Development and Preparation of ciprofloxacin Drug Derivatives for Treatment of Microbial Contamination in Hospitals and Environment

Aseel Mahmood Jawad[1], Nagham Mahmood Aljamali[2], Saher Mahmood Jwad[3]

[1]MRCS, FICMS, Board in Medicine,College of Medicine ,General Surgery Department, Baghdad, Iraq, [2]Asist. Professor.,Chemistry Department, College of Education for Girls ,Iraq, [3]Professor, Ph. D in Biology Department, College of Education, Kufa University, Iraq

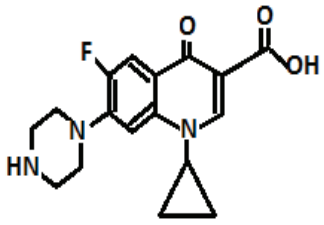
Abstract

This practical studying involved preparation and development of new medical derivatives of ciprofloxacin drug via series of chemical reactions to preparation new derivatives to resist types of bacteria in hospitals and environment.Various chemical routes have been used to prepare ciprofloxacin derivatives ,then all these derivatives reconnoitered with many spectral chemical techniques for instance (FT.IR ,H.NMR ,C.NMR)–spectrophotometric ,then studying of their effects on bacterial pollution.

Keywords: *Pollution, Bacteria, Ciprofloxacin, Environment.*

Introduction

Ciprofloxacin is cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid as chemical name[1] while the brand names are (Cipro,Ciprobay,Ciproxan,Ciprinol),its formula($C_{17}H_{18}FN_3O_3$), it is solid(Zhanel et al 2006.,Heidelbagh and Holmster. 2013)[1,2] powder has faint to light yellow colour with melting[3,4] point (255-257 °C)[5] .



Ciprofloxacin

Fig.(1):Ciprofloxacin Drug

Ciprofloxacin medication is a broad-variety fluoroquinolone antibiotic[5, 6] secondhand in the dealing of a wide series(Oliphant C and Green . 2002) of slight to reasonable gram-(positive & negative) toxicities.,which is used to indulgence or inhibit(Stevens et al 2005.,Osmon et al 2013) certain infections affected through bacteria like gonorrhea;pneumonia[8-11] and toxicities(*Vardakas K et al 2008 .,Donaldson P* et al 1994) or infection of the skin, bone, joint, stomach[12-16] region, and*(Karageorgopoulos* et al 2008 .,*Chow* et al 2012.,*Stephenson* et al 2013)

Prostate ciprofloxacin treatment is likewise used to delight or avoid and inhibit a serious infection that may be extent on tenacity[17-22] (*Corrao G et al 2006 .,Liu X* et al 2017) as portion of a bioterror round) and mouthful[23-27] *(Bolhuis et al 2001 .,Pommier et al 2010.,Goossens et al 2007)* anthrax[28] .

Experimental Part

Ciprofloxacin derivatives were inspected and identified thru :FT-IR spectra (FT-IR 8300 Shimadzu) in the range (400-4000) cm^{-1} as KBr discs.,1H.NMR–Spectra and C.NMR in DMSO–solvent.,in addition to resistance of ciprofloxacin derivatives against microbial pollution in hospitals and environment to improve their effect:

Corresponding Author:
Nagham Mahmood Aljamali
E-mail: dr.nagham_mj@yahoo.com

Preparation of Ciprofloxacin drug derivative

Preparation and development of Ciprofloxacin drug derivative{1}:

Ciprofloxacin drug developed by this paper thru preparation of its derivative{1} via three components reaction by following many chemical reactions like condensation reactions according to procedures[29-33] (Nagham 2016 .,Nagham et al 2015)to vintage precipitation, filtered ,dried and re crystallized to provide ciprofloxacin derivative{1}.

Preparation and development of Ciprofloxacin drug derivative{2}:

Ciprofloxacin drug advanced to new drug by this study thru synthesis of its derivative{2} via azotation reaction,imination reaction ,then formazanation reaction by following many steps according[29,30] to procedures(Nagham et al 2015.,Intisar and Nagham 2018)to format precipitation, filtered ,dried and re crystallized to provide ciprofloxacin derivative{2}.

Preparation and development of Ciprofloxacin drug derivative{3}:

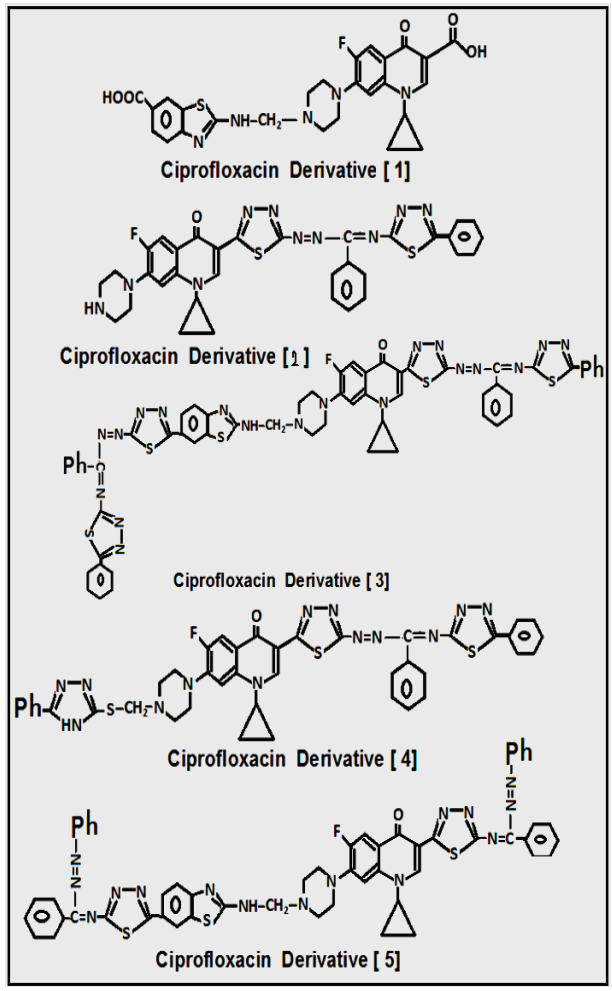
Ciprofloxacin drug developed via this work thru preparation of its derivative{3} via three components reaction, cyclization reaction, azotation ,imination reaction ,then formazanation step by following[29,30] procedures(Nagham et al 2015.,Intisar and Nagham 2018)to yield precipitation, filtered ,dried and re crystallized to provide ciprofloxacin derivative{3}.

Preparation and development of Ciprofloxacin drug derivative{4}:

Ciprofloxacin drug developed to derivative{4} via imination with formazanation reaction ,then three components reaction with triazole derivative according[29,30] to procedures(Nagham et al 2015.,Intisar and Nagham 2018)to give precipitation[35] ,filtered ,dried and re crystallized to produce ciprofloxacin derivative{4}.

Preparation and development of Ciprofloxacin drug derivative{5}:

Ciprofloxacin drug developed by this paper thru preparation of its derivative{5} via three components reaction, esterification, cyclization, imination reaction by following many chemical reactions like condensation reactions according[34-36] to procedures (Nagham 2016 .,Nagham et al 2015)to vintage precipitation, filtered ,dried and re crystallized to produce ciprofloxacin derivative{5}.



Scheme.1:Preparation of Ciprofloxacin drug Derivatives

Results and Discussion

The developed ciprofloxacin derivatives studied and identified with multiplicity spectral techniques represented by (FT.IR ,H.NMR ,C.NMR) spectra with microbial tests and bacterial resistance studying:

Identification via Spectral Techniques :

FT.IR-Spectra of Ciprofloxacin Derivatives: The spectra provided numerous absorption bands at ((C=N) endocycle:1656 .,(CO-O) carbonyl of carboxyl:1710.,(NH):3241 .,(CO) carbonyl of chalcone:1666 ,(OH) of carboxyl: (2740-3114),(C-S):794,(C-F):713 ,(CH)aliphatic: 2914 in Cipro-derivative{1},but numerous absorption bands at ((C=N) endocycle: 1642 .,(NH):3200 .,(CO) carbonyl of chalcone: 1698 ,(C-S):781 ,(C-F):745 ,(CH)aliphatic: 2936 ,(C=N) Imine group:1625 ,(CH=CH) of chalcone:3095 ,(N=N):azo group:1480

in Cipro-derivative{2}.,various absorption bands at ((C=N) endocycle:1639 .,(NH): 3227 .,(CO) carbonyl of chalcone:1692 ,(C-S):777 ,(C-F):713 , (CH)aliphatic: 2947 ,(C=N) Imine group: 1615 ,(CH=CH) of chalcone:3086 ,(N=N):azo group:1483 in Cipro-derivative{3}.,other absorption bands at ((C=N) endocycle: 1649 .,(NH):3262 .,(CO) carbonyl of chalcone: 1691 ,(C-S):778 ,(C-F):718 ,(CH) aliphatic: 2912 ,(C=N) Imine group:1611 ,(CH=CH) of chalcone:3087 ,(N=N):azo group:1469 ,(S-CH_2): 1235 in Cipro-derivative{4}.,while other absorption bands at ((C=N)endocycle: 1630 .,(NH):3211 .,(CO) carbonyl of chalcone: 1688 ,(C-S):798 ,(C-F):722 ,(CH) aliphatic: 2973 ,(C=N) Imine group:1618 ,(CH=CH) of chalcone:3099 ,(N=N):azo group:1461 in Cipro-derivative{5}.

^{1}H.NMR-Spectra of Ciprofloxacin Derivatives: Our spectra provided new signals point to prepared drug derivatives and formatted[29, 30] functional groups(Nagham et al 2015.,Intisar and Nagham 2018) in this work, the spectra of all derivatives appeared signal at (2.5) for solvent (DMSO) ,novel derivative{1} appeared many signals at δ (COOH) Protons of carboxyl group:12.10 .,(NH)proton of amine:5.01 .,Protons of aromatic ring:(6.68-7.24).,(N-CH_2-N) protons:3.64 .,(N-CH_2-CH_2-N) protons: (2.95-3.46) .,(CH=C-CO) proton of chalcone: (5.49).,(CH_2-CH_2-CH) protons of three membered ring:(0.83-1.46)., but derivative{2} appeared many signals at δ (NH)proton of amine:5.12 .,Protons of aromatic ring: (6.93-7.78) .,(N-CH_2-CH_2-N) protons: (2.61-3.54) .,(CH=C-CO) proton of chalcone: (5.56).,(CH_2-CH_2-CH) protons of three membered ring:(0.64-1.52) .,while derivative{3} appeared many signals at δ (NH)proton of amine:5.07 .,Protons of aromatic ring:(6.88-7.58).,(N-CH_2-CH_2-N) protons: (2.75-3.41) .,(CH=C-CO) proton of chalcone: (5.67).,(CH_2-CH_2-CH) protons of three membered ring:(0.73-1.89).,(N-CH_2-N) protons:3. 82 .,derivative{4} appeared many signals at δ (NH)proton of triazole:8.23 .,Protons of aromatic ring:(6.79-7.44).,(N-CH_2-CH_2-N) protons:(2.60-3.13).,(CH=C-CO) proton of chalcone:(5.81) .,(CH_2-CH_2-CH) protons of three membered ring:(0.82-1.54).,(S-CH_2-N) protons:3. 98 .,derivative{5} appeared many signals at δ (NH)proton of amine:5.00 .,Protons of aromatic ring:(6.84-7.67).,(N-CH_2-CH_2-N) protons:(2.86-3.57).,(CH=C-CO) proton of chalcone: (5.60).,(CH_2-CH_2-CH) protons of three membered ring:(0.94-1.34).,(N-CH_2-N) protons:3.90 .

The ^{13}C.NMR spectral of Derivatives:Our spectra provided new signals point to prepared drug derivatives and formatted functional groups in this work.,at the spectra of all derivatives appeared signal at (40.0) for solvent (DMSO)., novel derivative{1} appeared many signals at (172 .5) for (C ,carboxyl group COOH).,(114.9-148.4) for (C ,Aromatic ring).,(193.0) for (C ,carbonyl of Chalcone CO),(100.0 , 107.3) for (C ,carbons of alkene in chalcone C=CH) , (68.4–73.0) carbons of (N-CH_2-CH_2-N) .,(CH_2-CH_2-CH-)carbons of cycle: (23.0-20.1) ., 42.1:carbon of (N-CH_2-N) .,but derivative{2} appeared many signals at (154.09) for (C ,imine group C=N)., (110.1-132.91) for (C ,Aromatic ring).,(190. 0) for (C ,carbonyl of Chalcone CO) , (102.1 , 104.7) for (C ,carbons of alkene in chalcone C=CH) ,(60.2–73.0) carbons of (N-CH_2-CH_2-N).,(CH_2-CH_2-CH) carbons of cycle: (19.0-30.9) ., 44.1: carbon of (N-CH_2-N) .,While derivative{3} appeared many signals at (159.12) for (C ,imine group C=N)., (113.4-124.25) for (C ,Aromatic ring)., (196.4) for (C ,carbonyl of Chalcone CO), (101.9 , 104.3) for (C ,carbons of alkene in chalcone C=CH) ,(65.2–71.5) carbons of (N-CH_2-CH_2-N) .,(CH_2-CH_2-CH)carbons of cycle: (15.6-29.3) .,also derivative{4} appeared many signals at (158 .7) for (C ,imine group C=N)., (113.4 -130.76) for (C ,Aromatic ring)., (191.5) for (C ,carbonyl of Chalcone CO) ,(100.6 , 105.2) for (C ,carbons of alkene in chalcone C=CH) , (63.8–78.04) carbons of (N-CH_2-CH_2-N) .,(CH_2-CH_2-CH)carbons of cycle:(16.08-31.21) , 53.81:carbon of (S-CH_2-N) .,and the last derivative{5} appeared at (157.22) for (C ,imine group C=N)., (117.43-136.08) for (C ,Aromatic ring)., (188.91) for (C ,carbonyl of Chalcone CO) , (101.17 , 103.45) for (C ,carbons of alkene in chalcone C=CH) ,(69.78–74.27) carbons of (N-CH_2-CH_2-N).,(CH_2-CH_2-CH)carbons of cycle:(18.66-30.85), 55.61:carbon of (N-CH_2-N).

Selected Bacteria:

Pseudomonas aeruginosa is a common encapsulated, Gram-negative, rod-shaped bacterium that canister source of disease in plants and wildlife, involving humans. A species of considerable medical status, P. aeruginosa is a multidrug resistant pathogen renowned for its ubiquity, its intrinsically innovative antibiotic resistance mechanisms, and its connotation with grave infections–hospital-acquired infections like ventilator-associated pneumonia and numerous sepsis syndromes.

Staphylococcus aureus is a Gram-positive, round-shaped bacterium that is a member of the Firmicutes, also it is a usual associate[31,32] of the microbe(Nagham et al 2015.,Intisar and Nagham 2018) of the frame, regularly institute in the upper respiratory tract and on the skin. It is repeatedly positive for catalase and nitrate reduction and is a facultative anaerobe that can cultivate without the requirement for oxygen.

Klebsiella pneumoniae is a Gram-negative, non-motile, encapsulated, lactose-fermenting, facultative anaerobic, rod-shaped bacterium. It seems as a mucoid lactose fermenter on MacConkey agar.

Escherichia coli: also known as (E. coli) is a Gram-negative, facultative anaerobic, rod-shaped, coliform bacterium of the genus Escherichia that is normally originate in the inferior intestine of warm-blooded organisms .The bacterium raises immensely in additional fecal matter below aerobic situations for 3 days, but its facts failure gradually later.

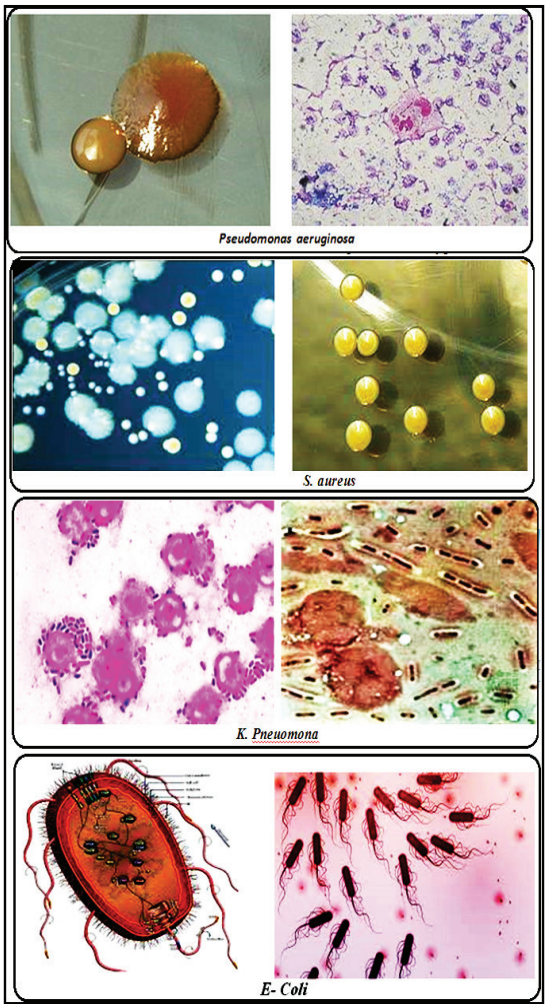


Photo.1: Selected Bacteria

Microbial Resistance Assay [35,36]:

Microbial tests for prepared ciprofloxacin derivatives have been screened for their antibacterial activities thru agar via following procedures[35-40] (Nagham et al 2015.,Intisar and Nagham 2018)The test of bacterial inhibition were done at (three concentrations) (10,15,20 micro gram) concentrations in (DMSO) with bacteria:(K. Pneuomona ,S. aureus ,P. aeruginosa ,E-Coli).These bacterial strains were incubated for (24 hr) at temperature (37ºC).

The test of resistance of the bacteria[40-44] ,which included kinds of bacteria to curtain the biotic activity of confident derivatives against bacteria.,Tables(1 and 2) appears the diameter of inhibition zone(mm) for vehicles chemical considered towards the bacteria.

TABLE.1: Inhibition test of derivatives in Concentration (15 micro gram)for (+ gram)

Ciprofloxacin Derivatives	S. aureus
Derivative{1}	+++
Derivative{2}	+++
Derivative{3}	+++
Derivative{4}	+++
Derivative{5}	+++

(+):inhibition(6-9)mm

(++):inhibition(10-14)mm

(+++):inhibition(15-18)mm

TABLE.2: Inhibition test of derivatives in Concentration (15 micro gram)for (- gram)

Ciprofloxacin Derivatives	K. Pneuomona	P. aeruginosa	E-Coli
Derivative{1}	++	+	+
Derivative{2}	++	++	+
Derivative{3}	+++	+++	+++
Derivative{4}	+++	++	++
Derivative{5}	+++	+++	+++

(+):inhibition(6-9)mm

(++):inhibition(10-14)mm

(+++):inhibition(15-20)mm

The grades in this work appeared that the sensitivity of ciprofloxacin derivatives{5,3} is higher than other derivatives in the inhibition of kind from selected bacteria, thiadiazole ring , formazan group(N=N-C=N) gave high resistance activity to these derivatives against selected bacteria. Ciprofloxacin derivatives are broadly recycled for the cure of numerous types of bacterial pollutions and infection. General, these antibacterial mediators can be measured safe and well accepted drugs. Relative studies have estimated the practice of quinolones in old and younger inhabitants.

There is no recognized cross-resistance among ciprofloxacin and other modules of antimicrobials. Especially the drug has 100 times higher attraction for bacterial DNA gyrase than for mammalian and prevents bacterial DNA gyrase, an enzyme important for DNA replication. The mechanisms of resistance are known by decreasing their binding affinity to quinolones, decreasing the drugs' effectiveness.

Conclusions

All ciprofloxacin derivatives appeared good resistance towered bacteria and the sensitivity of ciprofloxacin derivatives{5,3} is higher than other derivatives in the inhibition of kind from selected bacteria**.**

Conflict of Interest:There is no any Conflict of Interest

Ethical Clearance:Ethics committee refer that there is no plagiarism and there is no mistakes or wrong results in this work.

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