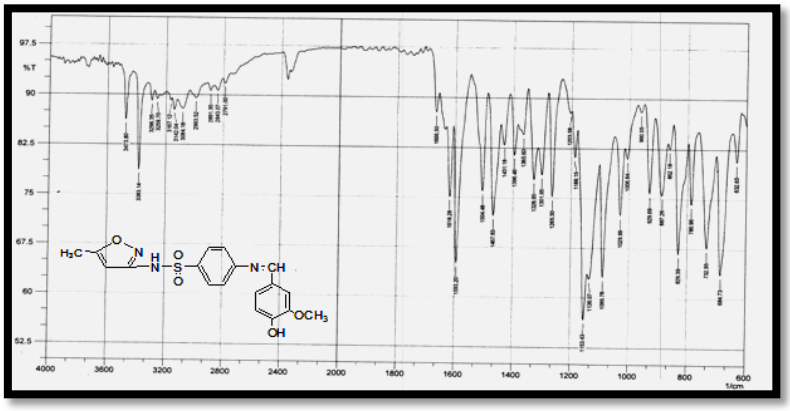


Figure (2):FT-IR Spectrum of compound 1 .

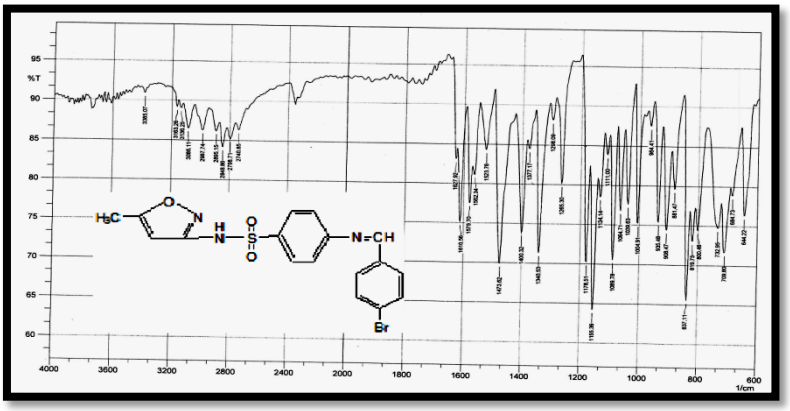


Figure (3): FT-IR Spectrum of derivative 3 **.**

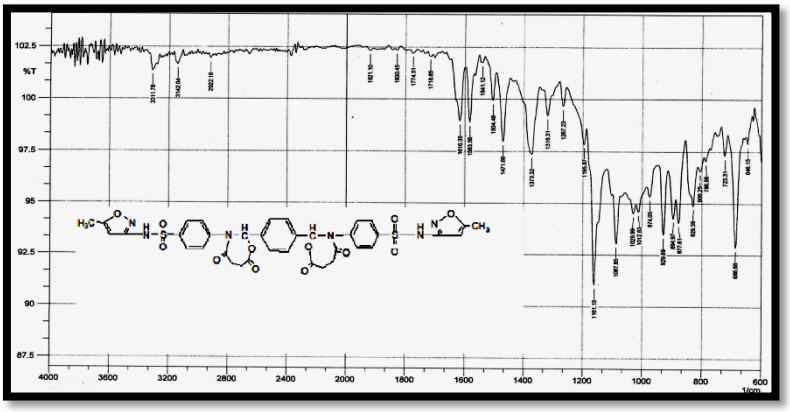


Figure (4): FT-IR Spectrum of derivative 6 .

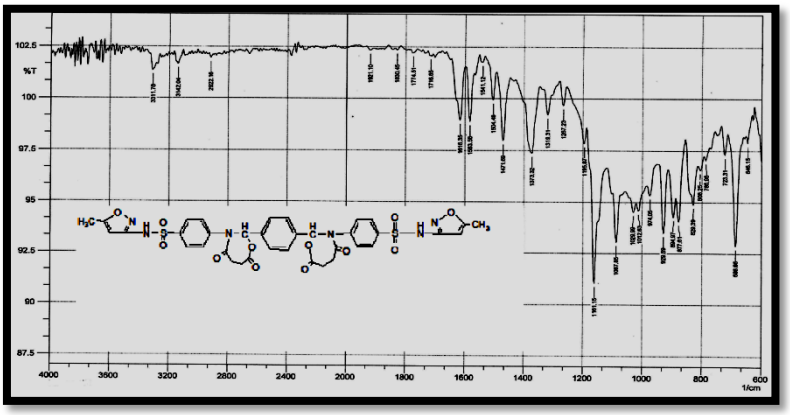


Figure (5):FT-IR Spectrum of derivative 11.

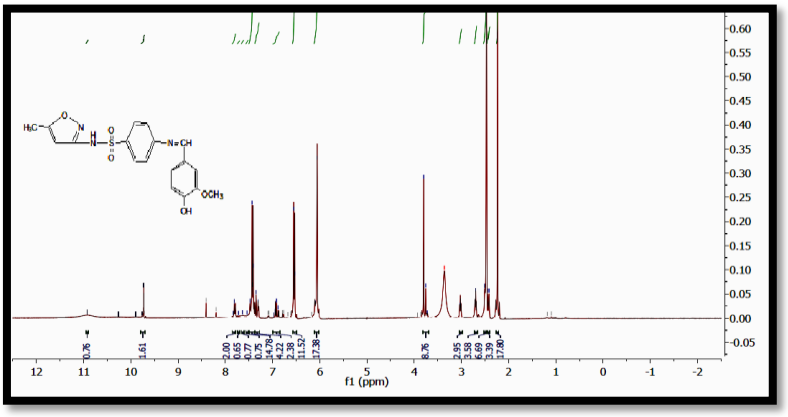


Figure (6): ^{1}H-NMR chart for derivative 1

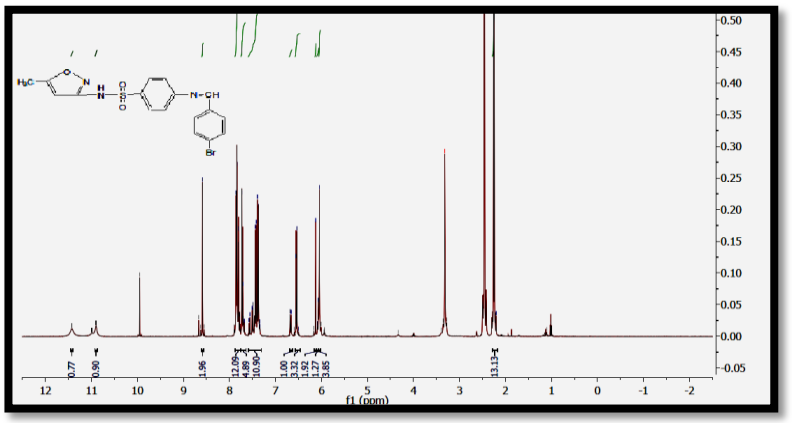


Figure (7): ^{1}H-NMR chart for derivative 3

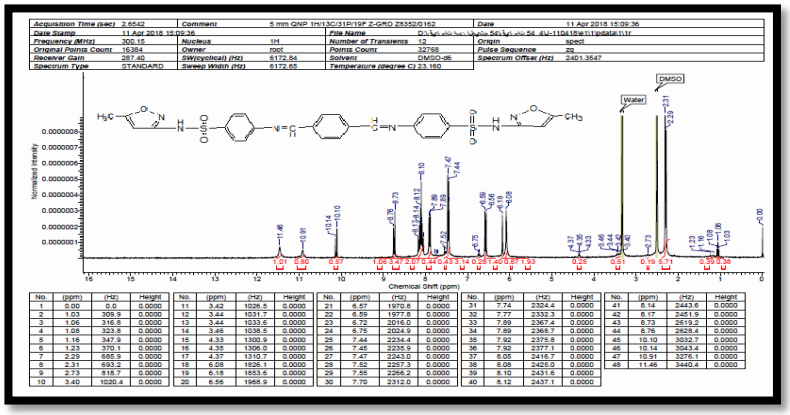


Figure (8): ^{1}H-NMR chart for derivative 6.

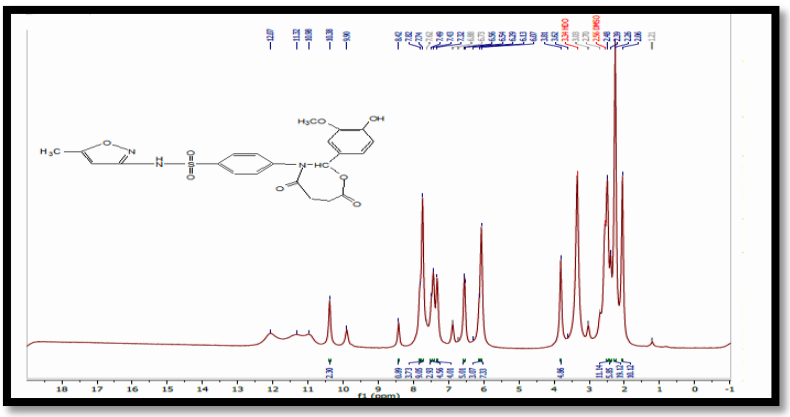


Figure (9): ^{1}H-NMR chart of derivative 7.

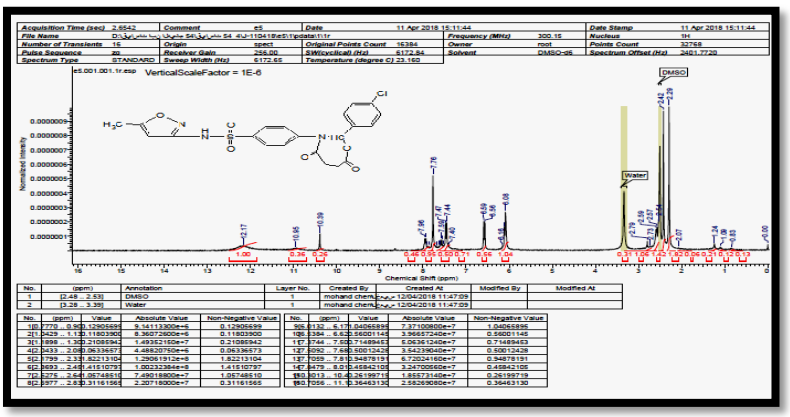


Figure (10): ^{1}H-NMR chart of derivative 10.

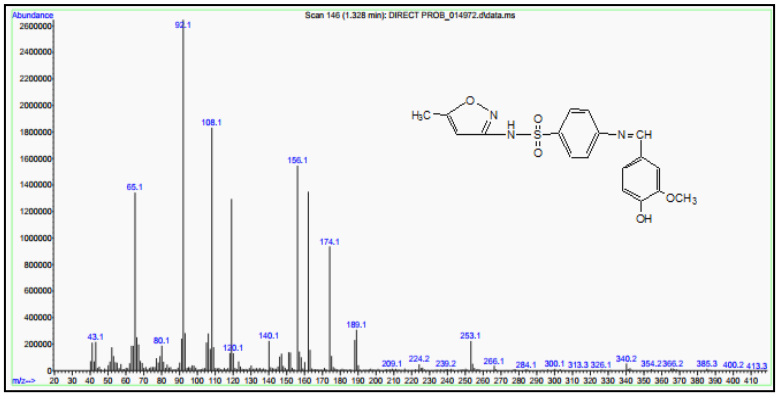


Figure (11): mass chart of derivative 1.

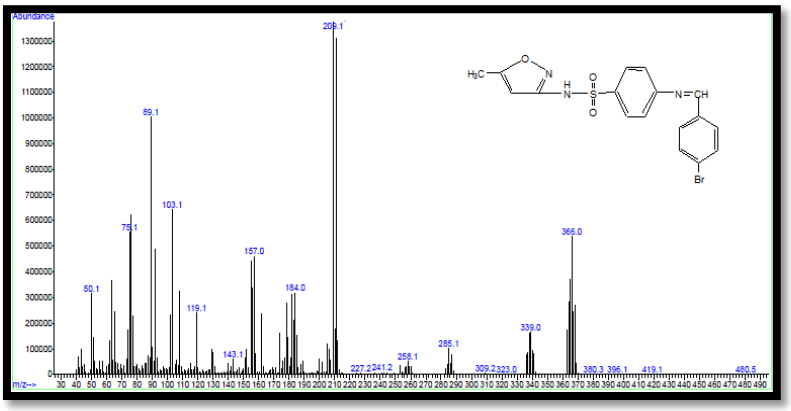


Figure (12): mass chart of derivative 3.

BIOLOGICAL ACTIVITY

Anti-bacterial activity

Three forms of pathogenic strains(*S. aureus*,*E.coli*and *P. aeruginosa*were used to test the antimicrobial activity of the synthesized compounds(2,4,7,10and11) using the agar diffusion process.Appropriate spaced separate holes were created by Muelle Hinton agar (6mm in diameter) appropriate spaced separate holes were filled with 0. 1mLconcentration of prepared compounds that dissolve in DMSO before spreading the bacteria on agar.These plateswere incubated for 24 hr at 37^{o}C,the bacteria growth inhibitionzone around the holeobser vedand measured in millimeter of diameter **(Entesar& Enaam, 2017; Saleh& Ali, 2020)**. Results and clarification are given in (Table 6).

Anti-fungal activity

The antifungal activity was tested against the fungal species, *C. albicans* at 10mg /mL concentration ofsome prepared compounds using DMSO as solvent.The results were reported as zone of inhibition compared to standard Nystatin as antifungal drugs. The results obtained showed that some of these derivatives showed commensurable activity like exhibited by (Table, 7) .

Table (6): Antimicrobial Activities of several prepared derivatives**.**

Deriv. No.	Sample No. (In image)	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
2	9	+ ++	+ +	+ +
4	8	++ +	+ +	+ +
7	3	++ +	++	+ +
10	10	++ +	+ +	----
11	15	++ +	+ +	----

(++) = 18- 24mm, (+++) = 28-33mm.

Table (7): Anti-fungicide activity for the prepared derivatives(6,7,and8) **.**

Deriv.No	*Candida albicans*
6	S
7	R
8	S
Nystatine	S

S: Sensitive,R: Resistance.

CONCLUSION

The results indicate that the synthesized compounds (2, 4,7,10 and 11) have a microbial activity against the tested organisms up to 3.2mg/ disk.Thesederivatives showed higheffect against *S. aureus*and moderately activity against*E.coli*and *P.aeruginosa*.the fungal species, *Candida albicans* showed higher sensitivity toward the compounds 6 and 8 more than compound 7 .

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