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Synthesis and Antibacterial activity of Mannich bases of Ciprofloxacin and Lomefloxacin with isatin and its derivative

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Mannich bases of ciprofloxacin and lomefloxacin with isatin and its derivative were synthesized by condensing acidic 'NH' group of isatin with formaldehyde and the secondary amino group (piperazine moiety) of ciprofloxacin and lomefloxacin and screened for antibacterial activity. Mannich bases of ciprofloxacin are equipotent or more potent than cirpofloxacin against certain pathogenic microorganisms. Mannich bases of lomefloxacin are equipotent to that of lomefloxacin.

ISATIN is an endogeneous compound identified in human and rat tissues for the first time in 1988[1]. Isatin has a range of actions in the CNS - MAO inhibition, anticonvulsant[2-6], anxiogenic[7] and antimicrobial activity[8]. Some Mannich bases of isatin appear to act as antibacterial agent[9-12]. Mannich bases of antibiotics shown better antibacterial activity than the parent molecule[13]. At present, fluoroquinolones are the most powerful antibacterial agents available in the market. In the present study we have aimed to achive better antimicrobial profile at lower doses by preparing Mannich bases with isatin and a derivative of isatin. This report deals with the synthesis of Mannich bases by condensing active hydrogen atom of isatin with formaldehyde and the secondary 'amino function (piperazino moiety) of ciprolfoxacin and lomefloaxacin. All the compounds (Table 1) synthesized were screened for antibacterial activity by agar dilution method[14].

EXPERIMENTAL

The Synthesized compounds were characterized by TLC, spectral and elemental analysis.

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Compound A. Synthesis of 1-Cyclopropyl 6-fluoro 1,4-dihydro 4-oxo 7{[N⁴(1'isatinyl) methyl] N' Piperazinyl} 3-Quinoline carboxylic acid.

Equimolar quantities (0.06 moles) of isatin, ciprofloxacin and 37% formalin (2 ml) were dissolved in 50 ml of methanol and the solution was refluxed for 78 h. Solvent was removed by distillation under reduced pressure and the solid obtained was recrystallized from chloroform:petroleum ether mixture. Yield 72.19% and M.P. 133-135°.

Antibacterial activity:

The Compounds were evaluated for antibacterial activity by agar dilution method against *Salmonella typhi, Escherchia coli, Vibrio cholerae, Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Shigella flexnari* and *Citrobactor ferundi* in the concentration range of 0.05-10 µg/ml. MIC of the compounds tested are shown in Table 2.

RESULTS AND DISCUSSION

Mannich bases of ciprofloxacin (A and B) are more potent than ciprofloxacin against *Vibrio cholerae*. Mannich

Table 1 : Physical constants

Code	M.P. (°C)	Yield (%)	Molecular formula	Molecular weight	IR (cm^{-1})
A	133-135	72.9	$C_{26}H_{23}O_5N_4F$	490	1725, 2920, 1180, 3240, 1650, 1450
B	100-102	82.0	$C_{27}H_{25}O_5N_4F$	504	1720, 2920, 1180, 1640, 3240, 1430
C	143-145	71.1	$C_{26}H_{24}O_5N_4F$	491	1710, 2900, 1190, 3000, 1460
D	178-180	86.0	$C_{27}H_{26}O_5N_4F$	505	1700, 2880, 1190, 3000, 1470

Table 2 : Antibacterial activity of test compounds

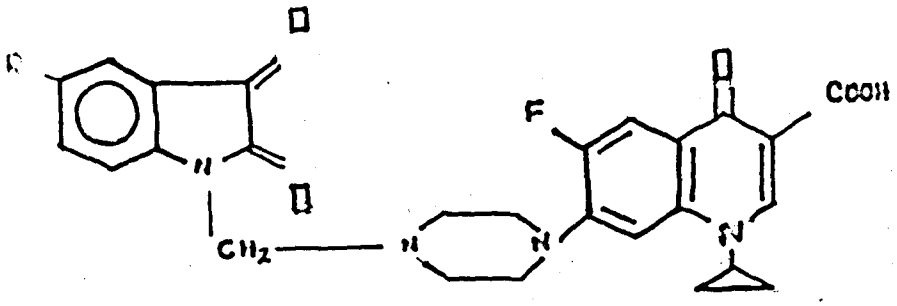
Test organisms	Compounds MIC (µg/ml)				Ciprofloxacin	Lomefloxacin
	A	B	C	D		
Salmonella typhi	0.19	0.19	1.50	1.50	0.15	1.50
Escherchia coli	0.10	0.10	0.25	0.50	0.10	0.50
Vibrio cholerae	0.10	0.10	1.50	1.50	0.15	1.50
Staphylococcus aureus	0.25	0.25	1.50	1.50	0.19	0.25
Staphylococcus epidermidis	0.15	0.25	0.50	0.50	0.15	0.50
Klebsiella pneumoniae	0.15	0.19	0.50	0.75	0.15	0.50
Pseudomonas aeruginosa	0.25	0.25	2.50	2.50	0.25	2.50
Shigella flexnari	0.50	0.50	2.50	2.50	0.25	2.50
Citrobactor ferundi	0.15	0.19	0.25	0.50	0.10	0.25

bases of ciprofloxacin are equipment to that of ciprofloxacin against *Escherchia coli, Pseudomonas aeruginosa.* Compound A is more potent than Compound B against *Staphylococcus epidermidis, Klebsiella pneumoniae, and Citrobactor ferundi.*

Mannich base of lomefloxacin (Compound C) is more potent than lomefloxacin against *E. coli.* Mannich bases of lomefloxacin are equipotent to that of lomefloxacin against *Salmonella typhi, Vibrio cholerae, Staphylococcus epidermidis,* and *Pseudomonas aeruginosa.* Compound C is more potent than Compound D against *E. coli, Klebsiella pneumoniae,* and *Citrobactor ferundi.*

CONCLUSION

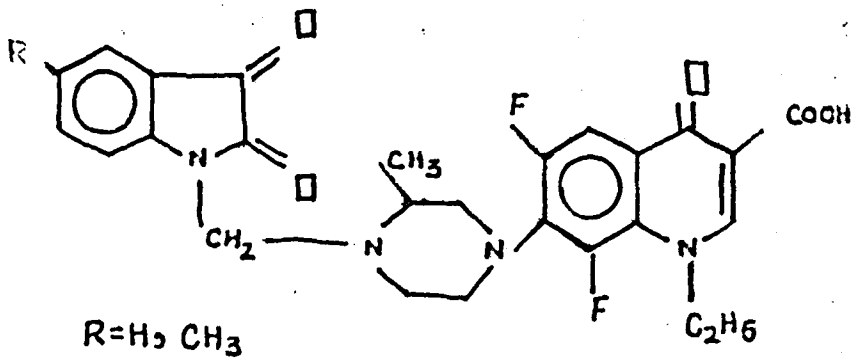
In conclusion, Mannich bases were prepared by condensing equimolar quantities of antibacterial agents (ciprofloxacin and lomefloxacin) with isatin and formaldehyde. The antibacterial activity of these Mannich



R=H,CH3

Compound A:R=H

Compound B:R = CH3



R=H, CH3

Compound C:R=H

Compound D:R=CH3

bases show equipotent or more potent activity than the parent molecule (ciprofloxacin and lomefloxacin).

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