Synthesis and Characterization of (Oxazepine,Diazepine,Tetrazole) for Derivatives of Sulfamethoxazole Drug

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(**Received:** 13 / 2 / 2012 ---- **Accepted:** 28 / 5 / 2012)

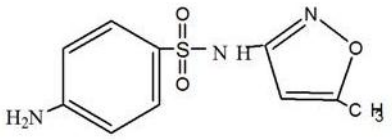
Abstract

The present work involved synthesis of serval new substituted (Oxazepine,Diazepine and tetrazole via Schiff bases for selfamethoxazole drug by four steps. The first step involved preparation Schiff bases (A_1-A_5) by condensation of selfamethoxazole drug with many substituted ketones,then ,the second step include ,preparation new five oxazepines compounds (B_1-B_5) by reaction of phthalic anhydrid with the prepared Schiff bases in first step . The third step including reacting compounds (B_1-B_5) which prepared in the second step with primary oramatic amines to give new five Diazepine compounds (C_1-C_5) . Finally the fourth step, preparation new tetrazole derivatives D1-D5 by reaction of the prepared Schiff bases (in the first step) with sodium azide in THF. The prepared compounds were characterized by physical properties ,(FT-IR,UV. and some of them by ^{1}H-NMR , ^{13}C-NMR spectroscopy) were recorded and the biological activity was evaluated against two kinds of bacteria gram positive and gram negative**.**

Keyword: sulfamethoxzale drug ,Schiff bases ,Oxazepine ,Diazepine tetrazole.

Introduction

Sulfamethoxazole is 4-Amino-N-(5-methyl-3-isoxazolyl) benzene sulfonamide with the following structural formula**.** [1, 2]



It is sulfonamide bacteriostatic antibiotic**.**Sulfonamides are structural analogs and competitive antagonists of para-amino benzoic acid (PABA)[3],sulfamethoxazole prevents.The formation of dihydrofolic acid,acompounds that bacteria must be able to make in order to survive[4]**.** It was reacted with selected ketone and testing give Schiff bases and it is complexest important biological activity[5] **.** Schiff bases are characterized by the N=CH (imine) group which important compounds in medicinal and pharmaceutical field[6-7]**.**They show biological activities including antibacterial,antifungal[9,10] ,anticancer[11], and herbicidal activities[12]**.** Furtheir more Schiff bases have been widely used as protective group of amino group in organic synthesis **.**Schiff bases react with phthalic anhydride, Maleic anhydride and substituted phathalic anhydride to give1,3-oxazepine-4,7-dione and test it is biological activity[5]**.** Oxazepine (benzodiazepine) derivative introduced in 1965 for use in relief of the psychoneuroses characterized by anxiety and tension, oxazepam is nonhomologous seven membered ring that contains, two heteroatoms (oxygen and nitrogen)[13]**.** The reaction of oxazepine with primary aromatic amine gives**.** The corresponding 1,3-diazepine-4,7-dione.Many of the benzodiazepines and their oxides show interesting sedatives ,muscie relaxant and anticonvulsant properties in animals[14]**.**Then sechiff bases react with sodium azide to give tetrazoles**.** They are aromatic five membered ring containing four nitrogen atoms, the first tetrazole was reported over acentury ago[15]**.** Tetrazoles have been found to exhibit antibacterial[10], antifungal, and antihistamine[12],and anti-inflammator properties[16]

Material and methods

General

Chemicals employed were of analytical grade and used without further purification ,melting points were determined in Gallen kamp melting point apparatus and were uncorrected.UV-Visible spectra were recorded on shimadzuT60u spectrophotometer using ethanol as a solvent, FT-IR spectra were recorded on shimadzu FT-IR-8400 Fourier Transform infrared spectrophotometer as KBr disc**.** ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker specrospin Ultra shield magnets 300 MHz in strument using tetramethyl silane (TMS)as an internal standared and DMSO**.**d_6 as asolvent in Al-Albate University in Jordan**.**

Preparation of Schiff bases(A_1-A_5)[6]:-

Aseries of Schiff bases (A_1-A_5) were prepared from the reaction of sulfamethoxazole (0.01mole) with different ketones (0.01mole) in 25 ml ethanol absolute and few drops of glacial acetic acid**.** This mixture was refluxed for 5hrs **.**The precipitate was filtered and recrystallized from ethanol **.**Melting points,Yield% data are listed in table (1**)**

Preparation of oxazepine derivatives(B_1-B_5)[17]:-

Amixture(0.001mole) of (A_1-A_5) compounds and (0.001mole) of phthalic anhydride (0.001mole) in 25ml of dry benzene was placed. The mixture was heated for 6hrs**.** In water bath at (80c^0), the precipitate was filtered and recrystallized from 1,4-dioxane. Melting points, Yield data are listed in table (1)**.**

Preparation of Diazepine derivatives(C_1-C_5)[18]:-

Amixture (0.001mole)of (B_1-B_5) oxazepine compounds and (0.001mole)of primary oramatic amine (p-nitro aniline) was dissolved in 30ml of tetrahydrofuran. The reaction mixture was refluxed in water bath at 85C^0 for (6hrs). then allowed to cool to room tempreture and separated crystalline was filterd and recrystallized from ethanol. Melting points, Yield % data are listed in table (1).

Preparation of Tetrazole derivatives (D_1-D_5)[19]:- Compounds of (B_1-B_5)(0.002mole)was dissolved in (20ml) tetrahydrofuran and mixed with (0.002mole) sodium azide. These mixtures were heated in water bath at $75C^0$ for 5 hrs**.** The precipitate was filtered and recrystallized from ethanol. The end of reaction was cheched by TLC in methanol [19].Melting points, yield % data are listed in table (1)**.**

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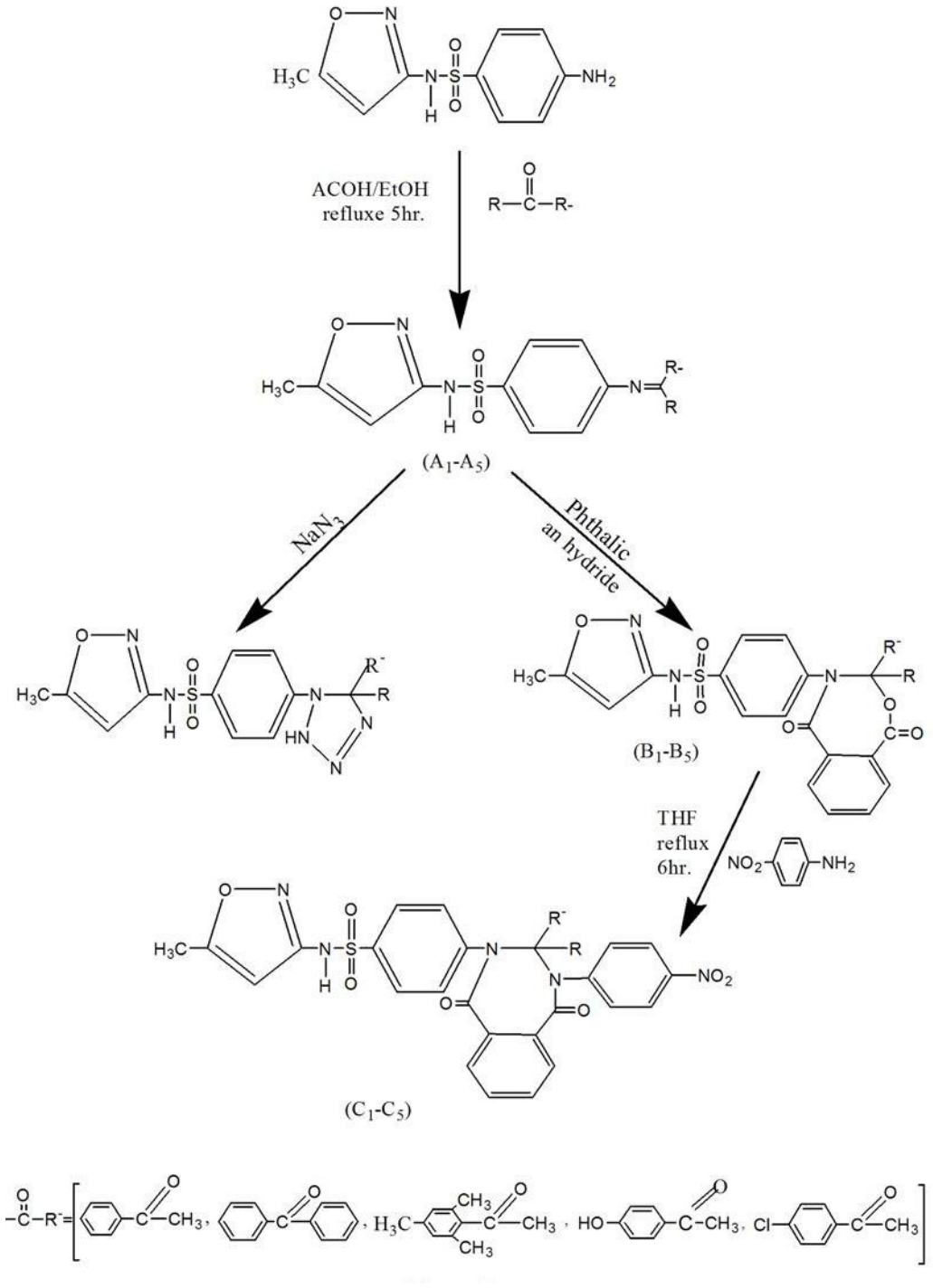


Scheme (1)

Table(1):physical properties of all product compounds

Comp. No.	R	R'	Molecular Formula	Color	Yield%	M.P. C^0	Solvent crystall.
A_1	ph	ph	$C_{23}H_{19}N_3O_3S$	Yellowesh brown	82.5	117-120	Ethanol
A_2	ph	CH_3	$C_{18}H_{17}N_3O_3S$	Yellowesh brown	74	153-155	Ethanol
A_3	Ph-4-Cl	CH_3	$C_{18}H_{16}N_3O_3S$ CL	Dark yellow	67	139-141	Ethanol
A_4	Ph-4-OH	CH_3	$C_{18}H_{17}N_3O_4S$	Light brown	89.6	87-90	Ethanol
A_5	Ph-2,4,6-CH_3	CH_3	$C_{21}H_{23}N_3O_3S$	Yellowesh brown	71	166-169	Ethanol
B_1	ph	ph	$C_{31}H_{23}N_3O_6S$	Light brown	74	150-180	1,4-Dioxen
B_2	ph	CH_3	$C_{26}H_{21}N_3O_6S$	brown	87	237-240	1,4-Dioxan
B_3	Ph-4-Cl	CH_3	$C_{26}H_{20}N_3O_6SCl$	yellow	65	157-160	1,4-Dioxan
B_4	Ph-4-OH	CH_3	$C_{26}H_{21}N_3O_7S$	red	81	235-239	1,4-Dioxan
B_5	Ph-2,4,6-CH_3	CH_3	$C_{29}H_{27}N_3O_6S$	brown	58	230-233	1,4-Dioxan
C_1	ph	ph	$C_{37}H_{27}N_5O_7S$	Yellowesh brown	43	155	Ethanol
C_2	ph	CH_3	$C_{32}H_{25}N_5O_7S$	Reddish brown	60	120-124	Ethanol
C_3	Ph-4-cl	CH_3	$C_{32}H_{24}N_5O_7SCL$	Light brown	37	235	Ethanol
C_4	Ph-4-OH	CH_3	$C_{32}H_{25}N_5O_8S$	Reddish brown	40	Oil	Ethanol
C_5	Ph-2,4,6-CH_3	CH_3	$C_{35}H_{31}N_5O_7S$	Dark brown	25	Oil	Ethanol
D_1	ph	ph	$C_{23}H_{20}N_6O_3S$	Light brown	67	139-143	Ethanol, 1,4-Dioxan
D_2	ph	CH_3	$C_{18}H_{18}N_6O_3S$	Yellowesh white	31	250	Ethanol, 1,4-Dioxan
D_3	Ph-4-cl	CH_3	$C_{18}H_{17}N_6O_3SCL$	Yellowesh brown	41	340	Ethanol, 1,4-Dioxan
D_4	Ph-4-OH	CH_3	$C_{18}H_{18}N_6O_4S$	Yellowesh white	33	174-176	Ethanol, 1,4-Dioxan
D_5	Ph-2,4,6-CH_3	CH_3	$C_{21}H_{24}N_6O_3S$	Yellowesh brown	44	Oil	Ethanol, 1,4-Dioxan

Results and Discussion

The present work involved four steps:

First step: include preparation of new five Schiff bases (A_1-A_5) were prepared by reaction of selfamethoxazole with different substituted Ketones.The synthesis of these compounds was carried out lined in scheme(1),and the physical properties for Schiff bases(A_1-A_5)including melting point range of (87-169)C^0 and% Yield were range of(67-89.6) and these compounds were identified by FT-IR, spectroscopy, FT-IR spectrum of compound(A_4) Showed characteristic absorption bands (1643)cm^{-1} ,(3140)cm^{-1} ,(2885-2997)$cm^{-1}$and(3321)cm^{-1} due to ν(C=N).ν(C-H),aromatic ν(C-H) aliphatic and ν(N-H) respectively as shown in table (3),Fig(5) attributed UV spectrum of compound(A_5)showed an absorption λmax at(220)nm,(280)nm which to (π→π*) and (n→π*). The absorption is listed in table (3), Fig(1).

Second step: The second step inclued preparation of new five Oxazepine (B_1-B_5) were prepared by reaction of Schiff bases (A_1-A_5) in (First step) with phthalic anhydride in dry benzene The synthesis of these compounds was carried out lined in scheme (1). and the physical properties for oxazepine(B_1-B_5) including melting point range of(150-240)C^0 and %Yield were range (58-87) and these compounds were identified by FT-IR and UV.spectroscopy. FT-IR spectrum of compound (B_4) showed clear absorption bands at (1716)cm^{-1} at tributed to(C=O) imide stretching frequency is good evidence for the success of this step of reaction.Also FT-IR spectra of oxazepine (B_1-B_5) showed clear absorption bands at(1168-1280)cm^{-1} due to ν(C-O-C)[20] while disappearance of ν(C=N).as shown in table (3),Fig(6). UV spectrum of compound [B_5] showed an absorption λ_{max} at (304)nm which at tributed to(π→π*).The absorbtion is listed in table (3),Fig(2).

Third step: in the third step including reaction derivatives of oxazepine (B_1-B_5) with p-nitro aniline (primary oramatic amine) to give new five Diazepine compounds (C_1-C_5).The physical properties for Diazepine (C_1-C_5) including Melting point rang (120-235)C^0 and %yield were rang (25-60),and these compound were identified by FT-IR, UV., ^{1}H-NMR and ^{13}C-NMR spectroscopy. FT-IR spectrum of compound (C_4) showed characteristic absorption bands at(1712)cm^{-1},(3410)cm^{-1}, (3471)cm^{-1} and (1307,1500)cm^{-1} due to ν(C=O),ν(N-H), ν(O-H) and V(C-NO_2) respectively as. shown in table (3),Fig(7).The structure of oxazepine substituted is combination of both lactone and lactam 7-membered heterocyclic ring.This is indicated by the appearance of the characteristic (C-N lactone ⁄C-N lactam)[21] absorption band at (1172-1182)cm^{-1} in their FT-IR spectra. The lacton group (cyclic ester) can be converted in to lactam group (cyclic amide) by reaction with aromatic primary amines [5].

In the ^{1}H-NMR spectrum of compound (C_1) showed the signal at (2.45) ppm was attributed to(CH_3) proton, and multiplet signals at (6.117-7.566)ppm due to aromatic protons and signlet signal at (7.968) ppm due to (N-H) proton for sulfamzthoxazole drug, while the signal at (10.988)ppm for oxazole ring., as shown in Fig(9).

In the ^{13}C-NMR spectrum of compound (C_1) showed the signal at (170.37) ppm for carbonyl group (C=O), while the signal at (112.84-136.11) ppm for aromatic carbons. While, the signal at (39.75) ppm for carbon of methyl group (CH_3), as shown in Fig (10). (UV) spectrum of compound (C_5) showed an absorption λ_{max} at (319)nm, (378)nm which attributed to (π-π^*) and ($n\rightarrow \pi^*$). The absorption is listed in table (3),Fig(3)

Fourth step: Tetrazole compounds (D_1-D_5) were synthesizd from the reaction of Schiff bases (A1-A5) with sodium azide in THF. All physical properties are listed in table(1) The infrared absorption bands, Fig(8),were utilized to characterize the specific structure of the synthesized compounds. The disappearance of band at (1614-1600)cm^{-1} attributed to C=N(imine group) stretching frequency is good evidence for the success of this step of reaction. Also FT-IR spectra of tetrazoles(D_1-D_5) showed clear absorption bands at(1550-1598)cm^{-1}due to ν(N=N). Beside this,the FT-IR spectra of these compounds were devoid of strong band at (2160-2120)cm^{-1}attributed to stretching frequency of azide group.The characteristic data are reported in table (3).

In the ^{1}H-NMR,the spectrum of compound (D_3) showed the (NH) from the triazole[23] ring was observed as asinglet at (10.978)ppm and signal at (2.275)ppm was attributed to (CH_3) protons, and multipl signals at(6.595-7.486)ppm duo to aromatic protons and signlet signal at(7.507)ppm due to(NH)for selfamethoxazole drug(exotetrazole), as shown in Fig (11).

In the ^{13}C-NMR spectrum of compound (D_3) the signal at (12.47)ppm for solvent DMSO, while ,the signal at (113.08-129.32)ppm for aromatic carbons, and the signat at (39.02-40.68)ppm for carbon of methyl group (CH_3) as shown in Fig(12).

UV spectrum of compound (D_5) showed an absorption λ_{max} at (304)nm, (345)nm which attributed to ($\pi\rightarrow\pi^*$) and ($n\rightarrow\pi^*$). The absorption is listed in table (3),Fig(4).

Biological Activity:

In this work the antibacterial test was performed according to the disic diffusion method[23]. Compounds (A_1-A_5),(B_1-B_5),(C_1-C_5),(D_1-D_5) were assayed for their antimicrobial activity in vitro against two strains of Gram negative bacteria (Escherichia coli,Klebsiella pneumoniae)and two strain of Gram positive bacteria (staphylococcus aurens and Enterococcus foaecalis). The inhibition zones caused by the various compounds were examined and shown in Figures(13-16).

Conclusions:

The biological activity of compounds were determined by measuring the diameter of the empty region around the well (In hibition zone)[24,25] . From the data obtained, it is found clearly that All compounds have the highest activity against staphylococcus aurens than others, while All compounds have the slight activity against (Enterococcus faeclis) Also compound (D_4) have hightly activity against of all bacteria (Gram negative and Gram positive). In addition, the prepared Schiff bases and tetrazole compounds show an activity more than compounds(oxazepine and Diazepine). Also most compounds have moderate activity on the bacteria of (Klebsiella pneumoniae and Escherichia coli). All these result are shown in table(2).

Tikrit Journal of Pure Science 17 (4) 2012 ISSN: 1813 - 1662

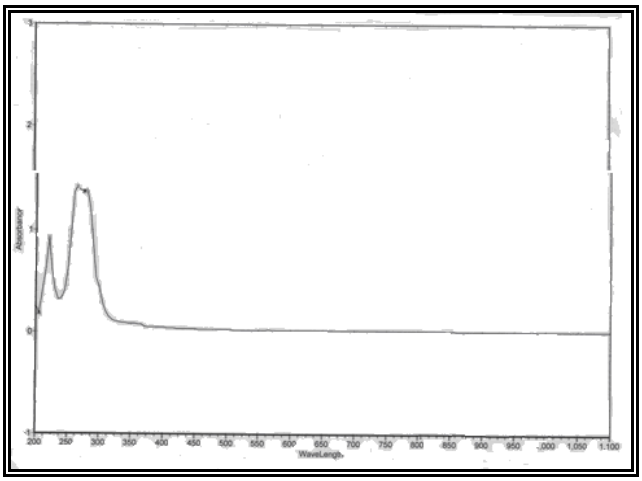
Table(2): Inhibition Zones of all Product Compounds

No.of Lab	Comp.No	Gram Negative		Gram Positive		No.of Lab	Comp.No	Gram Negative		Gram Positive	
		Klebsiella Pneumoniae	Escherichia Coli	Enterococcus faecalis	Staphylococcus aureus			Klebsiella Pneumoniae	Escherichia Coli	Enterococcus faecalis	Staphylococcus aureus
1	A_1	++	+	+	+	11	C1	++	+	+	++
2	A_2	+	++	+	+ +	12	C_2	+	+	-	+
3	A_3	+	++	+	++	13	C_3	+++	+	+	++
4	A_4	++	+	+	+	14	C_4	++	–	–	++
5	A_5	+	++	+	++	15	C_5	+	+	–	++
6	B_1	+	+	–	+++	16	D_1	+	+	+	+
7	B_2	–	+	–	++	17	D_2	+	++	++	+
8	B_3	+	+	–	+++	18	D_3	+	–	+	++
9	B_4	+	–	–	++	19	D_4	++	+++	+++	+++
10	B_5	+	+	+	++	20	D_5	+	++	++	+

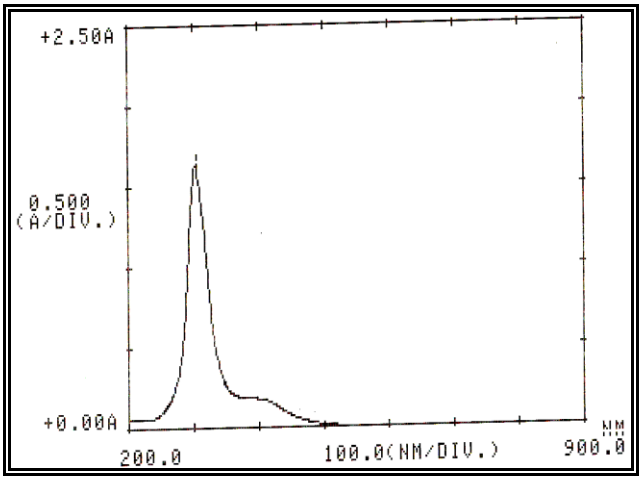
– = No inhibition = in active , + = (1-10)mm = slightly active , ++ =(11-19)mm = moderately active, +++ =(20-30)mm = highly ac

Table (3): FT-IR spectral data for all product compounds

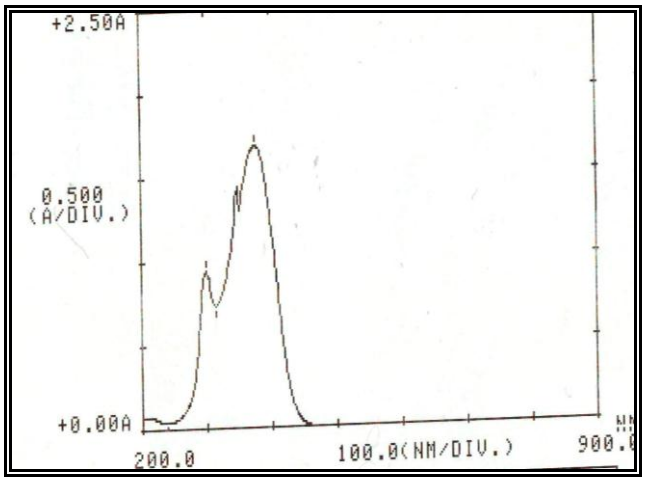
Comp No.	v(C=N) in out ring	v(C=O)	v(C-H) aromatic	v(C-H) alphatic	v(N-H)	v(C-N)	others	Peak	
								λ_{max} nm	ABC
A_1	1651	-	3055-3140	2858-2981	3394	1465		265,220,255	1.780 1.028 1.572
A_2	1620	-	3066-3143	2858-2989	3379	1469	-	270,220	2.092 1.137
A_3	1620	-	3062-3155	2866-2978	3321	1423	v(C-CL) 833,1091,1161	270,220	2.137 1.171
A_4	1643	-	3140	2885-2997	3321	1465	v(O-H) 3468	280,265,220	1.384 1.426 0.922
A_5	1631	-	3140	2908	3313	1500	-	280,220	2.237 1.409
B_1	-	1770	3082-3120	2854	3387	1496	v(O-C-O) 1188-1284	315	2.180
B_2	-	1712	3089-3163	2900	3414	1496	v(O-C-O) 1284	304	1.893
B_3	-	1708	3142	2989	3414	1465	v(C-CL) 1168 V(O-C-O) 1190-1280	300	1.762
B_4	-	1716	3174	2964 - 2985	3417	1496	v(O-H) 3471 v(O-C-O) 1168-1280	304	1.638
B_5	-	1793	3109 3174	2904 - 2924	3460	1465	v(O-C-O) 1172-1284	304	1.796
C_1	-	1770	3082	2893	3363	1500	-	376,313	1.672 0.835
C_2	-	1708	3097	2981	3468	1465	v(C-No_2) 1381-1500	178,319	2,054 1.206
C_3	-	1712	3078-3170	2981	3363	1469	v(C-No_2) 1597-1303 v(C-CL) 1168	375,313	1.694 0.497
C_4	-	1712	3101	2958-2985	3383	1465	V(O-H) 3471 V(C-NO_2) 1307,1500	376 300	1.682 0.936
C_5	-	1860	3162	2900	3390	1455	V(C-NO_2) 1369،1597	378 319	1.593 0.832
D_1	-	-	3159	2926	3420	1458	V(N=N) 1595	313	2.142
D_2	-	-	3050	2980	3386	1475 1625	V(N=N) 1595	315	2.273
D_3	-	-	3080	2904	3379	1471 1596	v(N=N) 1596 v(C-CL) 1157	313	2.182
D_4	-	-	3159	2981	3383	1438 1508	V(N=N) 1597 V(O-H) 3464	315	2.186
D_5	-	-	3159	2962	3379	1465 1697	V(N=N) 1597	345 304	1.866 1.705



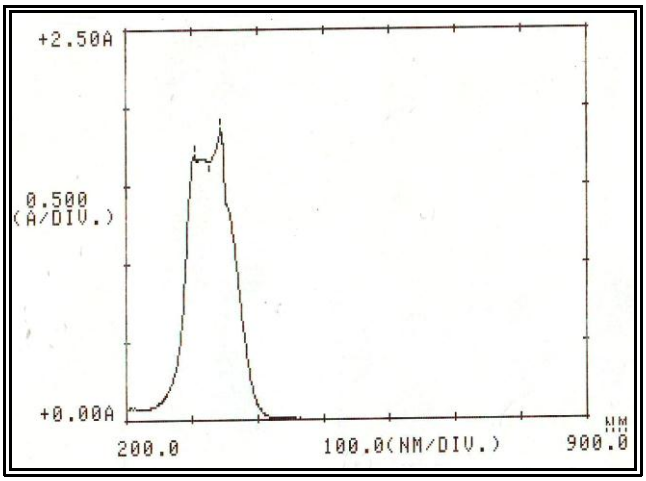
Fig(1):uv spectrum of the compound[A_5]



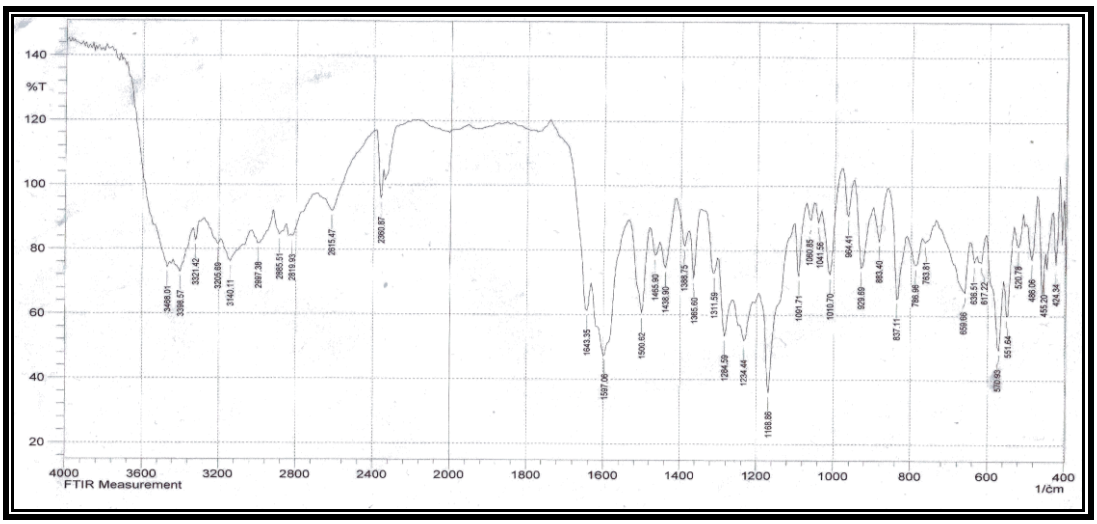
Fig(2):uv spectrum of the compound[B_5]



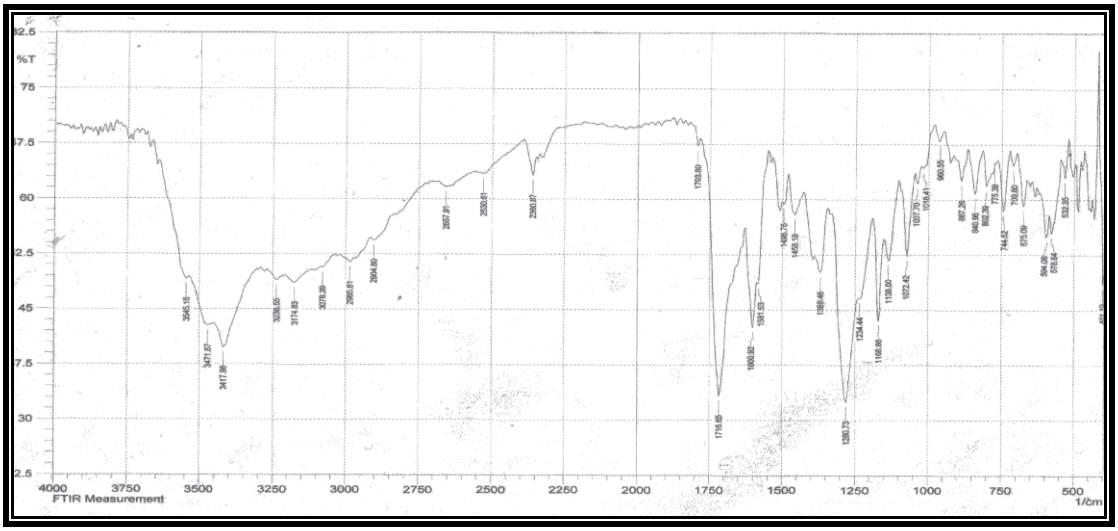
Fig(3):uv spectrum of the compound[C_5]



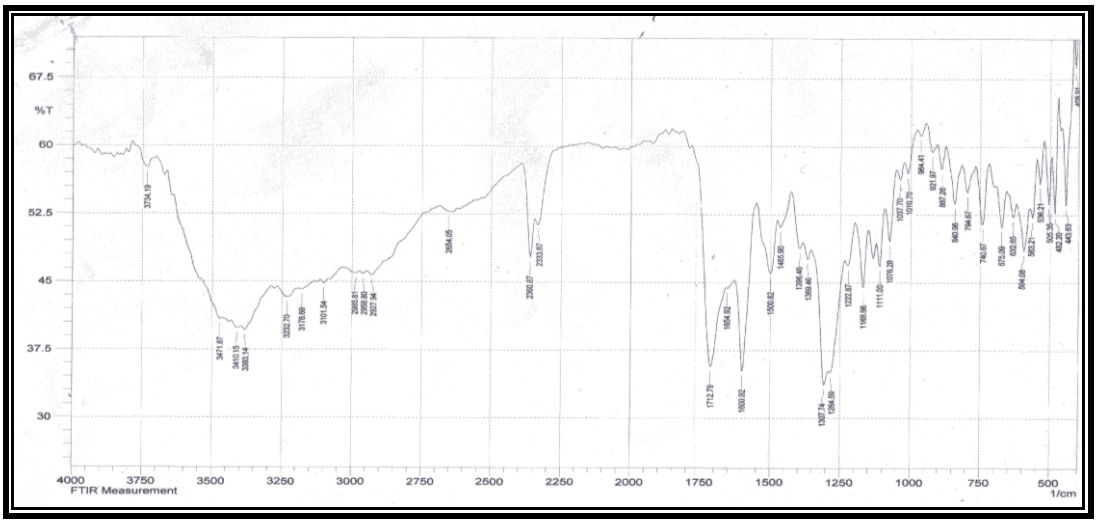
Fig(4):uv spectrum of the compound[D_5]



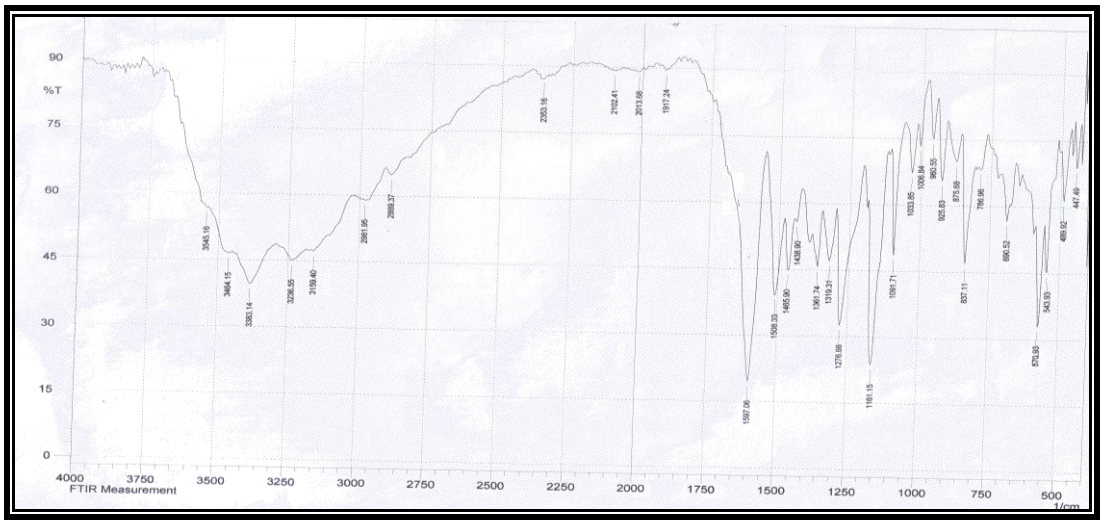
Figure(5): FT-IR spectrum of compound A_4



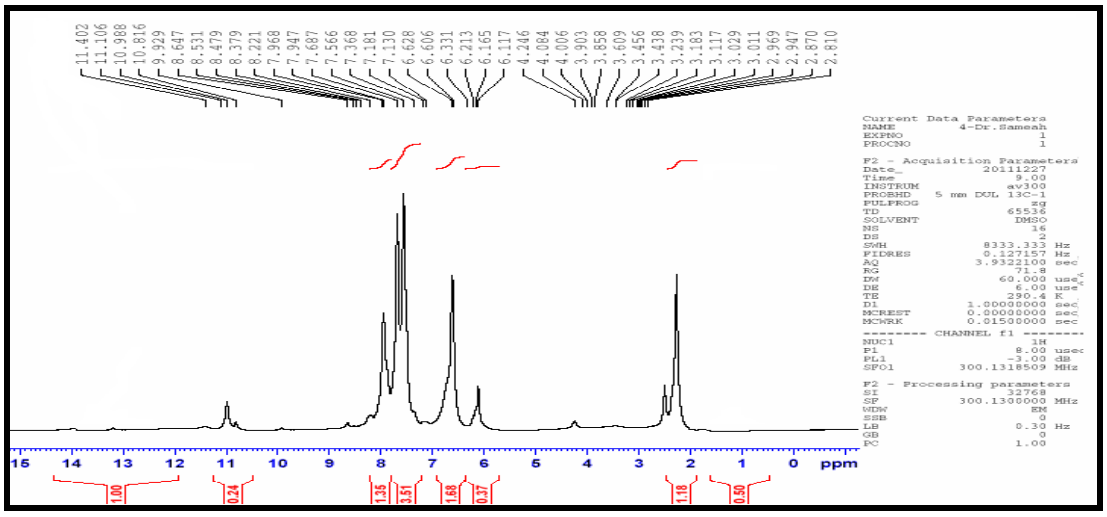
Figure(6): FT-IR spectrum of compound B_4



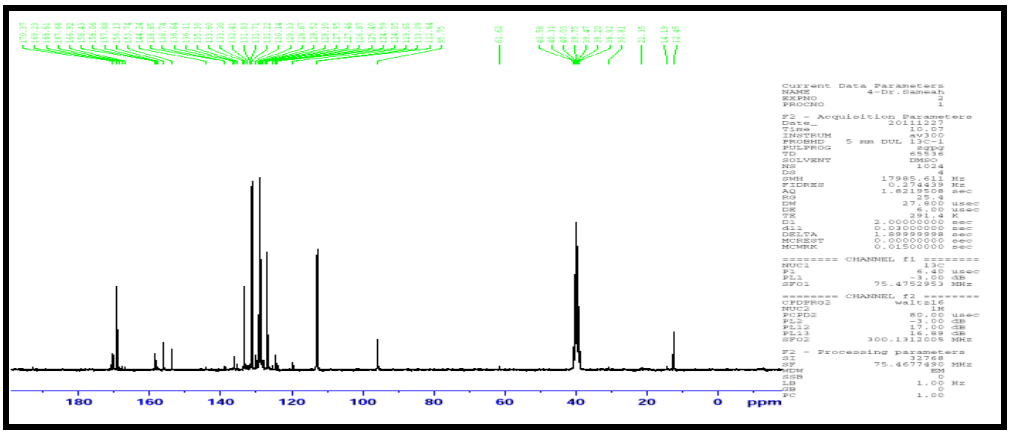
Figure(7): FT-IR spectrum of compound C_4



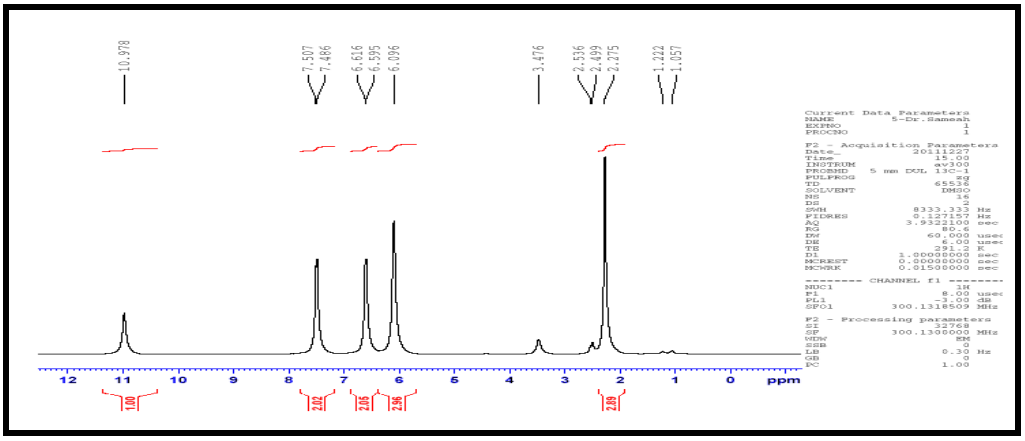
Figure(8): FT-IR spectrum of compound D_4



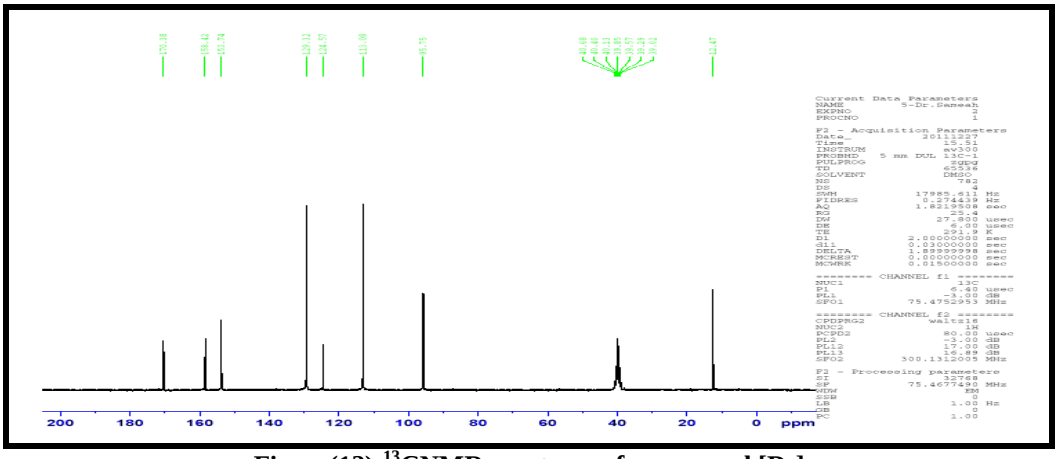
Figure(9):^{1}HNMR spectrum of compound [C_1]



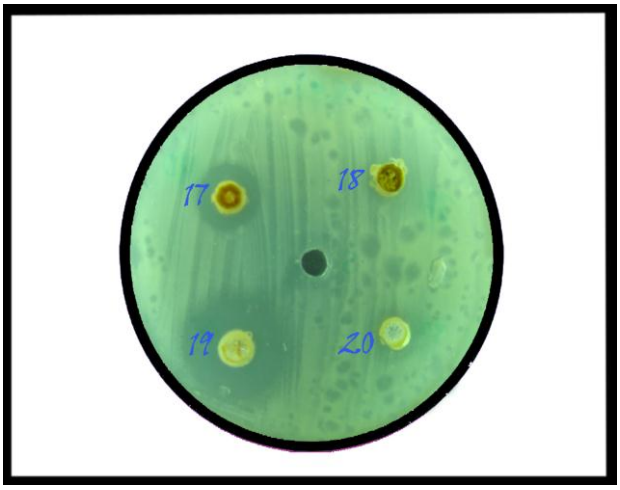
Figure(10): ^{13}CNMR spectrum of compound [C_1]



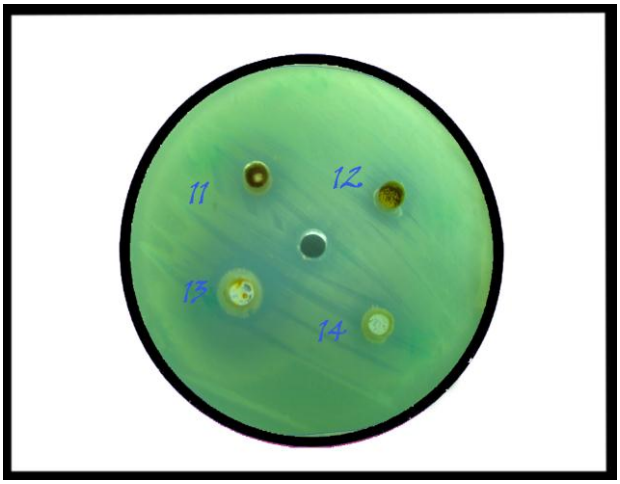
Figure(11):^{1}HNMR spectrum of compound [D_3]



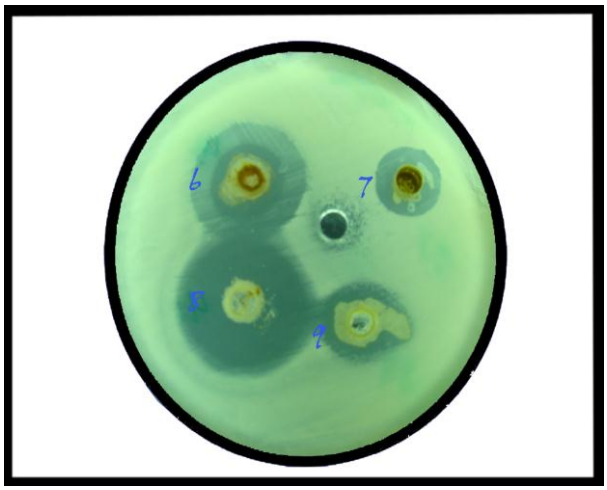
Figure(12):^{13}CNMR spectrum of compound [D_3]



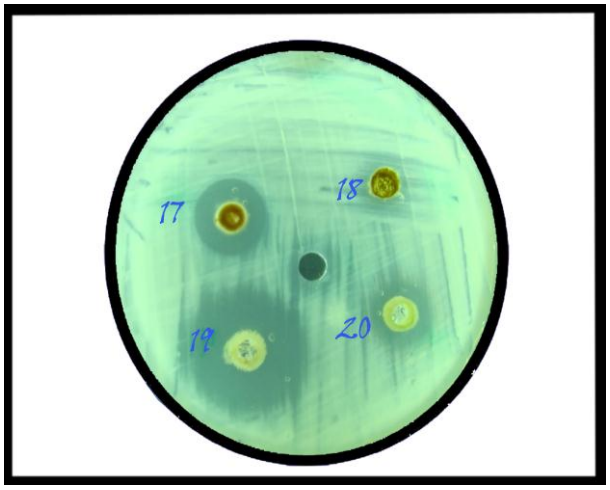
Figure(13): Effect of compounds[17-20]on Escherichia coli



Figure(14): Effect of compounds[11-14]on Klebsiella pneumoniae



Figure(15): Effect of compounds[6-9]on Staphylococcus aureus



Figure(16):Effect of compounds[17-20]on Eterococcus faecalis

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تحضير وتشخيص الاوكسازيبين،دايزيبين وتترازول المشتقة من دواء السلفاميثاوكسازول

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(تاريخ الاستلام: 13 / 2 / 2012 ---- **تاريخ القبول:** 28 / 5 / 2012)

الملخص

تم في هذا البحث تحضير بعض المعوضات الجديدة للاوكسازايبين ، دايزيبين وتترازول عن طريق قواعد شف لدواء السلفاميثاوكسازول وذلك من خلال إجراء أربعة خطوات ، حيث تضمنت الخطوة الأولى تحضير قواعد شف (A_1–A_5) وذلك بتكاثف دواء السلفا ميثاوكسازول مع بعض الكيتونات المختلفة ، أما في الخطوة الثانية فقد تم تفاعل قواعد شف المحضرة مع فثاليك انهيدريد فأعطت مشتقات الاوكسازوبين(B_1-B_5) ثم معاملتها لاحقاً في الخطوة الثالثة مع أمين أروماتي أولي فأعطت خمسة مشتقات جديدة من الدايزيبين (C_1-C_5). وأخيراً تضمنت الخطوة الرابعة تحضير خمس مشتقات جديدة للتترازول (D_1-D_5) من خلال تفاعل قواعد شف المحضرة في الخطوة الأولى مع أزيد الصوديوم بوجود THF كمذيب .

تم تشخيص المركبات المحضرة بأستخدام بعض الطرق الطيفية FT-IR و .UV و ^{1}H-NMR وكذلك ^{13}C-NMR بالإضافة إلى دراسة الخواص الفيزيائية وأيضاً قيمت الفعالية البايولوجية لهذه المركبات بأستخدام نوعين من البكتريا احدهما البكتريا السالبة والأخرى الموجبة .