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STUDY OF BIOLOGICAL ACTIVITY OF (CIPROPHLAXINE DRUGS AND MEFENAMIC ACID) –DERIVATIVES

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ABSTRACT

In this work, derivatives of ciprophlaxine drugs and mefenamic acid were synthesized, tested for antibacterial activity. A new series of ciprophlaxine drugs and mefenamic acid derivatives were synthesized via condensation reaction to produce nine derivatives compounds [1-9] are: ciprophlaxine derivatives [1-5] and mefenamic derivatives [6-9].

The new drugs derivatives [1-9] have been evaluated for their antimicrobial activity against various gram positive and gram negative bacteria which was comparable to activity of past studies(ciprophlaxine andmefenamic). All the newly synthesized drugs derivatives wereidentified byspectro –methodslike (FT.IR- spectra and H.NMR spectra) aschemical indicatorsfor synthesis of new derivatives

KEYWORDS: Ciprophlaxine, Mefenamic, Antibiotic

INTRODUCTION

The ciprophlaxine drug is a group of antibiotics that has increased in applications in recent yearsit is known as a major class of antibacterial agents and widely used to treat patients with infections. Due to the increasing of resistance of various infections by bacteria and fungi to antibiotics, several works and studies described various methods to synthesis its derivatives[(1-5)].

Mefenamicacidderivatives are verypromising properties regarding biological activities as shownin literaturesurvey.

Because of resistance to some of antimicrobial agents andincreasing of infectious diseases we needtodiscover new chemotherapeuticagents to overcome the emergence of resistance the antibiotics have been approved for treatment of infectionscontinuous ambulatory peritonealdialysis infections, skin structure infectionsdiarrheainfection which works byinterfering with the bacteria cell wall formationcausing it to rupture and killing the bacteria[(6-9)].In this work, ciprophlaxine andmefenamic acidhave been incorporated to sulfurheterocycles which increased of its biological activity.

EXPERIMENTAL PART

Materialsand Instruments

All synthetic works were carried out by using laboratory reagents and analytical grade solvents, to the solvents and reagents were purified and dried according to standard procedure. The progress of all reactions was monitored byTLC-

Technique.

The chemical materials that we used from (Fluka, BDH) company and ciprophlaxine drug from samara factory. The FT.IR- spectra were recorded by KBr disk using a Perkin – Elmer 1600-series H.NMR- spectra were recorded by using DMSO- asa solvent in Jordan University.All biological studied and measurement of bacteria carried out in bio-Lab in Facultycollege.

GeneralMethods (Synthesis of Ciprophlaxine Derivatives)[3]: Compounds [1-5]

A mixture ofciprophlaxine (0.01mole) andthiosemicarbazide (0.01mole) was refluxed in ethanol in presence of$POCl_3$for (3hrs).,completion of reaction was monitored on TLC- plate., solid was filtered and recrystallized toyield(86%) ciprophlaxine derivative compound [1]., which dissolved in (3ml) HCl and sodium nitrite solution at (0-5) C^o then 4-methyl Phenol was added to mixture, after (48hrs) filtered and recrystallized to produced (84 %) ciprophlaxine derivative [2]. (0.01mole) of compound [1] refluxed with beuzaldehyde (0.01mole) in presence of ethanol with drops of glacial acetic acid for 2hurs to yield (82%) ofciprophlaxine derivative compound [3].

A mixture of ciprophlaxine (0.01mole) and (0.01mole) of thiourea (0.01mole) of thioacetamide)respectively refluxed for (4hrs) in presence of(5ml) of sulfuric acid to yield (84 % 82 %) of ciprophlaxine derivatives compounds [4 and5] respectively.

GeneralMethods (Synthesis ofMefenamic Derivatives): Compounds [6-9]

A mixture of mefenamic acid (0.01mole) andthiosemicarbazide (0.01mole) was refluxed in presence of ethanol with $PoCl_3$ for (3hrs)., completion of reaction was monitored on TLC- Plate., the solid was filtered and recrystallized to yield (80 %) of mefenamic derivative compound [6]., which nitrite in (0-5)C^o after that, 4- methyl Phenol added to mixture to yield (88%)ofmefenamic derivative compound [7].

A mixture of (0.01mol) compound [6] and P- hydroxylbenzaldehyde (0.01mole) refluxed in presence of ethanol with drops of glacial acetic acid for (2hrs) to yield(85%) ofmefenamic derivative compound [8].

While mefenamic derivative compound [9] prepared from reaction between (0.01mol) ofmefenamic acid with (0.01mole) ofortho- phenylene diamine in presence of Ethanol with (4N) ofHClandrefluxing for (4hrs) to yield (80%)ofmefenamic derivative compound [9].

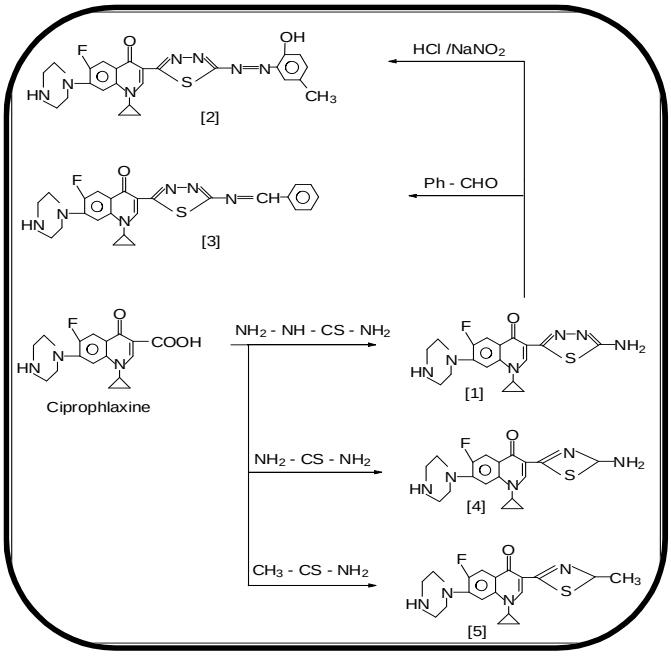

Figure 1: Synthesis ofCiprophlaxine Derivatives [1-5]

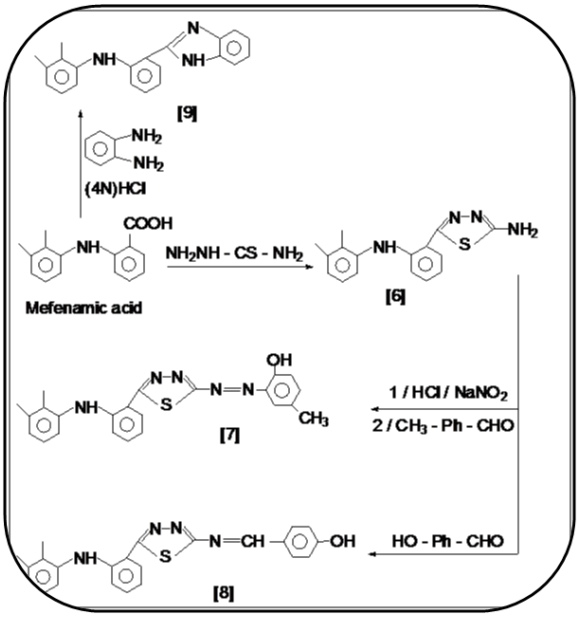

Figure 2: Synthesis ofMefenamic Derivatives [6- 9]

RESULTS AND DISCUSSIONS

In this study, derivatives of ciprophlaxine drug andmefenamic acid were synthesized whichincorboratedwithheterocycles of sulfurlike (thiadiazoleimidazole….) and with active groups like (imine group azo group thiosemicarbazide) which due toithas Pharmaceutical applications andbiological activity.

The derivatives [1-9] have been characterized by chemical techniques like (FT.IR and H.NMR)- spectra with

melting points and other studies**:**

TheFT.IR- Spectrum

Showed appearance of many absorption bands indicateto synthesis of derivatives [1-9] and all data of functional groups shown in table 1

Table 1: FT.IR- Data (Cm^{-1}) of Drugs Derivatives

Comp. No.	I.R $_{(Kbr)}$(Only Important Groups)
[1]	(C=N)endothiadiazole**:** 1605, (NH_2)**:** 3240, 3255.,(-CO-)Ketonin ciprophlaxine**:** 1718.
[2]	(C=N) endothiadiazole**:** 1608., (-N=N-)**:** 1440., (-OH)**:** 3420, (-CO-) Keton inciprophlaxine **:**1716.
[3]	(C=N) endothiadiazole**:** 1610**.,** (-CH=N)**:** 1628**.,** (-CO-) ketonin ciprophlaxine**:** 1715.
[4]	(C=N) endocycle **:** 1612., (NH_2)**:** 3280, 3300**.,** (-CO-) keton in ciprophlaxine**:** 1714.
[5]	(C=N) endo cycle**:** 1610**.,** (CH) aliphatic**:** 2975**.,** (-CO-) keton in ciprophlaxine**:** 1715.
[6]	(C=N) endothiadiazole**:** 1608, (NH_2): 3260, 3285.
[7]	(C=N) endothiadiazole**:** 1614**.,** (-N=N-)**:** 1470., (-OH)**:** 3420., (CH) aliphatic**:** 2995.
[8]	(C=N)endothiadiazole**:** 1610**.,** (CH=N)**:** 1630. (OH): 3400.
[9]	(C=N) endoimidazole**:** 1612**.,** (NH)**:** 3190.

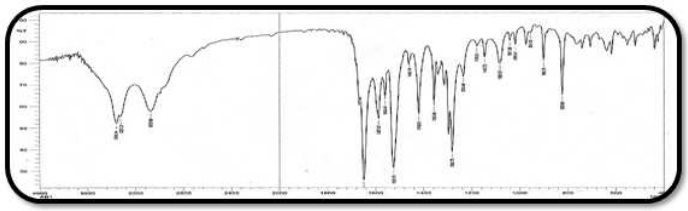

Figure 3: FT.IR of Compound [2]

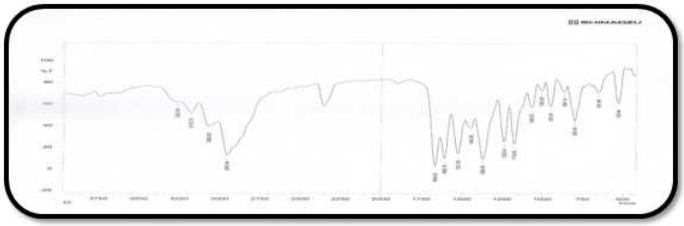

Figure 4: FT.IR of Compound [3]

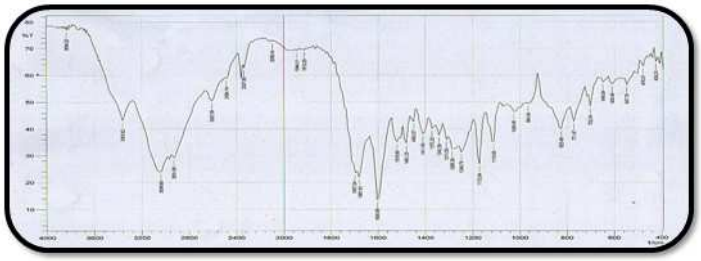

Figure 5: FT.IR of Compound [5]

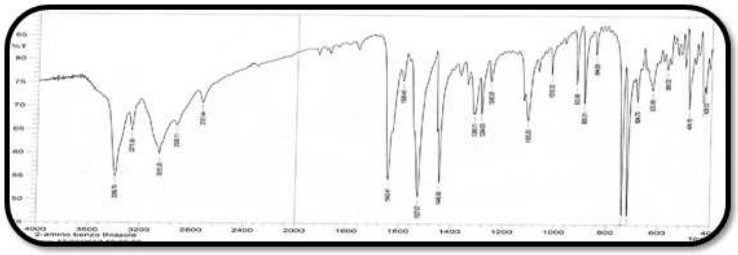

Figure 6: FT.IR of Compound [6]

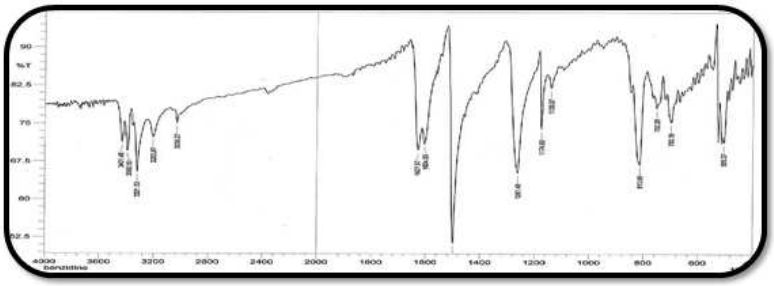

Figure 7: FT.IR of Compound [7]

TheH.NMR- Spectrum

Which gave good evidence to synthesis of derivatives through disappearance of absorption bands in some compounds and appearance of other derivatives which due to formation of derivatives., all signals anddata Analytical intable 2.

Table 2: H.NMR- Data (ɓ PPm) of Derivatives

Comp. No.	H.NMR- Data(Only Important Peaks)
[1]	5.45(NH_2) 5.12(NH) (0.81-1.42) for (CH_2) alkane of cycles., (6.9 -7.20)phenyl ring.
[2]	9.3(OH), 0.98(CH_3), (0.78 -1.34) for (CH_2) alkane of cycles, (6.83 -7.5)phenyl rings.
[3]	8.2(CH=N) imine, (0.82- 1.30)for (CH_2) alkane of cycles, (6.92-7.45) phenyl rings.
[4]	5.24(NH_2), (0.91- 1.48)for (CH_2) alkane of cycles, (6.85- 7.23) phenyl ring.
[5]	0.97(CH_3), (0.98 -1.37)for (CH_2) alkane of cycles, (6.87- 7.46) phenyl ring.
[6]	5.62(NH_2), 5.13(NH), (0.83, 0.98)for (CH_3) groups, (6.72- 7.26) phenyl groups
[7]	10.4(OH), (0.92- 1.22) for (CH_3) groups, (6.5- 7.47) phenyl groups.
[8]	9.4(OH), (0.841.02) for (CH_3) groups 8.32(CH=N) imine, (6.77- 7.36) phenyl groups.
[9]	5.11(NH), (0.78 0.95) for (CH_3) groups, (6.82- 7.8) phenyl groups.

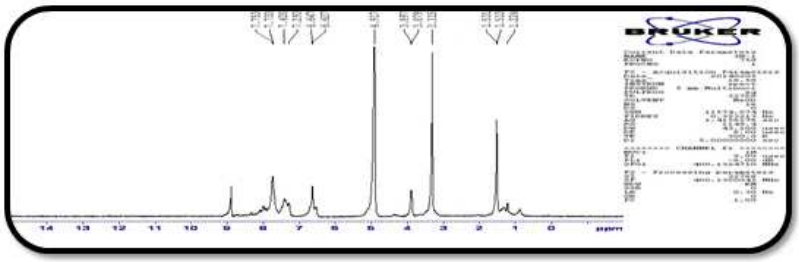

Figure 8: H.NMRof Compound [2]

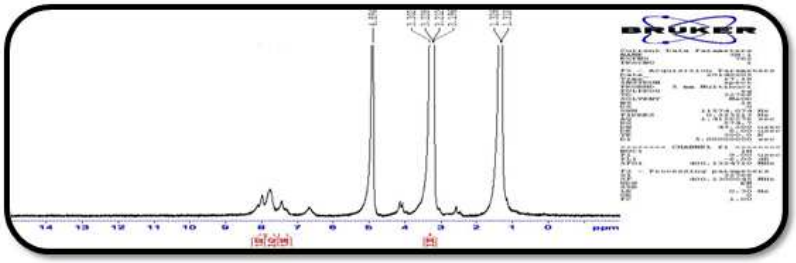

Figure 9: H.NMRof Compound [3]

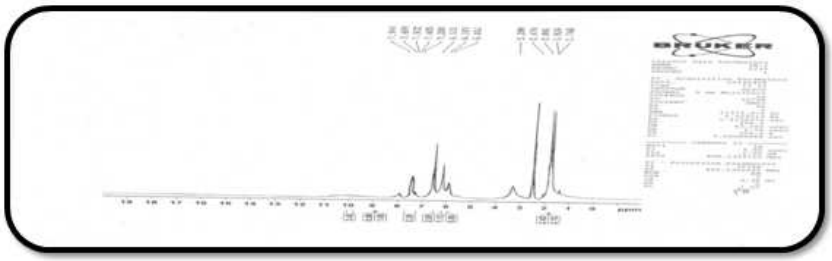

Figure 10: H.NMRof Compound [6]

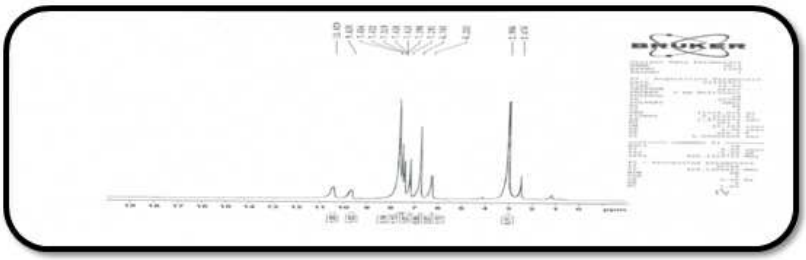

Figure 11: H.NMRof Compound [7]

AnalyticalMeasurements

Their melting points, products %, color are listed in table 3.

Table 3: Physico- Analytical Data of Derivatives

Comps.No.	M.P(C^0)	Yield%	Color
[1]	229	86	Pale yellow
[2]	245	84	Pale orange
[3]	236	82	Yellow
[4]	216	84	Pale green
[5]	208	82	Yellow
[6]	157	80	Pale yellow
[7]	197	88	Orange
[8]	184	85	Yellow
[9]	176	80	Yellow

Biological Study

Bacteria supplied from bio- Labin FacultyofEducationthe derivatives of ciprophlaxine andmefenamic acid [1-9] were screened for their antimicrobial affects againstthreeGram- positive organisms namely (*Staphylococcus aureus StreptococciandBacillus. SPP*) andfourGram- negative organisms (*E-coli, Klebsiellapneumoniae, Pseudomonas.*

SPPandShigelladysenteriae).

Antibacterial activity was determined by measuring the diameter (mm) of zones showing extent ofinhibition each sample was (150 µg)the same procedure was doneintriplicate.

From the results it is observed that all derivatives showed good activities against most of the Gram-positiveandGram- negative strains., butciprophlaxine derivatives [1, 2 and 3] exhibited better activity against most ofthe Gram- positive and Gram- negative strains compared to other derivatives due to its structures which contain thiadiazolring[10-13] consequentlythese compounds become more effective in precipitating proteins on bacteria cell walls, these atoms (sulfur and nitrogen in their structures)[14-17] from hydrogen bonds with cell wall protein and destroying the cell membrane Tables 1 2andPictures (1) (2).

Table 4: Antibacterial Activity of Compounds 1-9 againstGram- Positive Bacteria (+)

Samples	Gram(+) Bacteria / Diameter of Zone (Mm)		
	Staphylococcus Aureus	Streptococci	Bacillus. SPP
Compound[1]	22	16	16
Compound[2]	26	18	18
Compound[3]	24	18	16
Compound[4]	20	16	16
Compound[5]	20	16	16
Compound[6]	16	12	12
Compound[7]	18	14	14
Compound[8]	18	14	12
Compound[9]	16	14	12

Table 5: Antibacterial activity of compounds [1-9] against Gram- negative bacteria (-)

Samples	Gram(-) Bacteria / Diameter of Zone (Mm).			
	Pseudomnas. SPP	Shigella Dysenteriae	KlebsiellaPneumoniae	E-Coli
Compound[1]	28	24	18	16
Compound[2]	34	30	24	16
Compound[3]	30	26	24	16
Compound[4]	24	24	18	14
Compound[5]	24	24	18	12
Compound[6]	22	18	16	12
Compound[7]	24	20	16	12
Compound[8]	22	18	16	8
Compound[9]	20	14	12	6

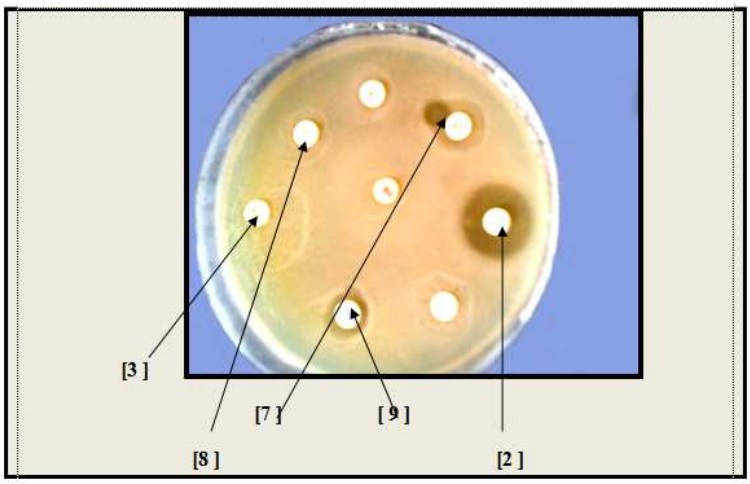

Figure 12: Inhibition Zone onStreptococciBacteria

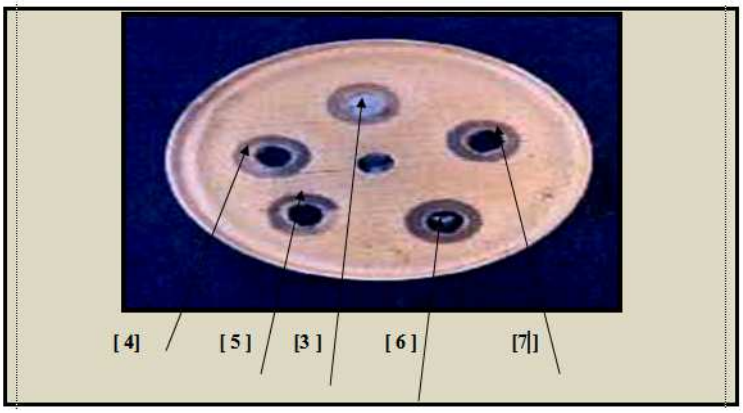

Figure 13: Inhibition Zone onE- ColiBacteria

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