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Research Article

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Synthesis and spectral studies of noval benzyl derivative of ciprofloxacin and their Cu (II) and Co (II) complexes

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ABSTRACT

Reaction of 1-cyclopropyl-6-flouro-1, 4-dihydro-4oxo-7- (1-piperazinyl)-3quinolone carboxylic acid (ciprofloxacin) with The benzyl chloride in presence of base triethylamine,with introduction of amide group in ciprofloxacin to form new benzyl derivative of 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(phenyl carbonyl) piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylic acid(Cip-d) and their Cu(II) and Co(II)complexes were established on the basis of spectral studies 1HNMR,IR,Mass spectroscopy .

Key Words: Ciprofloxacin Derivative (Cip.D), Synthesis, Antimicrobial activity.

INTRODUCTION

The emergence of bacterial resistance to different classes of antibacterial agents, such as B-lactans, quinolones fluroquinolone and macrolides, is an alarming problem that seriously affects human health [1], To combat this situations, humorous efforts have been made in the development of new approaches to treat bacterial infections, particularly for therapeutics with novel mechanisms of action and little or no cross resistance [2, 4]. As a result, new antibacterial agents against hospital- acquired. Gram-positive bacterial pathogens[5], especially against methicillin-resistance staphylococaus aureas (MRSA) and vancomycin- resistance enterococci (VRE), have become the centre of attention in this highlighted research field [6].Ciprofloxacin hydrochloride, second-generation quinolone antibiotic, is active against both Gram- positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division [].. Ciprofloxacin has been approved for the treatment of infections, especially urinary tract infections, prostatitis, shigellosis [7, 8, 9]. It has also been found to show anti-tumour activity against P388 leukemia (Yamashita et al., 1992).ciprofloxacin is quinolone drug having a bicyclic ring structure having carbonyl group at position 3,a keto at position 4 ,a fluorine atom at position 6 and nitrogen hetrocycle moiety at 7 position..The nature of substitute at C-7 position has a great on potency, spectrum ,solubility and pharmacokinetics, Ciprofloxacin have nitrogen heterocyclic linked to the C-7 position of quinolines ring through the heterocyclic nitrogen[10,11].extensively investigate substituent at N-H in piparizin respect significant modification. Structure of Cip-D is as follow. Early we isolate the Cip-D by the **r**eaction of 1-cyclopropyl-6-flouro-1, 4-dihydro-4oxo-7- (1-piperazinyl)-3quinolone carboxylic acid (ciprofloxacin)with the 4-methoxy 1-chlorobenzen in presence of base triethylamine,with introduction of amide group in ciprofloxacin to form derivative 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(phenyl carbonyl) piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylic acid(Cip-D)[12]

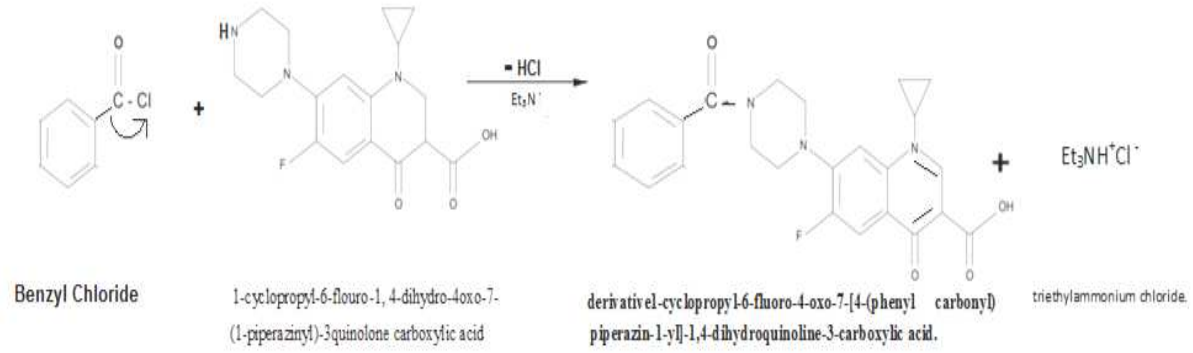


Figure 1; Synthesis of ciprofloxacin Derivative(Cip-D)

EXPERIMENTAL SECTION

(a)Regeneration of free ciprofloxacin:-
A solution of ciprofloxacin hydrochloride (l0 g) in water (50 ml) was treated with excess of 5% aqueous sodium bicarbonate solution resulting in the formation of white precipitates which were filtered through suction filtration and left to cry as a neutral ciprofloxacin (8.3 & 83%).

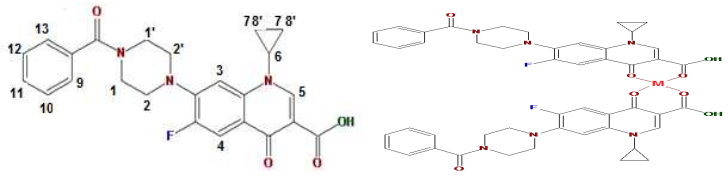
(b)Procedure for ciprofloxacin derivative
Ciprofloxacin was dissolve in one molar equivalent of appropriate 4-methoxy 1-chlorobenzen and result mixture was refluxed. The product was analyses by TLC .Cool the resultant mixture, remove excess solvent in vacuum and residue was suspended in brine and extracted with dichloromethane (3x50) the organic phase was dried over $CaCl_2$ and evaporated in presence of chloroform to afford the solid product in pure form.

(c)Complexes of Copper acetate [Cu $_2$(Cip.D) $_2$]-
Take gm copper acetate (1mM) (anhydrous).Dissolved in 5ml ethanol and 5ml distilled water. Now take 0.872 gm (2Mm) cip-d in 5ml ethanol and 5ml distilled water. Add sol^n of copper acetate (1mM) drop by drop with constant stirring in solution of Cip-D. Solid complex digested on water bath at 60C.on cooling pass through filter paper. Wash with 50% alcohol

(d)Complex Cobalt-[C0 (Cip.D) $_2$]
Take gm Cobalt nitrate (1mM) (unhydrous).Dissolved in 5ml ethanol and 5ml distilled water. Now take 0.872 gm (2Mm) Cip-d in5ml ethanol and 5ml distilled water. Add Sol^n of copper acetate (1mM) drop by drop with constant stirring in solution of cip-d.PH of sol^n was maintained 6.0-6.5 by HCl and NH4OH.Reflux for an hour, yellow coloured complex was formed. It was filtered dried in air, Recrystallised from chloroform. Wash with 50% alcohol

RESULTS AND DISCUSSION

The structure of the synthesized compound were established on the basis of IR and NMR spectra data and element analysis as shown in table(1,2).Cip-D isolated by the **r**eaction of 1-cyclopropyl-6-flouro-1, 4-dihydro-4oxo-7- (1-piperazinyl)-3quinolone carboxylic acid (ciprofloxacin)with The benzyl chloride in presence of base triethylamine,with introduction of amide group in ciprofloxacin to form derivative 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(phenyl carbonyl) piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylic acid(Cip-D) and their complexes of Cu(II)and Co(II).the carbonyl C=O stretch was absent in Cip-D complexes of cu and co at the region of at1724.35,which is present in Cip-D shows the bonding through c=o stretch. Similarly five extra peak at7.589, 7.613, 7.941, 7.964, 7.985(m, 5H) shows the substitution of benzoyl group in cip-D[H-9, 10, 11, 12 and13].1HNMR studyCu(II)andCo(II)metal ion with ciprofloxacin derivative(Cip-D) shows slight shift of H-5.In Cip-D the peak observed at 8.673(S, 1H) while in complex of Cu(II) and CO(II) it shift higher position at10.220(S, 1H) because of bonding with metal ion.



(a) **(b)**

Fig-2 (a)Cip-D,(b)Cip-D comlexes.

Element analysis

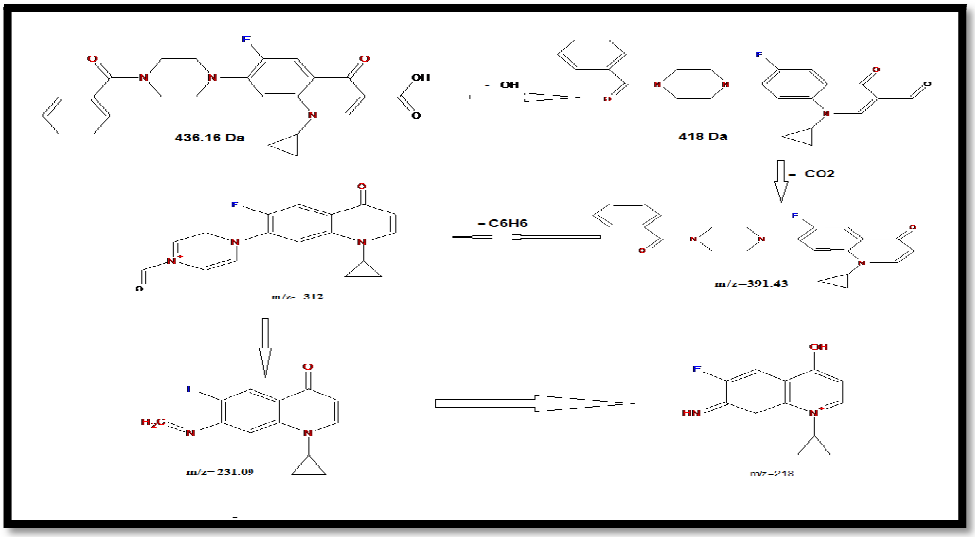
Sr.No	M.P	Mol.wt	Molecular formula	Element analysis		
				C	H	N
Ciprofloxacin	255-257	331.34	$C_{17}H_{18}FN_3O_3$	61.623360	5.475509	12.681645
Cip-d	274	435.44	$C_{24}H_{22}FN_3O_4$	66.198358	5.092303	9.649729
[Cu $_2$(Cip.D)$_2$]	269-271	933.448	C48H43F2N6O8Cu	65.782686	4.830312	3.196379
[C0 (Cip.D)$_2$]	266-267	928.835	C48H43F2N6O8Co	66.130749	4.855870	3.213291

TABLE -2

Sr. No	Name of compound	IR	1H-NMR
1.	**Ciprofloxacin**	Spectra of ciprofloxacin at1724.35 c; C=O stretch of Keton at1624.99 cm; $^{-1}$ 3099.35 cm^{-1} assigned C-Hstr.CH2	1.296 (m-2H)-H 8, 8',1.339(t-2H)-H, 7-7', 2.892(t-4H)-H 1-1,3.210(t, 4H)-H2-2,3.386(m, 1H) H-6,8.673(S, 1H)-H-5,7.852(d, 1H)-H-4,7.501(d, 1H)-H-3,
2.	**Cip-d**	3527-3207 cm^{-1}O-H stretch; 3180.4 cm^{-1} C-H stretch of aromatic; 3051 cm^{-1} C-H stretch of CH2; 2854.45 cm^{-1} for C-H stretch of CH_3; C=O Carboxylic acid is 1720.39 cm^{-1}.C=O Keton in 1616.24 cm^{-1}	1.274 (m-2H)-H 8, 8'; 1.333(t-2H)-H, 7-7'; 3.010(t-4H)-H 1-1, 3.125(t, 4H)-H2-2; 3.286(m, 1H) H-6 ;8.673(S, 1H)-H-5; 7.920(d, 1H)-H-4; 7.479 (d, 1H)-H-3; 7.589, 7.613, 7.941, 7.964, 7.985(m, 5H) [H-9, 10, 11, 12 and13 (Benzoyl group).
3.	**Cu**	3083.53 cm^{-1} is of C-H stretch of aromatic; 2916.38 cm^{-1} is the C-H stretch of CH2.28O4.45 cm^{-1} is the band for C-H stretch of CH_3; of Keton in 1629.77	2.500(t-4H)-H 1-1,1.240 (m-2H)-H 8, 8',3.344 (m, 1H) H- 6, 7.857, 7.436, 7.357, 7.354, 7.350, (m,5H(Benzoyl group),
4.	**CO**	3082.13 cm^{-1} is of C-H stretch of aromatic; 2915.12 cm^{-1} is the C-H stretch of CH2; 28O4.45 cm^{-1} is the band for C-H stretch of CH_3; Keton in 1629.17	1.274 (m-2H)-H 8, 8'; 1.333(t-2H)-H, 7-7'; 3.010(t-4H)-H 1-1, 3.125(t, 4H)-H2-2; 3.286(m, 1H) H-6 ;8.673(S, 1H)-H-5; 7.920(d, 1H)-H-4; 7.479 (d, 1H)-H-3; 7.589, 7.613, 7.941, 7.964, 7.985(m, 5H) [H-9, 10, 11, 12 and13 (Benzoyl group).

Mass Spectrum:

The molecular ion peak is observed at m/z 436 corresponding to the calculated molecular weight of the Cip.D. The other peak at m/z 418,391.43, 312,231.09,210 also observed.



Mass Fragmentation of Cip.D.

Fig.4-1H-NMRCIP-D

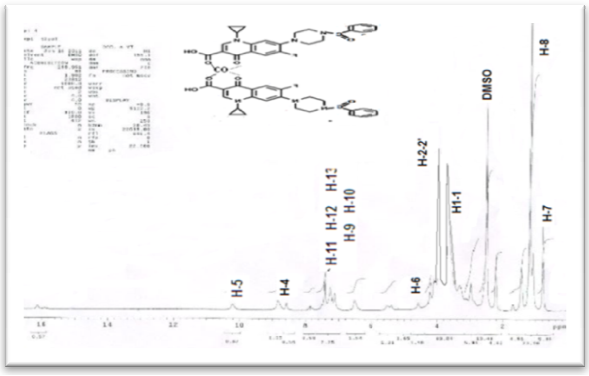
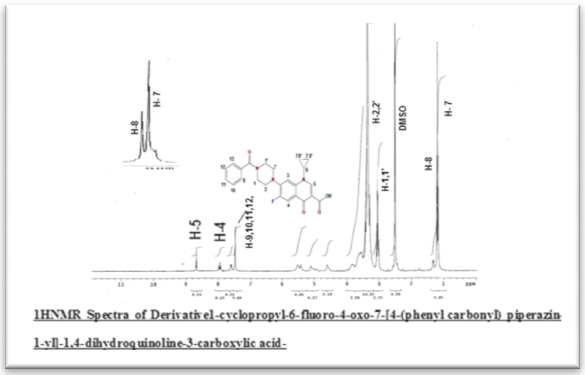


Fig.3-1H-NMR of Ciprofloxacin



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