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Synthesis, structural characterization and antibacterial studies of Fluoroquinolone Drug-Ciprofloxacin

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Abstract

The vibrational spectroscopy, such as FTIR has been used to measure the vibrational modes of fluoroquinolones, provides information about structural differences of its individual members. Form the interpreted spectral data Ciprofloxacin has been distinguished by the presence of different substituents in their parent nucleus.

FTIR study provides the most direct and definitive identification of fluoroquinolone and offer a means for qualitative analysis of newly synthesized fluroquinolone drug-Ciprofloxacin.

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. This includes bone and joints infection intra abdominal infection certain types of infectious diarrhea, respiratory tract infection skin infections, typhoid fever and urinary tract infections.

Key words : Fluoroquinolones, Ciprofloxacin, Bronchitis, Bacterial Gasteroenteritis, Spectrum.

Inroducton

Fluoroquinolones have been associated with a significant number of serious adverse drug reactions such as tendon damage and peripheral neuropathy[1], such as reactions may manifest long after therapy had been completed and in severe cases may result in lifelong disabilities[2]. They are associated with severe psychiatric[3,4] adverse reaction. The reaction was detailed within Stephen fried's book Bitter Pills (1999). Hepatotoxicity has also been reported with the use of some fluoroquinolones[5,6].

Ciprofloxacin is one of the synthetic chemotherapeutic fluoroquinolone antibiotics. Ciprofloxacin is an agent of choice for the treatment of bacterial gastroenteritis[7] caused by gram negative

bacilli such as enteropathogenic E. coli, salmonella (including S. typhi), Shigella spp., Vibrio spp. and Aeromonas hydrophilla. It is widely used for the treatment of respiratory tract infections and is particularly effective for controlling bronchitis and pneumonia caused by Gram-negative bacteria.

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. This includes bone and joints infection intra abdominal infection certain types of infectious diarrhea, respiratory tract infection skin infections, typhoid fever and urinary tract infections. For some infections it is used in Ciprofloxacin is a first generation fluoroquinolone that has been available for treatment of bacterial infections for many years. Like other fluoroquiolones, Ciprofloxacin is active against a wide range of aerobic gram positive and gram negative organism and is believed to act by inhibition of bacterial DNA gyrase[8,9] and tropoisomerase IV that are required for synthesis of bacterial mRNA (transcription) and DNA replication. In contrast DNA gyrases are not present in human and other eukaryotic cells and the equivalent tropoisomerases are not sensitive to fluoroquinolone inhibition[10,11].

In ciprofloxacin carbon atoms of both ketonic carbonyl and carboxyl carbonyl groups are sp^2 hybridised. Hence, they are planar. Further, the both carbonyl groups are coplanar with each other. This coplanarity of both carbonyl groups gives rise to antibacaterial property to ciprofloxacin. Further, the presence of piperazine ring also contributes the antibacterial to ciprofloxacin. Conclusively, the antibacterial property of ciprofloxacin depends on the coplanarity of both carbonyl groups and piperazine ring.

Materials and Methods

All chemicals are of analytical grade and purchased from CDH and Merck. Melting points are determined in an open capillary tube and are uncorrected. An infrared spectrum has been recorded in KBr on Perkin-Elmer RXI spectrometer at CDRI, Lucknow. The 1H-NMR were measured in CDCl3 solution on a brucker DRX-300 MHz spectrometer using tetramethyl silane (TMS) as an internal reference and chemical shift in ppm at CDRI, Lucknow. Elemental analyses were carried out with elementar vario El, III elemental analyser at department of biotechnology IIT, Kharagpur.

Synthesis of Ciprofloxacin :

The compound was refluxed in autoclave at 150^0 C for two hours. Sodium hydroxide was with continuous stirring for 10 minutes. Thereafter, 10 g of piperazine was added and the mixture was added and the mixture was refluxed for 30 hrs in a 250 ml of three necked flask equipped wath a reflux condenser and mechanical stirrer. Sodium carbonate was added until the mixture was alkaline. The excess solvent was removed by steam distillation. The residual solution was kept in a refrigerator until crystallization was completed. The solution was filtered on a Buchner funnel and washed with 10 ml of saturated sodium chloride solution.

Now, the solution of 40 g of sdium hydroxide and 160 ml of water were added in a one liter round bottomed flask equipped with a reflux condenser. The mixture was heated to boil until the compound was disappeared. The reaction mixture was diluted with an equal volume of water. When cold, the reaction product was poured with vigorous stirring into 125 ml of concentrated hydrochloric acid. Then, it was allowed to cool at room temperature. The compound was filtered at the pump and washed with a little water and characterized. It is crystalline in nature.

Table - 1

Table: elemental analysis (in %)

	C	H	N
Found	61.57	5.43	12.68
Calculated	61.37	5.31	12.42

Pure sample of Ciprofloxacin ($C_{17}H_{18}FN_3O_3$) were obtained from external agency. The drug were 99.8% to 98.0% pure. FTIR spectroscopy is an important analytical technique which detects various characteristics of functional groups in molecule on interaction of an infrared light with the matter chemical bonds would, stretch, contract and bond as a result each chemicals functional group tend to absorb infrared radiation in a specific wavelength range regardless of the structure of the rest molecule. Based

on this principle functional groups present in composite materials are identified. It is performed in a FTIR spectro photometer interfaced with infrared(IR) microscope operated in reflectance mode. IR spectrum of fluoroquinolone drug-Ciprofloxacin has been recorded in the range 4000-400 cm^{-1}. The spectrum was interpreteted considering few main peaks observed.

Results and Discussion

Ciprofloxacin is the yellowish to light yellow crystalline substance with molecular mass 385.8 g/mol and empirical formula ($C_{17}H_{18}FN_3O_3$).

IR spectra were recorded as KBr pellets in the region of 4000-400 cm^{-1} on a Perkin-Elmer Spectrophotometer.

IR spectrum of fluoroquinolone drug-Ciprofloxacin has been recorded in the range 4000-400 cm^{-1}. The spectrum was interpreteted considering few main peaks observed.

The ^{1}H-NMR spectra were recorded on a Hitachi FT–NMR model R-600 spectrometer using $CDCl_3$ as the solvent. The chemical shifts are given in ppm relative to tetramethylsilane.

The electron impact (EI) spectrum of ciprofloxacin is recorded using a shimadz PQ-5000 GC-MS spectrometer and the spectrum shows peak at $(M/Z)^+$ 332 and a base peak at $(M/Z)^+$ 288 resulting from the group, which corresponds to the molecular formula $C_{17}H_{18}FN_3O_3$ which is the molecular formula of Ciprofloxacin.

The IR spectrum of ciprofloxacin shows an absorption band at 3028 cm^{-1} indicating the presence of aromatic C=C-H proton. It shows a characteristics band at 1043 cm^{-1}, which indicates the presence of C–F group in the molecules. The compound shows a characteristic band at 1610 cm^{-1} and 1485 cm^{-1}, those are responsible for benzene ring. The band at 1636 cm^{-1} indicates the presence of olefinic C=C. It shows a band at 3035 cm^{-1} indicating the presence of C=C–H linkage. It also shows a frequency at 1675 cm^{-1}, which indicates the presence of conjugated C=O group. The absorption bands appear at 1214 cm^{-1} and 1085 cm^{-1} indicating the presence of carboxyl (COOH) group. The band appears at 1050 cm^{-1} indicating the presence of –O– linkage. The compound shows absorption bands at 2890 cm^{-1} and 1433 cm^{-1}. These bands indicate the presence of CH_2 and CH group respectively.

The compound ciprofloxacin shows singlet peak in ^{1}H-NMR spectrum at δ7.2, which indicates the molecule contains aromatic CH proton. The spectrum of compound contains a singlet peak at 6.8 indicating the C=CH group49. It shows a triplet peak at δ4.3 ppm indicating the presence of two equivalent protons at its adjacent position in the molecule. It also shows a doublet peak at 3.15 ppm for CH_2 group. The spectrum of ciprofloxacin shows a singlet peak at 3.0 ppm for CH_2. The NMR signal of –OH group appears at δ11.3 indicating its highly deshielded nature.

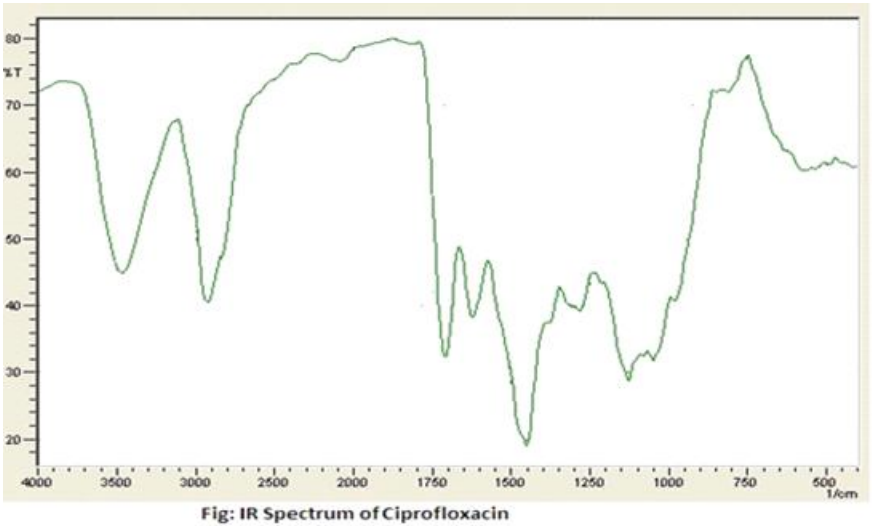


Fig: IR Spectrum of Ciprofloxacin

Antibacterial Studies :

In ciprofloxacin carbon atoms of both ketonic carbonyl and carboxyl carbonyl groups are sp^2 hybridised. Hence, they are planar. Further, the both carbonyl groups are coplanar with each other. This coplanarity of both carbonyl groups gives rise to antibacaterial property to ciprofloxacin. Further, the presence of piperazine ring also contributes the antibacterial to ciprofloxacin. Conclusively, the antibacterial property of ciprofloxacin depends on the coplanarity of both carbonyl groups and piperazine ring.

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. This includes bone and joints infection intra abdominal infection certain types of infectious diarrhea, respiratory tract infection skin infections, typhoid fever and urinary tract infections.

A wide range of techniques is available which correspond to those used in other forms of microbiological assay. The principal of these tests is similar, namely the preparation of a concentration gradient of the antibiotic in a nutrient medium and the observation of whether or not growth takes place when the medium is seeded with the indicator bacterium and incubated. The concentration gradient may be continuously varied or discontinuously varied as in a series of tubes of liquid medium or plates of agar medium. In tests to determine the sensitivity of a newly isolated bacterium, known amounts of antibiotics are added to the medium. In assays or titrations of antibiotics, (e.g. in blood fluids) a bacterium of known sensitivity to the antibiotic is used as an indicator.

In the present research work, in order to antibacterial studies two gram positive say Escheria coli and Salmonella typhae and two gram negative bacteria say Klebsiella pneumoniae and Bacillus dysenteriae were selected:

The conventional disc-diffusion was followed. The results will be available only after 24 h.

The MIC of any antibiotic for a bacterial isolate can be estimated from a measurement of the zone of inhibition in the disc test by reference to standard graph (previously prepared), which relates the MIC to the zone diameter for a standard.

Table - 2

Table: Antibacterial Screening

	Ciprofloxacin		
Concentration	10^{-3}	10^{-2}	10^{-1}
Escheria coli	++	+++	++++
Salmonella typhi	++	+++	++++
Klebsiella pneumoniae	++	++	+++
Bacillus dysenteriae	+	++	+++

Conclusion

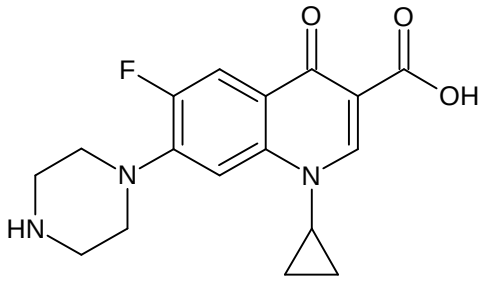
The contents of the paper deal with the cyclisation of several substituted aromatic ring, which were obtained by means of standard method.

During the work ciprofloxacin antibiotics have been synthesized. During the synthetic processes we have prepare different intermediate compounds through which it is clear that how conjugation affects the reactivity, what happens to a carbonyl group when it is conjugated with double bond. How the double bond becomes electrophile and can be attacked by nucleophile. Through the synthesis one arrives at electron deficient ring that allows substitution reactions with nucleophiles rather than the usual electrophiles.

Co planarity of carbonyl group at C-6 and C-7 and piprazine rings are generally responsible for the antibacterial activity of the ciprofloxacin. The approach of synthesis of the drugs and their derivatives may changes its assay. This should be topic studies as it has become interest for research one.

Scope of future work of to studies of new approach for the synthesis of some other quinolone life ciprofloxacin, antibacterial studies which depends on co planarity of carbonyl group at C-6 and C-7 and piprazine rings shall be done after the synthesis of the some well known fluoroquinolone drugs and their derivatives.

On the basis of FTIR spectral analysis of Ciprofloxacin, the structure of Fluoroquinolone-Ciprofloxacin may be drawn as



Ciprofloxacin

Figure - 2

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