IMPACT: Journal of Research in Applied, Natural and Social Sciences (IMPACT: JRANSS)
ISSN(E): Applied; ISSN(P): Applied
Vol. 1, Issue 1, Jun 2015, 85-94

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 and mefenamic). All the newly synthesized drugs derivatives were identified by spectro –methods like (FT.IR- spectra and H.NMR spectra) as chemical indicators for synthesis of new derivatives

KEYWORDS: Ciprophlaxine, Mefenamic, Antibiotic

INTRODUCTION

The ciprophlaxine drug is a group of antibiotics that has increased in applications in recent years it 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)].

Mefenamic acid derivatives are very promising properties regarding biological activities as shown in literature survey.

Because of resistance to some of antimicrobial agents and increasing of infectious diseases we need to discover new chemotherapeutic agents to overcome the emergence of resistance the antibiotics have been approved for treatment of infections continuous ambulatory peritoneal dialysis infections, skin structure infections diarrhea infection which works by interfering with the bacteria cell wall formation causing it to rupture and killing the bacteria[(6-9)].In this work, ciprophlaxine and mefenamic acid have been incorporated to sulfurheterocycles which increased of its biological activity.

EXPERIMENTAL PART

Materials and 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 by

TLC- 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- as a solvent in Jordan University.All biological studied and measurement of bacteria carried out in bio-Lab in Faculty college.

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

A mixture of ciprophlaxine (0.01mole) and thiosemicarbazide (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 to yield (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%) of ciprophlaxine 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 and 5] respectively.

General Methods (Synthesis of Mefenamic Derivatives): Compounds [6-9]

A mixture of mefenamic acid (0.01mole) and thiosemicarbazide (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%) of mefenamic derivative compound [7].

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

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

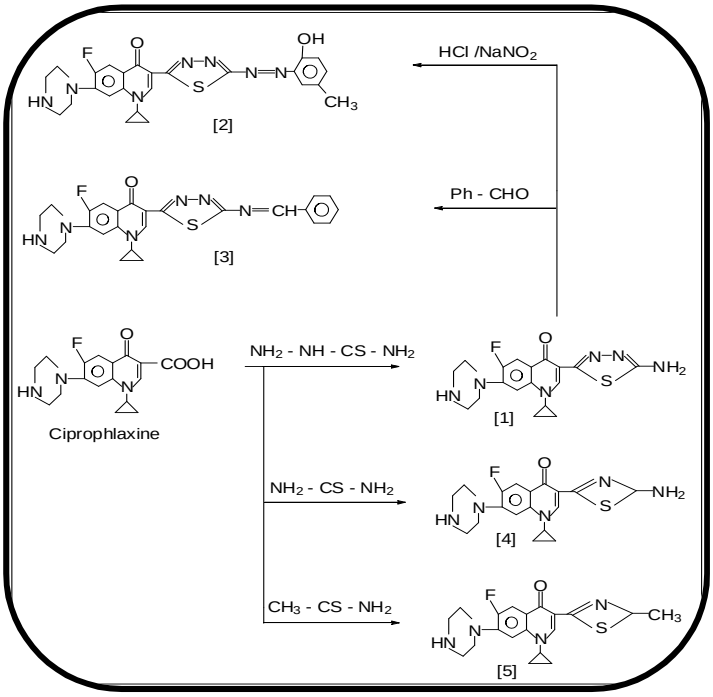

Figure 1: Synthesis of Ciprophlaxine Derivatives [1-5]

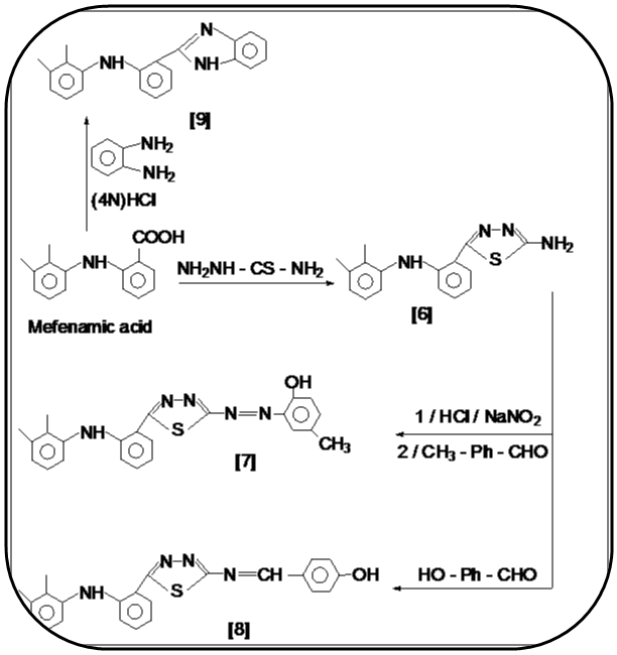

Figure 2: Synthesis of Mefenamic Derivatives [6- 9]

RESULTS AND DISCUSSIONS

In this study, derivatives of ciprophlaxine drug and mefenamic acid were synthesized which incorborated with heterocycles of sulfur like (thiadiazole imidazole….) and with active groups like (imine group azo group thiosemicarbazide) which due to it has Pharmaceutical applications and biological activity.

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

melting points and other studies**:**

The FT.IR- Spectrum

Showed appearance of many absorption bands indicate to 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)endo thiadiazole**:** 1605, (NH_2)**:** 3240, 3255.,(-CO-)Keton in ciprophlaxine**:** 1718.
[2]	(C=N) endo thiadiazole**:** 1608., (-N=N-)**:** 1440., (-OH)**:** 3420, (-CO-) Keton in ciprophlaxine **:**1716.
[3]	(C=N) endo thiadiazole**:** 1610**.,** (-CH=N)**:** 1628**.,** (-CO-) keton in ciprophlaxine**:** 1715.
[4]	(C=N) endo cycle **:** 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) endo thiadiazole**:** 1608, (NH_2): 3260, 3285.
[7]	(C=N) endo thiadiazole**:** 1614**.,** (-N=N-)**:** 1470., (-OH)**:** 3420., (CH) aliphatic**:** 2995.
[8]	(C=N)endo thiadiazole**:** 1610**.,** (CH=N)**:** 1630. (OH): 3400.
[9]	(C=N) endo imidazole**:** 1612**.,** (NH)**:** 3190.

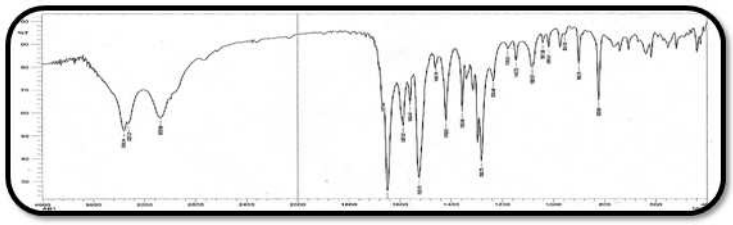

Figure 3: FT.IR of Compound [2]

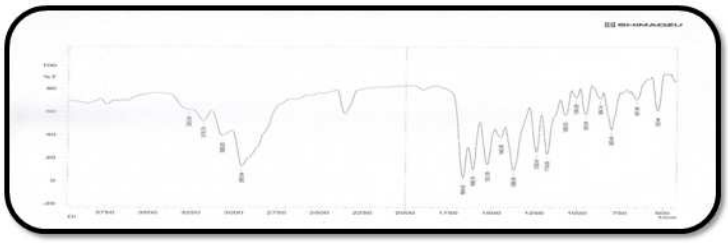

Figure 4: FT.IR of Compound [3]

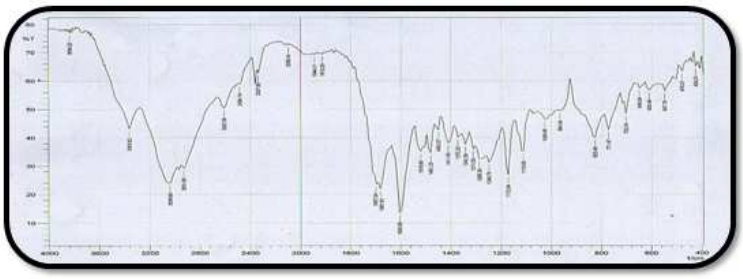

Figure 5: FT.IR of Compound [5]

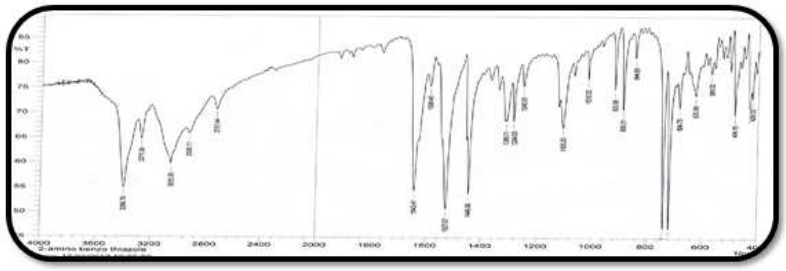

Figure 6: FT.IR of Compound [6]

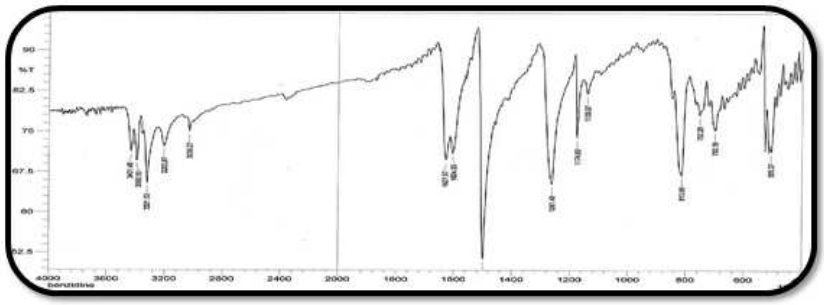

Figure 7: FT.IR of Compound [7]

The H.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 and data Analytical in table 2.

Table 2: H. NMR- Data (ƃ 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.

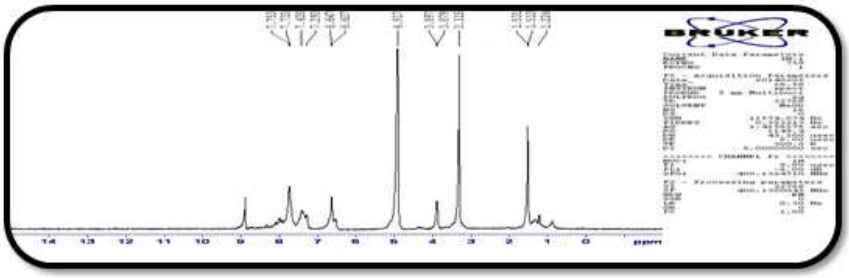

Figure 8: H.NMR of Compound [2]

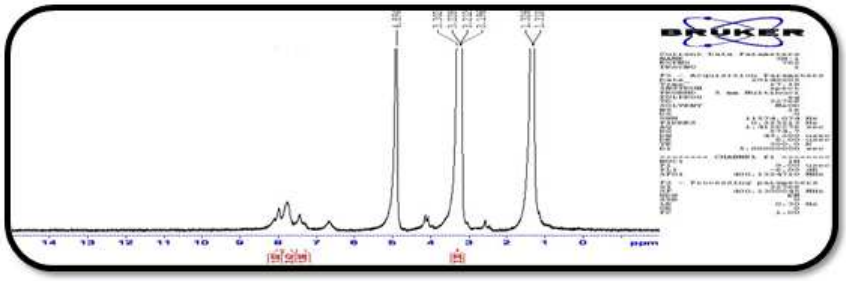

Figure 9: H.NMR of Compound [3]

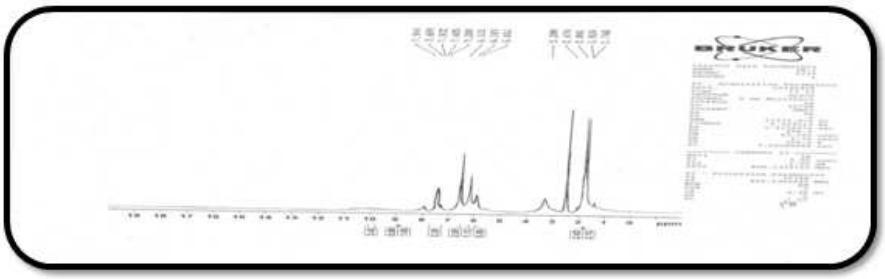

Figure 10: H.NMR of Compound [6]

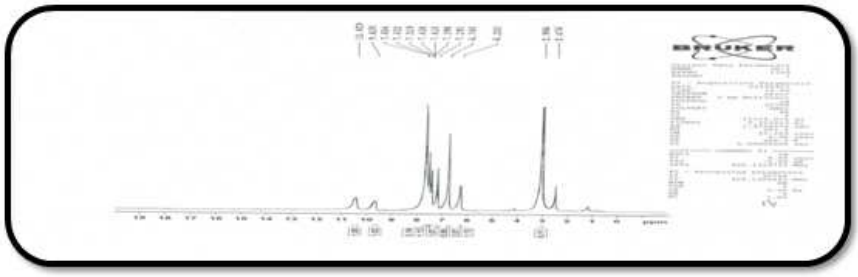

Figure 11: H.NMR of Compound [7]

Analytical Measurements

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

Table 3: Physico- Analytical Data of Derivatives

Comps. No.	M.P (C^{o})	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- Lab in Faculty of Educationthe derivatives of ciprophlaxine and mefenamic acid [1-9] were screened for their antimicrobial affects against three Gram- positive organisms namely (*Staphylococcus aureus*

Streptococci and Bacillus. SPP) and four Gram- negative organisms (*E-coli, Klebsiella pneumoniae, Pseudomonas. SPP and Shigella dysenteriae*).

Antibacterial activity was determined by measuring the diameter (mm) of zones showing extent of inhibition each sample was (150 µg) the same procedure was done in triplicate.

From the results it is observed that all derivatives showed good activities against most of the Gram- positive and Gram- negative strains., but ciprophlaxine derivatives [1, 2 and 3] exhibited better activity against most of the Gram-positive and Gram- negative strains compared to other derivatives due to its structures which contain thiadiazol ring[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 2 and Pictures (1) (2).

Table 4: Antibacterial Activity of Compounds 1-9 against Gram- 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	Klebsiella Pneumoniae	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

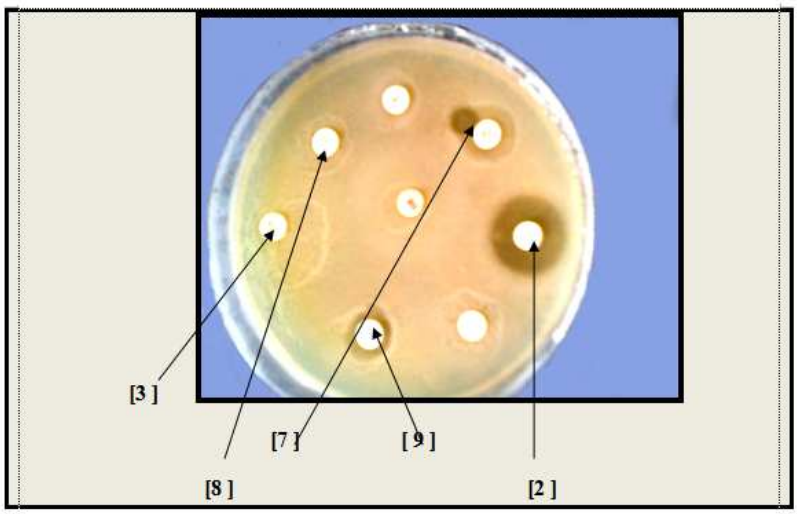

Figure 12: Inhibition Zone on Streptococci Bacteria

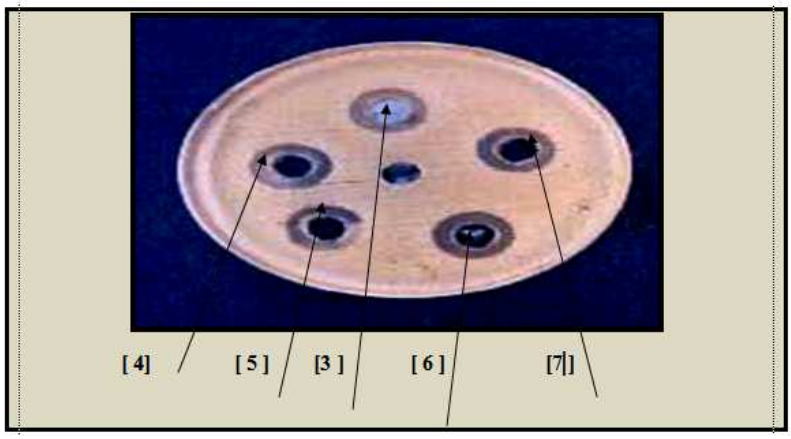

Figure 13: Inhibition Zone on E- Coli Bacteria

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