DOI 10.5012/bkcs.2011.32.2.483

Synthesis, Characterization and Biological Evaluations of Ciprofloxacin Carboxamide Analogues

Najma Sultana,[†] Muhammad Saeed Arayne, Syeda Bushra Shakeb Rizvi,[‡,*] and Urooj Haroon[§]

Department of Chemistry, University of Karachi, Karachi-75270, Pakistan
[†]Department of Pharmaceutical Chemistry, Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan
[‡]Department of Pharmaceutical Chemistry, Faculty of Pharmacy Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan. [*]E-mail: sbushrarizvi@gmail.com
[§]Department of Chemistry, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan
Received June 23, 2010, Accepted November 30, 2010

Present work comprises of synthesis various analogues of ciprofloxacin by introducing new functionality at carboxylic group position *via* ester aminolysis reaction. For this purpose the carboxylic group at C-3 was esterified and later subjected to nucleophilic attack at the carbonyl carbon by various aromatic amines. Structure of the analogues was confirmed by different techniques i.e. IR, ^{1}H NMR and mass spectrometry. The antibacterial activity of the derivatives was also assessed with the parent against a series of Gram-positive and Gram-negative bacteria. The synthesized compounds showed diverse antimicrobial profile among which most compounds possessed a comparable or better activity in comparison to the ciprofloxacin. Additionally unlike ciprofloxacin, some of the derivatives were also found to show antifungal activity.

Key Words: Ciprofloxacin, Ester aminolysis reaction, Antibacterial activity, Antifungal activity

Introduction

Fluoroquinolones have a very useful role in the treatment of many bacterial infections[1,2] Ciprofloxacin (Figure 1), 1-cyclopropyl-6-fluoro-l,4-dihydro-4-oxo-7-(l-piperazinyl)-3-quinolinecarboxylic acid ($C_{17}H_{18}FN_3O_3$) is a broad spectrum antibiotic belongs to second generation of flouroquinolone. It inhibits DNA relplication, repair of bacterial DNA and RNA transcription of Gram negative and Gram positive cocci acting upon DNA topoisomerase enzyme [3] which eventually leads to blockage of bacterial cell growth.[4,5]

Advances in quinolone field are likely to provide better compounds capable of dealing with the resistant strains. These research efforts have been rewarded by very significant improvements in antibacterial potency as well as *in vivo* efficacy. Most of the quinolone antibacterial research has been focused on the functionality at C-7 position.[6] The structure activity relationship (SAR) reveals that the C-7 substituent is the most adaptable site for chemical change and is an area that determines potency and target preference.[7] During recent years a number of quinolones with substitution on piperazine ring at C-7 position of the basic structure of quinolones were synthesized.[8,9] The hypothesis of this study was that new fluoroquinolone agents with a carbon-linked nitrogen-containing side chain at the C-7 of the quinolone-carboxylic acid nucleus may offer new insight into the structural-activity relation of the quinolone antibacterials.[10,11]

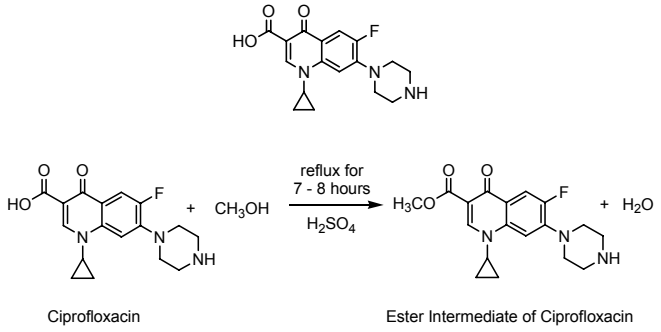


Figure 1. Ciprofloxacin.

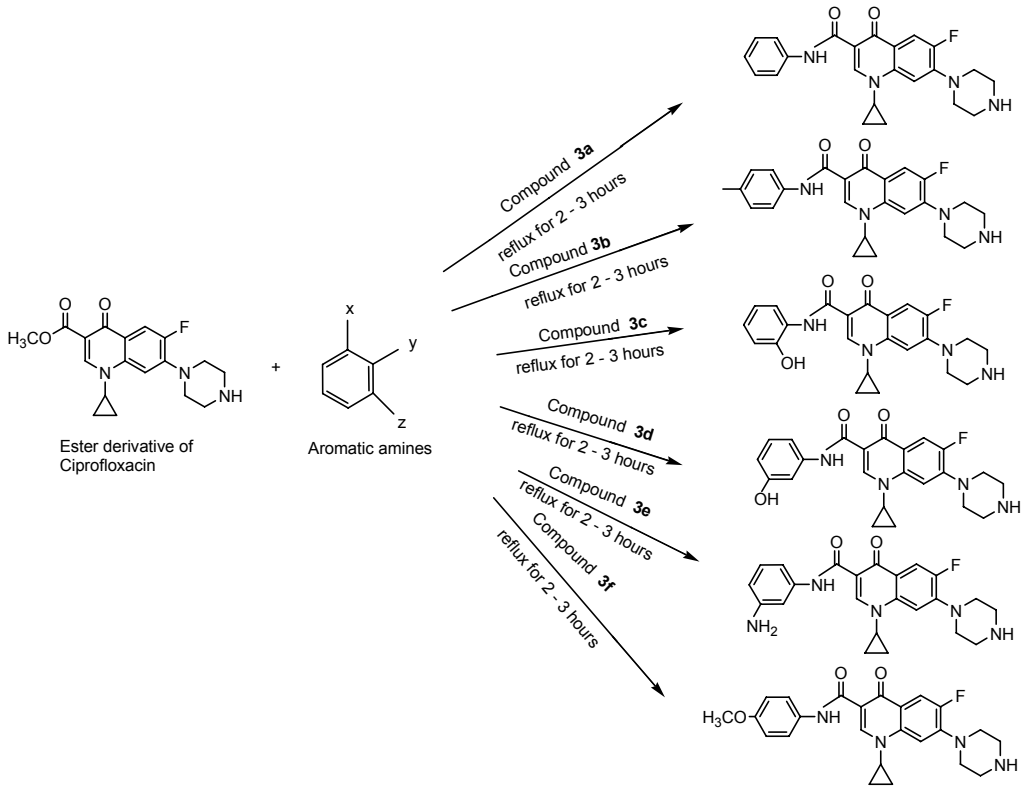
Because of the lack of data in the literature concerning analogues of quinolones at carboxylic position, to investigate the potential of 3-carboxylic quinolone derivatives as anti Gram positive and Gram negative agents, we have recently reported some novel levofloxacin,[12] enoxacin[13] carboxamide analogues. In extension of our previous work we are reporting here second generation broad spectrum azafluoroquinolone antibacterial agents, by introducing new functionality at carboxylic group position. These efforts on fluoroquinolone research have intensified their activity against Gram-positive organisms as well as on Gram-negative organisms.

The present study enlightens the synthesis, spectroscopic analysis (including IR and ^{1}HNMR), mass spectrometry and evaluation of biological activities of ciprofloxacin carboxylic derivatives carrying amino-containing aromatic ring.

Experimental

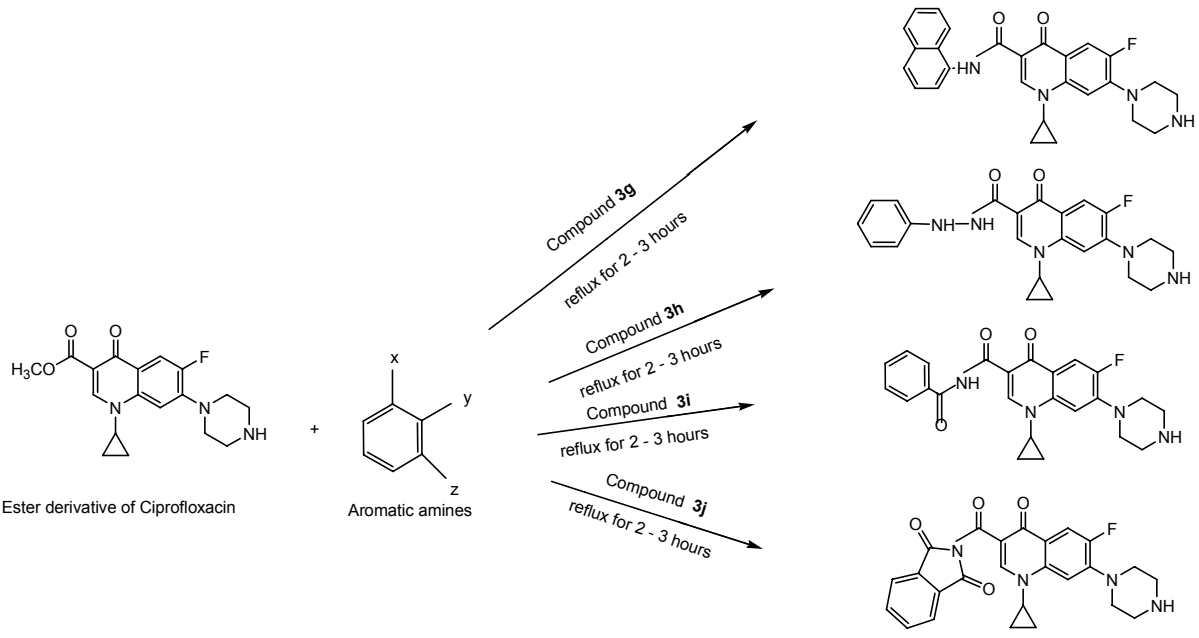
Material and Equipments. Ciprofloxacin was gift from Ali Gohar Pharmaceutical Ltd., Karachi, Pakistan. All the reagents used were of analytical grade. All the glassware was washed with chromic acid followed by a thorough washing with freshly prepared de-ionized water.

Melting points were obtained manually by capillary method. The IR spectra were obtained on shimadzu prestige-21 200 VCE



3a; x = NH_2, y = H, z = H **(Aniline)**
3b; x = NH_2, y = H, z = CH_3 **(Toluidine)**
3c; x = NH_2, y = OH, z = H **(o'amino phenol)**
3d; x = NH_2, y =H, z = OH **(3' aminophenol)**
3e; x = NH_2, y = H, z = NH_2 **(Phenylenediamine)**
3f; x = NH_2, y = H, z = OCH_3 **(Anisidine)**

Figure 2. Synthetic pathway of series **3a-3f** analogues.



3g; x = H, y and z = (phy)NH_2 **(Alpha naphthylamine)**
3h; x = NH-NH_2, y = H, z = H **(Phenylhydazine)**
3i; x =H, y = H, z = $CONH_2$ **(Benzamide)**
3j; x = H, y and z = $(CO)_2NH$ **(Phthalimide)**

Figure 3. Synthetic pathway of series **3g-3j** analogue.

coupled to a P IV- PC and loaded with IR solution version 1.2 software (potassium bromide disks). The absorption peaks were recorded in frequency (cm^{-1}). NMR spectra were recorded on Bruker FT - NMR 500 MHz with the compounds dissolved in deuterated methanol. Chemical shifts are reported in parts per million (δ) relative to tetra methyl silane as an internal standard. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet); and number of proton(s). The mass spectra were recorded on Finnign-MAT212 under electron impact (EI) ionization condition. Thin layer chromatography (TLC) was performed on HSF-254 TLC plate and compounds visualized under UV lamp.

General Procedure for Preparation of Derivatives (3a-3j). Synthesis of various derivatives of ciprofloxacin was attempted with various aromatic amines i.e., aniline, toludine, *o*-aminophenol, 3'aminophenol, phenylenediamine, anisidine, α-naphthylamine, phenylhydraize, benzamide and phthalimide. Ciprofloxacin (0.01 moles) was added to the round bottomed flask containing 60 mL of methanol. 1 mL of sulphuric acid was added to the flask and the reaction was refluxed for about 7 - 8 hours. After the consumption of ciprofloxacin (examined by TLC) 0.01 molar solutions of aromatic amines (prepared in methanol) were added individually with continuous stirring and the reaction was again refluxed for about 2 - 3 hours till completion, indicated by TLC. While for compound **3i** and **3j** NaOH was added in the methanolic mixture of benzamide and phthalimide and heat it afterwards they were added in the reaction flask containing ciprofloxacin ester intermediate. Reaction was again refluxed for about 2 - 3 hours till completion. Thin layer chromatography was used to monitor reaction. The volume of the reaction mixture was then reduced by rotary-evaporation. The precipitates were filtrated off, washed with methanol-chloroform (2:8) to give compound.

Spectral Data.

1-Cyclopropyl-*N*-phenyl-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3a): ($C_{23}H_{23}FN_4O_2$) yield; 68%, mp 271 °C, IR (KBr) ν_{max} ; 1660, 1622 (C=O) and 3167 (N-H) cm^{-1} , ^1H-NMR (300 MHz- $CDCl_3$) δ 8.08 (s, 1H, 2'aryl H), 7.19 (d, 1H, 5'aryl H, J = 12.98), 3.47;2.78 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;028 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide), 7.43 (m, 5H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 406.18 (77) M^+.

1-Cyclopropyl-*N*-*p*-tolyl-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3b): ($C_{24}H_{25}FN_4O_2$) yield; 56%, mp 279 °C, IR (KBr) ν_{max} ; 1656, 1623 (C=O) and 3367 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.09 (s, 1H, 2'aryl H), 7.19 (d, 1H, 5'aryl H, J = 13.5), 5.93 (s, 1H, 8'aryl H), 2.35 (m, 3H, methyl H), 3.47;2.78 (m, 8H, piperznyl H), 0.54;028 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide) 7.39 (m, 4H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 420.20 (37) M^+.

1-Cyclopropyl-*N*-(2-hydroxyphenyl)-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3c): ($C_{23}H_{23}FN_4O_3$) yield; 72%, mp 275 °C, IR (KBr) ν_{max}; 1643, 1625 (C=O) and 3176 (N-H) cm^{-1} , ^1H-NMR (300 MHz- $CDCl_3$) δ 8.11 (s, 1H, 2'aryl H), 7.21 (d, 1H, 5'aryl H, J = 13.1), 5.93 (s, 1H, 8'arylH), 3.47;2.78 (m, 8H, piperznyl H), 0.53;029 (m, 4H, cyclopropane),1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide), 7.40 (m, 4H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 422.18 (40) M^+.

1-Cyclopropyl-*N*-(3-hydroxyphenyl)-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3d): ($C_{23}H_{23}FN_4O_3$) yield; 72%, mp 276 °C, IR (KBr) ν_{max}; 1655, 1625 (C=O) and 3300 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.09 (s, 1H, 2'aryl H), 7.20 (d, 1H, 5'aryl H, J = 13.4) 3.47;2.78 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;028 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide), 7.36 (m, 45H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 422.18 (62) M^+.

1-Cyclopropyl-*N*-(3-aminophenyl)-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3e): ($C_{23}H_{24}FN_5O_2$) yield; 62%, mp 285 °C, IR (KBr) ν_{max}; 1653, 1624 (C=O) and 3263 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.07 (s, 1H, 2'aryl H), 7.17 (d, 1H, 5'aryl H, J = 13.9) 3.47;2.78 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;028 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide) 7.42 (m, 4H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 421.19 (17) M^+.

1-Cyclopropyl-*N*-(4-methoxyphenyl)-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3f): ($C_{24}H_{25}FN_4O_3$) yield; 44%, mp 279 °C, IR (KBr) ν_{max}; 1642, 1619 (C=O) and 3166 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.06 (s, 1H, 2'aryl H), 7.22 (d, 1H, 5'aryl H, J = 13.5) 3.47;2.75 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 3.73 (s, 3H, methoxy H), 0.53;029 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide) 7.49 (m, 4H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 436.19 (41) M^+.

1-Cyclopropyl-*N*-(naphthalen-1-yl)-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3g): ($C_{27}H_{25}FN_4O_2$) yield; 39%, mp 277 °C, IR (KBr) ν_{max}; 1649, 1625 (C=O) and 3276 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.11 (s, 1H, 2'aryl H), 7.16 (d, 1H, 5'aryl H, J = 13.6) 3.47;2.78 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;029 (m, 4H, cyclopropane),1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide) 7.28 (m, 7H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 456.20 (28) M^+.

1-Cyclopropyl-*N*-*N*'-phenyl-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3h): ($C_{23}H_{24}FN_5O_2$) yield; 51%, mp 281 °C, IR (KBr) ν_{max}; 1635, 1619 (C=O) and 3165 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.08 (s, 1H, 2'aryl H), 7.19 (d, 1H,5'aryl H, J = 12.9) 3.47;2.75 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;028 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide) 7.35 (m, 5H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 421.19 (52) M^+.

1-Cyclopropyl-*N*-oxo-phenyl-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3i): ($C_{24}H_{23}FN_4O_3$) yield; 60%, mp 269 °C, IR (KBr) ν_{max}; 1643, 1625 (C=O) and 3133 (N-H) cm^{-1}, ^1H-NMR (300 MHz- $CDCl_3$) δ 8.09 (s, 1H, 2'aryl H), 7.05 (d, 1H, 5'aryl H, J = 13.8) 3.47;2.79 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;028 (m, 4H, cyclopropane), 1.36 (m, 1H of cyclopropane), 7.9-8.1 (s, NH of amide) 7.21 (m, 5H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 434.18 (38) M^+.

1-Cyclopropyl-*N*-dioxo-phenyl-6-fluoro-4-oxo-7-(piperazinyl)-1,4-dihydro-3-quinoline Carboxamide (3j): ($C_{25}H_{22}FN_4O_4$) yield; 69%, mp 287 °C, IR (KBr) ν_{max}; 1650, 1624 (C=O), ^{1}H-NMR (300 MHz- $CDCl_3$) δ 8.11 (s, 1H, 2'aryl H), 7.22 (d, 1H, 5'aryl H, J = 13.4) 3.47;2.77 (m, 8H, piperznyl H), 5.93 (s, 1H, 8'aryl H), 0.53;028 (m, 4H, cyclopropane), 1.35 (m, 1H of cyclopropane), 7.69;8.13 (m, 4H, phenylic H), EIMS: *m*/*z* (rel. abundance %) 461.16 (19) M^+.

Antimicrobial Assay. The antimicrobial susceptibility of all the derivatives was tested by the disc diffusion technique developed by Bauer *et al*..[14] For this purpose 50 μgmL^{-1} stock solution of ciprofloxacin and its derivatives were prepared. The stock solution was diluted to 3 different concentrations i.e. 5, 10 and 20 μgmL^{-1}. Commercially available filter paper discs were soaked in the prepared drug and derivatives solution, dried and applied on the surface of solid culture media (Nutrient Agar), which had been streaked with standardized bacterial inoculums and incubated at 37 °C for 24 h. This method is based on the determination of an inhibited zone proportional to the bacterial susceptibility to the antimicrobial present in the disk.

The results were compared with the parent against 11 different strains of Gram positive and Gram negative organism (*Staphylococcus aureus*, *Bacillus subtilis*, Streptococcus *pneumoniae*, *Corynebacterium hoffmannii*, *Klebsiella Pneumoniae*, *Proteus mirabilis*, *Shigella flexneri*, *Escherichia coli*, *Pseudomonas areuginosa*, *Citrobacter species*, and *Salmonella typhi*).

Antifungal Assay. For the antifungal assay, 100 μgmL^{-1} stock solution of ciprofloxacin and its derivatives were prepared in hot methanol. The stock solutions were diluted to 3 different concentrations i.e. 30, 40 and 50 μgmL^{-1}. Commercially available filter paper discs were impregnated with the prepared solutions of the drugs and its analogues, dried and applied on the surface of the agar plate over which a culture of micro organism was already streaked. After 24 hours of incubation the clear zone of inhibition around the disc was determined, this is proportional to the fungal susceptibility for the antimicrobial agent present in the disk.

Ciprofloxacin and its derivatives were tested for antifungal activity against the fungi; *Aspergillus purasiticus*, *Saccharomyces cervics*, *Candida albicans* and *Fusraium solani*.

Result and Discussion

Spectral Analysis. On comparison of the IR spectra of the derivatives with ciprofloxacin revealed that the band at 3520 cm^{-1} in the ciprofloxacin spectrum, ascribed to the absorption of the carboxylic OH group was not detected in the spectrum of derivatives, indicating the consumption of carboxylic group in amide formation. However, the IR spectra of all the derivatives exhibit a new band in the region 3100 - 3350 cm^{-1} which was allocated to the NH vibration of amide group. The carboxylic C=O absorption was shifted to the right at 1661 - 1635 upon amide formation. While absorption of the ring C=O at 1625 cm^{-1} in the spectrum of ciprofloxacin was more or less same in the spectra of the derivatives.

The ^{1}H NMR spectra of derivatives were similar to the ciprofloxacin spectrum except the resonance of acidic proton at 11.02 ppm which was absent in all derivatives spectra, showing the utilization of this moiety in amide formation. Along with the disappearance of carboxylic proton, all derivatives also showed a singlet in the region 7.9 - 8.1 ppm which corresponds to the absorption of sec-amide. Reaction at carboxylic site of the ciprofloxacin showed a significant difference of the chemical shifts up to 0.5 - 1 ppm of aryl protons in the spectra of all the compounds. The signals for the aliphatic and piperazinyl protons practically remained same as they were distant from the group modification site of the drug. Further signals corresponding to their respective chemical structure are mentioned in the spectral data.

The electron impact mass spectra (EIMS) of ciprofloxacin showed M^+ peak at *m*/*z* 331.54 which is also the base peak. However all the compounds showed a very low percentage of M^+ peaks owing to their unstable nature.

Antibacterial Activity. The *in vitro* antibacterial activity of 3-substituted carboxylic acids against drug-sensitive bacteria Gram positive (*Staphylococcus aureus*, *Bacillus substilis*, *Streptococcus pneumoniae*, *Corynebacterium hoffmannii*) and Gram negative organisms (*Klebsiella Pneumoniae*, *Proteus mirabilis*, *Shigella flexneri*, *Escherichia coli*, *Pseudomonas areuginosa*, *Citrobacter species*, and *Salmonella typhi* are summarized in Tables (1 & 2) along with patent drug.

All analogues, we aimed to synthesize showed comparable activity towards ciprofloxacin against all the tested strains. Results indicate that compound **3a** was active against *Bacillus subtilus* and *Shigella flexneri* while the presence of electron donating group in the phenyl ring **3b** also showed significant activity against *Salmonella typhi*, *Escherichia coli*, and *Staphylococcus aureus.* Introduction of OH group to aryl amine **3c** showed respectable activity against *Bacillus subtilus* and *Shigella flexneri*. Compound **3e**, bearing amino group on the phenyl substituent exhibited better activity against *Corynebacterium hoffmannii*, *Pseudomonas areuginosa* and Streptococcus *pneumoniae.* However, methoxy group modification to this primary amine **3f** was of assistance to their antibacterial activities. Compound **3g** have shown significant enhancements of potency against *Corynebacterium hoffmannii* and Streptococcus *pneumonia*. It is also meaningful to point out that formation of hydrazide at 3 postion **3h** exhibited the highest activity against most of the Gram-positive strains tested, more potent than reference agent. Compound **3i** and **3j** showed drastically decrease in their activity against all the bacterial tested.

In the terms of structure-activity relationship, results suggest that the antibacterial activity profile against all bacterium was altered by addition of amino group in ciprofloxacin molecule. However, the alteration of substitution in amino ring also made marked differences in activity. It seems that expansion of activity is due to better interaction of molecule with target enzymes or for penetration into these bacteria.

Antifungal Activity. Ciprofloxacin is antimicrobial drug and inactive against fungi, only moxifloxacin and gatifloxacin showed activity against *Candida specices* [15] but in order to evaluate the result of addition of different functional groups to its basic structure, the antifungal activity of its derivatives was carried out against various fungi; *Aspergillus purasiticus*, *Saccharomyces cervics*, *Candida albicans* and *Fusraium solani*. It was found from the result that compounds **3c**, **3g** and **3h** has got

Table 1. Zone of inhibition (mm) of ciprofloxacin and their derivatives against various microorganisms

↓ Organisms	Ciprofloxacin			**3a**			**3b**			**3c**			**3d**			**3e**		
(μgmL^{-1}) →	5	10	20	5	10	20	5	10	20	5	10	20	5	10	20	5	10	20
S. aureus	11	14	18	8	13	16	12	19	29	10	14	17	10	14	18	8	12	17
Citrobacter	13	19	21	14	17	18	15	19	20	15	17	19	16	16	21	12	19	21
S. pneumoniae	13	16	21	11	12	14	14	17	21	11	15	18	14	17	20	14	25	28
S. flexneri	9	12	17	14	21	25	11	13	16	13	17	29	12	13	16	11	15	16
E. coli	13	16	22	15	16	17	15	20	27	14	16	20	11	16	22	12	15	19
S. typhi	13	15	20	12	14	16	14	24	30	9	13	18	14	16	19	12	14	16
P. aeruginosa	13	14	17	11	12	12	11	12	12	12	15	18	12	15	16	10	14	15
B. substilis	10	12	14	16	22	28	10	11	14	14	25	32	11	13	14	16	20	29
K. pneumoniae	12	16	24	12	15	18	10	14	18	11	14	18	13	16	22	11	16	22
P. mirabilis	11	14	21	16	19	25	10	11	15	12	13	15	12	13	22	11	13	14
C. hofmanii	10	11	12	8	10	12	10	11	13	10	11	13	9	9	12	14	18	22

Table 2. Zone of inhibition (mm) of ciprofloxacin and their derivatives against various microorganisms

↓ Organisms	Ciprofloxacin			**3f**			**3g**			**3h**			**3i**			**3j**		
(μgmL^{-1}) →	5	10	20	5	10	20	5	10	20	5	10	20	5	10	20	5	10	20
S. aureus	11	14	18	9	13	15	10	11	18	10	15	17	10	14	15	13	13	17
Citrobacter	13	19	21	14	17	19	15	16	20	15	18	20	12	13	17	14	19	20
S. pneumoniae	13	16	21	11	15	17	16	18	29	14	18	28	14	17	18	12	15	20
S. flexneri	9	12	17	18	21	30	11	13	16	9	11	17	11	15	16	10	12	14
E. coli	13	16	22	15	18	21	10	13	20	14	16	20	13	16	21	13	15	19
S. typhi	13	15	20	12	15	16	14	17	18	12	13	17	10	13	15	12	14	16
P. aeruginosa	13	14	17	11	15	16	15	19	26	14	19	29	11	13	14	11	14	15
B. substilis	10	12	14	13	17	27	11	13	14	11	13	16	11	10	12	10	14	15
K. pneumoniae	12	16	24	12	17	18	12	17	22	11	17	18	9	12	12	11	17	19
P. mirabilis	11	14	21	12	14	20	13	15	20	12	12	15	11	13	14	12	13	14
C. hofmanii	10	11	12	8	10	12	13	16	27	16	19	32	9	9	11	10	10	12

Table 3. Zone of inhibition (mm) of ciprofloxacin and compounds against fungi

Compounds	*Candida albicans*			*Fusraium solani*		
	30 μgmL^{-1}	40 μgmL^{-1}	50 μgmL^{-1}	30 μgmL^{-1}	40 μgmL^{-1}	50 μgmL^{-1}
Ciprofloxacin	-	-	-	-	-	-
3a	9	12	14	-	-	-
3c	14	15	15	12	14	15
3g	15	16	17	10	12	12
3h	12	14	15	12	12	14

enhanced activity against *Candida albicans* and *Fusraium solani.* The compound **3a** also showed moderate activity against *Candida albicans.* These consequences suggest that antifungal activity of analogues is probably governed by the functional group variation. It is evident that the phenyl attachment *via* amide linkage of ciprofloxacin has incorporated antifungal property in the drug.

Conclusion

Conclusively, we have described a convenient synthesis of some derivatives of ciprofloxacin through ester aminolysis. Development of bacterial resistance has led to the synthesis of newer and more potent quinolones. As detailed above, ten carboxamide analogues have been synthesized, characterized and evaluated for their biological activities *in vitro* in order to discover potent agents against Gram-positive bacteria and Gram negative bacteria.

It was observed that when an aromatic amino group was introduced to carboxylic side, significant enhancements of potency against organisms were achieved from the ciprofloxacin nucleus. Moreover some of the derivatives were also found to be antifungal which is unlike to parent drug.

Acknowledgments. The authors acknowledge Higher Education Commission of Pakistan for providing financial support to Ms. Bushra Rizvi under Indigenous Ph.D. 5000 Scholarship Program Batch III.

References

1. Hooper, D. C. *Biochim. Biophys. Acta* **1998**, *1400*, 45-61.
2. Mascellino, M. T.; Farinelli, S.; Iegri, F.; Iona, E.; De Simone, C. *Drugs Expert. Clin. Res.* **1998**, *24*, 139-151.
3. Kampranis, S. C.; Maxwell, A. *J. Biol. Chem*. **1998**, *273*(35), 22615-22626.
4. Hooper, D. C. *Drug Resist Updates* **1999**, *2*, 38-55.
5. Drlica, K.; Zhao X. *Microbiol Mol. Biol. Rev*. **1997**, *61*, 377-392.
6. Jazayeri, S.; Moshafi, M. H.; Firoozpour, L.; Emami, S.; Rajabalian, S.; Haddad, M.; Pahlavanzadeh, F.; Esnaashari, M.; Shafiee,

A.; Foroumadi, A. *European Journal of Medicinal Chemistry* **2009**, *44*, 1205-1209.
7. Foroumadi, A.; Emami, S.; Mehni, M.; Moshafi, M. H.; Shafiee, A. *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 4536-4539.
8. Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem*. **2001**, *44*, 2374-2377.
9. Fang, K. C.; Chen, Y. L.; Sheu, J. Y.; Wang, T. C.; Tzeng, C. C. *J. Med. Chem*. **2000**, *43*, 3809-3812.
10. Foroumadi, A.; Mansouri, S.; Kiani, Z.; Rahmani, A. *Eur. J. Med. Chem*. **2003**, *38*, 851-854.
11. Ma, X.; Zhou, W.; Brun, R. *Bioorganic & Medicinal Chemistry Letters* **2009**, *19*(3), 986-989.
12. Sultana, N.; Arayne, M. S.; Rizvi, S. B. S.; Mesaik, M. A. *Bull. Korean Chem. Soc.* **2009**, *30*(10), 2294-2298.
13. Arayne, M. S.; Sultana, N.; Haroon, U.; Mesaik, M. A.; Asif, M. *Arch. Pharm. Res.* **2009**, *32*(7), 967-974.
14. Bauer, A. W.; Kirby, W. M. M.; Sherris, J. C.; Turck, M. *Am. J. Clin. Pathol*. **1966**, *45*, 493-496.
15. Ozdek, S. C.; Miller, D.; Flynn, P. M.; Flynn, H. W., Jr. *Ocular Infections* **2006**, *14*(6), 347-351.