ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis, Characterization & in Vitro Biological Studies of Novel N-Aryl Piperazinyl Fluoroquinolones

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ABSTRACT

A series of 5-amino-l-cyclopropyl-6,8-difluoro-7(4-piperazinyl derivatives) 4 1(H)-oxoquinoline-3-carboxylic acids (**6a-6i**) were prepared; the C-5 substituent in these compounds comprised of amino groups and the C-7 functional group included variously substituted piperazines. In vitro antibacterial screening results indicated that the amino group was optimal among the C-5 substituents. A combination of the C-5 amino group and the C-7 benzyl piperazine appendage in this series conferred the best overall antibacterial property. These compounds were screened for qualitative (zone of inhibition) and quantitative antibacterial activity (MIC). These are new and novel compounds, (5-Amino-1-cyclopropyl-6, 7, 8-trifluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid) as the starting material. Among the synthesized compounds in this series compound **6g** [named,5-amino-l-cyclopropyl-6,8-difluoro-7-(4-benzyl-piperazinyl)-4(1H)-oxoquinoline-3 carboxylic acid] was found to exhibit significant antibacterial activity.

Keywords: Piperazinyl; Difluoroquinolones; Antibacterial activity; MIC

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ISSN: 0975-8585

INTRODUCTION

During recent years, much attention is increasingly been given to the synthesis of quinolone antibacterial as a source of new agents.[1(a-c)] Successful chemical modifications[1(e-g)] in this area to date are realized especially at positions (fig. 1a) C-1 (ethyl, fluoroethyl, cyclopropyl, fluorophenyl, and methylamino), C-6 (fluoro), C-7 (4-pyidyl,piperazinyl , aminopyrrolidinyl), C-8 (fluoro and chloro), and N-1-C-8 (-$CH(CH_3)CH_2CH_2$- and -$CH(CH_3)CH_2O$-) of the quinolones. The properties of the quinolone class of antibacterials have been known for over 40 years [1d].

Since, the discovery of nalidixic acid by Lesher in 1962 [2], a number of analogues have been synthesized, and some of them, in particular the fluoroquinolone derivatives such as norfloxacin,[3] pefloxacin,4 enoxacin,5 ofloxacin,6 and ciprofloxacin,7 exhibited broader antibacterial spectrum and enhanced potencies. These agents were shown to be specific inhibitors of the bacterial DNA gyrase,8-10 an enzyme which is responsible for negatively supercoiling covalently closed circular DNA, and also in catenation and decatenation reactions.11Fluoroquinolone drugs are important antibiotics. Since their discovery in the early 1960s, the basic structure of the quinolones was modified to increase their antibacterial spectrum and potency, as well as to improve their bioavailability making the quinolones useful agents for the treatment of urinary, systemic, and respiratory tract infections. After the discovery of prototypic norfloxacin, most of the research concerning quinolone antibacterial has been focused on the basic group at the C-7 position. As a results, ciprofloxacin, ofloxacin, lomefloxacin, fleroxacin, and sparfloxacin have been successfully introduced into the market, all of which contain a piperazine derivatives at the C-7 position.12 In 1986, Warner-Lambert reported that this piperazine group has been successfully replaced with 3-(aminomethyl) pyrrolidine.13 The introduction of this pyrrolidine derivative to the quinolone nucleus resulted in a dramatic improvement of in vitro Gram-positive activity compared to piperazinyl analogues. This change, however, also gave rise to undesirable side effects such as cytotoxicity.14 In order to circumvent these problems; additional attempts have been made to modify the pyrrolidinyl moiety. Nevertheless, so far no quinolone antimicrobial agent possessing a pyrrolidine derivative has been approved on a worldwide basis.15 Most of the quinolones currently on the market or under development have only moderate activity against many Gram-positive cocci including staphylococci and streptococci. This insufficient activity has not only limited their use in infections caused by these organisms, such as respiratory tract infections, but has also been believed to be one of the reasons for the rapidly developing quinolone resistance. Therefore, recent efforts have been directed toward the synthesis of new quinolones that can provide improved Gram-positive antibacterial activity, while retaining the good Gram-negative activity of ciprofloxacin.16 In this paper, we wish to describe the design, synthesis and antibacterial activity of a series of new fluoroquinolone compounds. These arylpiperzines difluoroquinolones are structurally unprecedented, having an different functional group on the 2,3,and 4-position of phenyl ring attached to piperazine and an amino group on the 5 position of the difluoroquinolones. We report herein the synthesis of these new difluoroquinolones derivatives.17Among the quinolone antimicrobial agents, relatively few fused tricyclic analogues have been found to possess outstanding antibacterial activity.18 We planned to modify C-7 position group into differently substituted piperazinyl groups while amino group at C-5 were kept. An alternative synthetic route for this purpose

was developed starting from the compound 1(Scheme 1). The synthesis of novel difluoroquinolones derivatives is outlined in Scheme 1. From the literature we found that nucleophilic displacement of 5,6,7,8-tetrafluoroquinolones19 proceeds regioselectively at the C-5 or C-7 position, depending on adopted conditions. This finding accordingly permitted us to introduce an optional nucleophile preferentially into either the C-5 or the C-7 position, or stepwise into both positions with a desired combination of nucleophiles. Treatment of precursor 4 with piperazine derivatives in pyridine gave compounds 6a-6i (Table 1). Treatment of compound 1 with benzyl amine gave the intermediate 2. The benzyl group of intermediate 2 was removed by hydrogenation treatment to give the corresponding intermediate 3. Debenzylation of intermediate 2 was carried out on hydrogenation treatment with Pd/C in acetic acid plus ethanol (see procedure), giving intermediate 3. Acid treatment intermediate 3 underwent the hydrolysis of the ester, with concomitant debenzylation giving precursor 4. The C-7 fluorine atoms of precursor 4 were then displaced with various piperazines derivatives to give the corresponding compounds 6a-6i (Scheme 2.).The yield of products obtained is good .The products (6a-6i) easily recrystallized from ammonia.

PHARMACOLOGY

In vitro antibacterial activity

A series of piperazine derivatives (6a-6i) with the C-5 with amino group as a substituent were tested against a variety of organisms. Table 2 and 3 shows the data expressed as zone of inhibition (in cm) and as minimum inhibitory concentrations (MICs in µg/mL) against representatives of Gram-negative bacteria E. coli (ATCC 9637),Klebsiella pneumoneae (ATCC 10031), Pseudomonas aeruginosa (ATCC 27853) and Gram-positive bacteria Staphylococcus aureus (ATCC 29213), Salmonella cholearesuis (ATCC 14028), Bacillus subtilis. In vitro antibacterial activity of the C-5 amino substituted quinolones with variants of the piperazine derivatives at C-7 is given in Table 2 and 3.

RESULT AND DISCUSSION

In order to know an effect of varying the C-7 substitution on activity, a series of 5-aminoquinolones 6a-6i were tested where one / two different or same types of functional groups were inserted into different positions of the phenyl ring attached to piperazinyl moiety. The zone of inhibition and MIC's values of quinolones derivatives were determined by Well Diffusion Bio assay20 and Broth dilution method 21 using pathogenic strains (Table 2 and 3) of B1: E. coli (ATCC 9637), B2: Klebsiella pneumoneae (ATCC 10031), B3: Pseudomonas aeruginosa (ATCC 27853), B4: Staphylococcus aureus (ATCC 29213), B5: Salmonella cholearesuis (ATCC 14028) and B6: Bacillus subtilis (clinical isolate).The experimental result of antibacterial activity indicated variable degree of efficacy of the compounds against different strains of bacteria (Table 2 & 3). We have synthesized these quinolone derivatives (6a-6i) for antimicrobial activity. Compound 6g shows potent antibacterial activity against strains B1: E. coli (ATCC 9637) , B3: Pseudomonas aeruginosa (ATCC 27853), B5: Salmonella cholearesuis (ATCC 14028) and B6: Bacillus subtilis (clinical isolate) with MIC values are at 15.7,15.7,15.7 and 31.3 µg/ml respectively and zone of inhibition are at 2.8,2.9,2.9 and 2.5 cm respectively, however, it did not show significant

much effect on strains B2: Klebsiella pneumoneae (ATCC 10031) and B3: Pseudomonas aeruginosa (ATCC 27853) strains with MIC values are at 125 and 125 µg/ml and zone of inhibiton are at 1.2 and 1.5 cm of bacteria used in experiment. Similarly compound 6a was effective against strain B2: Klebsiella pneumoneae (ATCC 10031) only, the MIC being 31.3 µg/ml with zone of inhibition of 2.1 cm (Table 3 and 2). Compound 6e shows potent antibacterial activity against strain B4: Staphylococcus aureus (ATCC 29213) with MIC value 15.65 µg/ml and zone of inhibition 3 cm (Table 3and 2), but moderate activity against other five bacterial strains. Compounds 6g showing better activity in comparison to other compounds used in study which might be due to the presence of benzyl group at 4-position of piperazine nucleus. When compared to other piperazine derivatives 6a-6f ,6h and 6i ,compound 6g displays a increase in activity against both Gram-positive and Gram-negative bacteria. Presence of an amino group at C-5 position (compounds 6a-6i), results in an increase in potency of these compounds :this finding is consistent with the conclusion described by Domagala.22 In vitro antibacterial activity of the C-7 substituted quinolones with variants of the piperazine derivative is given in Table 2 & 3. From the data for the series 6a (2-fluorophenyl-1-piperazinyl), 6b (4-fluorophenyl-1-piperazinyl), 6c (2-methylphenyl-1-piperazinyl), 6d(2-Cyanophenyl-1-piperazinyl), 6e (1-phenyl-1-piperazinyl), 6f (2,3 –dichloro-phenyl-1-piperazinyl), 6g (N-Benzyl-1-piperazinyl), 6h (Biphenyl-methyl-1-phenyl-1-piperazinyl), 6i (3-Methoxy-phenyl-1-piperazinyl), it follows that contribution of the C-7 substituent to antibacterial activity increases in the order in different bacterial strains(B) as follows,

B1:6h<6f=6e=6c<6b<6d=6i<6a<6g
B2:6h=6e=6i<6c=6f<6g<6b<6d<6a
B3:6a=6b=6c=6d=6e=6f=6h=6i<6g
B4:6f<6h<6c<6b<6d<6a<6i<6g<6e
B5:6h<6f<6c=6i<6b=6e<6d<6a<6g
B6:6h<6f<6b=6c=6e<6i<6d<6a<6g

The activity fluctuates in a narrow range, depending on the attached site, number, and stereochemistry of the functional group, with the exception of 6h, whose activity considerably decreases. Other compounds appeared as broad spectrum, as they show mild to moderate effect on most of the strains used in the experiment.

CONCLUSION

In conclusion, compounds (6a-6i) were firstly prepared. We have described simple, convenient and practical methods for the synthesis of (5-amino-1-cyclopropyl-6,8-diflouro-7-[(4-piperazin-1-yl)]-4-oxo-1,4-dihydro quinoline-3-carboxylic acid) derivatives (6a-6i) . The present procedure for synthesis of 5-amino-1-cyclo-6,8-difluorodihydroxy quinolones-3-carboxylic acid derivatives provides a very simple and efficient methodology. A C-5 amino group in the l-cyclopropyl- 6,8-difluoroquinolone derivatives serves to enhance in vitro activity, especially against gram-positive and gram negative bacteria. A combination of the C-5 amino group and the C-7 , 4-benzyl piperazinyl appendage conferred the best overall antibacterial properties. Therefore, compound 6g [named,5-amino-l-cyclopropyl-6,8-difluoro-7-(4-benzyl-piperazinyl)-4(1H)-oxoquinoline-3 carboxylic acid] showing better activity in comparison to other compounds used in study.

ISSN: 0975-8585

EXPERIMENTAL

All reagents used were of AR grade. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 NMR spectrometer in d-DMSO (with TMS for ^{1}H and DMSO-d for ^{13}C as internal references) unless otherwise stated. Mass spectrum was recorded on High resolution mass JEOL LMS-SX102 spectrometer at 70 Ev ionization potential. The reactions were monitored by thin layer chromatography (TLC) using aluminium sheets with silica gel 60 F254 (Merck). Yields are of purified products and are not optimized.

Procedure for the synthesis of 4 (5-Amino-1-cyclopropyl-6, 7, 8-trifluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid). (Scheme 1.) A mixture containing 10.g (3.04 mol) of compound 1, 3.5 g (3.27 mol) of benzylamine, and 9.2 g (9.11 mol) of triethylamine in 200 ml of toluene was heated to reflux for 1 hr.The reaction mixture was concentrated to dryness under reduced pressure to get intermediate 2. The residue was crystallized with Ethanol and the wet product as such proceeded for hydrogenation with 1.6 gm 5% Pd / C in 80 ml acetic acid and 80 ml of Ethanol at room temperature until the required volume of hydrogen had been taken up. The solids intermediate 3 were collected by filtration and taken up in the mixture of 200 ml acetic acid-water-concentrated H_2SO_4 (8:6:1) was heated to 100°C for 30 min, and poured in to ice-water. The resulting precipitates were collected by filtration, washed with water, and recrystallized from ethanol gave 5.0 gm of precursor 4.

General procedure for the synthesis of N-aryl piperazines 6a-6i(Scheme-2): A mixture of precursor 4 (5-Amino-1-cyclopropyl-6, 7, 8-trifluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid) 1.0 mmol and piperazine derivatives ,1.2 mmol in 10 ml pyridine was heated at 80°C for 40 min.The reaction mixture was concentrated under reduced pressure.The residue was diluted with water and extracted with $CHCl_3$.The organic layer was dried and concentrated to leave a crude product, which was recrystallized from aqueous ammonia to give compounds (6a-i) 80-89% yield.

(6a) (5-amino-1-cyclopropyl-6,8-diflouro-7-[(4-(2-fluoro-phenyl)-piperazin-1-yl)]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 87%.mp 253-258°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):
8.42(1H,s),7.43(s,2H),6.92(m,4H),3.114(t,J=4.8,8H),2.401 (m,1H),1.04(m,4H)
^{13}C NMR (75MHz, d-DMSO) (δ ppm):
190.00,171.00,165.00,163.00,156.50,149.498,146.00,139.20,138.00,134.10,124.44,122.25,119.36,116.00,106.00,50.60,47.50,8.04
EIMS m/z (% of relative abundance): 459.2(M+1)

(6b) (5-amino-1-cyclopropyl-6,8-diflouro-7-[(4-(4-fluoro-phenyl)-piperazin-1-yl)]- 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 88%.mp 257-262°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):

14.19(b,1H,s),8.27(s,1H),6.76(m,4H),3.24(m,4H),3.06 (m,4H),2.25(m,1H),0.89(m,4H)
^{13}C NMR (75MHz, d-DMSO) (δ ppm):
196.00,194.0,179.38,164.87,149.46,147.62,136.00,134.00,133.00,120.10,117.36,115.05,102.00,98.00,50.24,49.70,48.25,8.14.
EIMS m/z (% of relative abundance): 459.1(M+1)

(6c) (5-amino-1-cyclopropyl-6,8-diflouro-7-(4-(4-o-tolyl-piperazin-1-yl)- 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid 84%.mp 260-263°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):14.08(s,1H),8.51(s,1H),7.16(J=7.5,t,1H),7.06(m,2H), 6.98(J= 6.9, d,1H),3.48(m,4H),2.29(m,4H),2.48(m,1H),2.31(s,3H),1.10(m,4H).
^{13}C NMR (75MHz, d-DMSO) (δ ppm):
183.4,179.29,171.90,164.78,150.89,149.36,137.90,136.05,133.80,131.72,130.40,127.80,126.11,122.75,118.79,105.69,103.90,51.84,50.83,43.00,17.05,8.07.
EIMS m/z (% of relative abundance): 455.20(M+1)

(6d) (5-amino-7-(4-(2-cyano-phenyl)-piperazin-1-yl)-1-cyclopropyl-6,8-diflouro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 89%.mp 256-262°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):8.47(s,1H),7.59(J=7.5,d,1H),7.51(t,J=7.5,1H), 7.13(J= 8.1, d,1H),7.05(J=7.5 t,1H),3.43(m,4H),3.25(m,4H),2.40(m,1H),1.04(m,4H).
^{13}C NMR (75MHz, d-DMSO) (δ ppm): 179.50,168.5,166.5,164.84,
158.00,154.75,149.47,141.50,138.00,136.00,133.81,128.00,121.84,119.08,118.00,105.74,104.79,51.51,50.37,47.00,8.05.
EIMS m/z (% of relative abundance): 466.20(M+1)

(6e) (5-amino-1-cyclopropyl-6,8-diflouro-4-oxo-7-(4-phenyl-piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 85%.mp 240-243°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):
14.6(s,1H),8.50(s,1H),7.23(J=8.1,t,2H),6.97(d,J=8.1,2H), 6.80(J= 7.2,
t,1H),4.01(s,2H),3.47(m,4H),3.28(m,4H),2.69(m,1H),2.48(m,4H).
^{13}C NMR (75MHz, d-DMSO) (δ, ppm): 179.95,164.77,151.00,149.50,
128.61,128.00,118.90,117.20,115.50,105.73,50.24,48.96,44.30,8.10.
EIMS m/z (% of relative abundance): 441.20 (M+1)

(6f) (5-amino-1-cyclopropyl-7-[(4-(2,3-dicloro-phenyl)-piperazin-1-yl)]-6,8-diflouro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 80%.mp 262-266°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):
8.53(s,1H),7.30(m,3H), 4.04(s,2H),3.49(m,8H),1.90(m,1H),1.11(m,4H).

^{13}C NMR (75MHz, d-DMSO) (δ, ppm):
182.85,173.99,160.18,149.45,146.00,134.00,136.00,132.42,129.2,128.00,124.27,123.00,119.47,99.14,91.54,71.36,51.35,50.52,8.03,3.64.
EIMS m/z (% of relative abundance): 509.10 (M+1)

(6g) (5-amino-7-(4-benzyl-piperazin-1-yl)-1-cyclopropyl-6,8-diflouro- 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 77%.mp 222-227°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):14.43(s,1H),8.48(s,1H),7.33(m,4H),7.25(J=3.6 ,t,1H),7.03(s,2H), 3.99(m,1H),3.33(m,4H),2.53(m,4H),1.10(m,4H).
^{13}C NMR (75MHz, d-DMSO) (δ ppm):
179.28,164.83,159.00,137.61,136.02,133.78,128.43,127.69,126.48,122.50,105.65,105.19,61.77,52.75,50.32,44.20,8.06.
EIMS m/z (% of relative abundance): 455.20 (M+1)

(6h) (5-amino-7-(4-benzhydryl-piperazin-1-yl)- 1-cyclopropyl-6,8-diflouro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 82%.mp 290-292°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):
14.40(s,1H),8.50(s,1H
),7.29(m,10H),4.44(m,1H),3.98(s,2H),3.38(m,4H),2.50(m,4H),1.07(m,4H).
^{13}C NMR (75MHz, d-DMSO) (δ, ppm):
190.00,179.95,164.77,141.94,139.20,137.10,135.50,133.90,131.10,
127.99,127.38,126.43,51.61,50.40,48.10,8.03.
EIMS m/z (% of relative abundance): 531.30 (M+1)

(6i) (5-amino-1-cyclopropyl-6,8-diflouro-7-[(4-(3-methoyx-phenyl)-piperazin-1-yl])- 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid)

Yellow solid, yield 89%.mp 200-200.3°C
H^{1}NMR (300MHz, d-DMSO)) (δ ppm):
8.49(s,1H),7.25(s,2H),7.12(t,J=8.1,1H),,6.56(J=8.1,1H,d),6.49(s,1H),6.38(d,J=7.5,1H),4.00 (m,1H),3.70 (m,4H),3.24(m,4H),1.07 (m,4H)
^{13}C NMR (75MHz, d-DMSO) (δ ppm):
179.80,165.80,160.39,152.55,150.26,141.00,138.00,136.50,134.00,129.915,128.10,108.58,105.71,104.80,102.03,55.05,50.64,49.30,45.80,8.64.
EIMS m/z (% of relative abundance): 471.20 (M+1)

Well Diffusion Bio assay for antimicrobial activity

The antimicrobial activities of all the compounds were evaluated according to the well diffusion method [20]. The compounds (6a-6i) were tested against E. coli (ATCC 9637), Klebsiella pneumoneae (ATCC 10031), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 29213), Salmonella cholearesuis (ATCC 14028) and Bacillus subtilis (clinical isolate). Briefly, a loopful of the respective test culture was inoculated in 5

ISSN: 0975-8585

ml nutrient broth tube and incubated at 37°C for 18 h. The broth culture was then diluted to McFarland standard 0.5. Well (5 mm) were cut in the nutrient gar plates that had previously been swabbed with the diluted broth cultures of the respective bacteria. The solutions of the compounds to be tested were prepared in DMSO at a concentration of 1000 ug/ml and were then added to the wells. The plates were incubated at 37°C for 24h and zones of inhibition were measured. In this assay, gentamycin was used as a positive control.

Broth dilution method for antimicrobial activity

Minimum inhibitory Concentration Determination (MIC) values for the compounds were determined against the same human pathogenic bacteria taken for well diffusion assay. MIC's were determined according to a broth microdilution procedure[21]. A solution of each of the compounds (1000 ug/ml) in dimethyl sulfoxide was diluted 2-fold with nutrient broth to give a series of dilutions ranging from 1000 to 0.425 ug/ml, respectively. Each dilution (1000 ul) was dispensed in rows of micro well titre plates . Appropriately diluted (according to McFarland Standard 0.5) test organism (10ul) was added to each well. Gentamycin and ciprofloxacin solutions in DMSO were taken as positive controls. Nutrient broth (100ul) with 10ul DMSO in the absence of the test compound was used as negative control. The plates were incubated at 37°C for 24h. The lowest concentration of the compound at which the test organism did not demonstrate visible growth was taken as the MIC.

ACKNOWLEDGEMENTS

We are pleased to acknowledge financial support from DST, New Delhi [Grant No. SR/FTP/CS-62/2006] for this investigation.

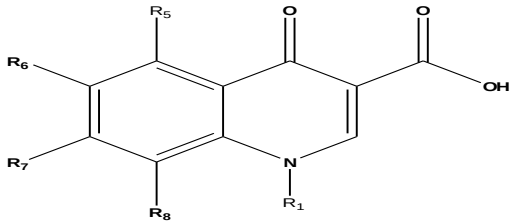
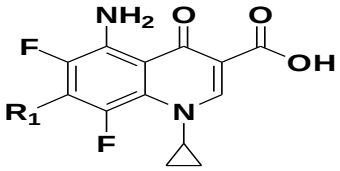
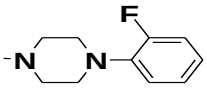
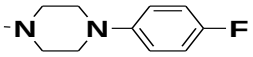
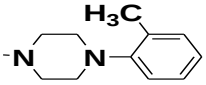
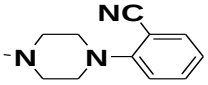
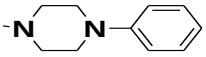
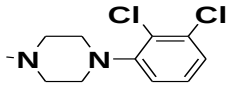
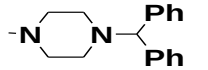
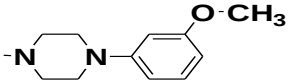


Fig.1a: Quinolone precursor used as a model for modification at various position especially C-1,C-6,C-7,C-8 where R_1,R_5,R_6,R_7,R_8 are various diff. or same substituents

ISSN: 0975-8585

Table 1: Precursor 4 with different piperazine substituent at C-7 resulting in compound 6a-6i



Compound No.	R_1	Yield(in %)[a]
6a		87
6b		88
6c		84
6d		89
6e		85
6f		80
6g		70
6h		82
6i		89

[a] All the yields are on isolated basis.

Table 2: Antibacterial activity of compounds 6a-6i showing zone of inhibition (cm) against selected pathogenic strains (B).

Compounds	B1	B2	B3	B4	B5	B6
6a	2.1	2.1	–	2.3	2.3	1.8
6b	1.5	1.3	–	1.9	1.5	1.2
6c	1.1	1.1	–	1.6	1.4	1.2
6d	1.6	1.6	–	2.0	1.8	1.5
6e	1.1	–	–	3.0	1.5	1.2
6f	1.1	1.1	–	1.0	1.1	0.8

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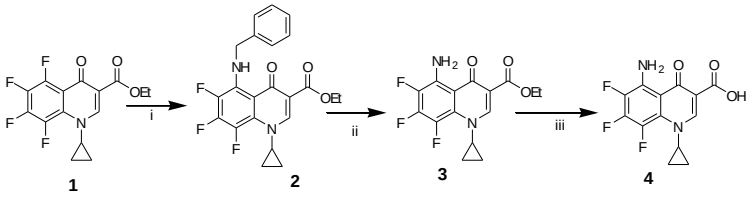
6g	2.8	1.2	1.5	2.9	2.9	2.5
6h	–	–	–	1.2	–	–
6i	1.6	–	–	2.5	1.4	1.4
Sparfloxacin as reference standard	4.2	4.2	4.5	4.5	4.6	4.1

Table 3: Antibacterial activities of compounds 6a-6i showing MIC values (µg/ml) against selected pathogenic strains (B).

Compounds	B1	B2	B3	B4	B5	B6
6a	31.3	31.3	–	15.65	62.5	62.5
6b	62.5	125	–	62.5	62.5	125
6c	125	125	–	62.5	125	125
6d	62.5	62.5	–	31.3	31.3	62.5
6e	125	–	–	15.65	62.5	125
6f	250	250	–	250.0	250	250
6g	15.7	1.2	125	15.7	15.7	31.3
6h	–	–	–	250	–	–
6i	125	–	–	31.3	125	125
Sparfloxacin as reference standard	2.0	2.0	2.0	1.0	1.0	2.0

B1: E. coli (ATCC 9637), B2: Klebsiella pneumoneae (ATCC 10031), B3: Pseudomonas aeruginosa (ATCC 27853),B4: Staphylococcus aureus (ATCC 29213), B5: Salmonella cholearesuis (ATCC 14028), B6: Bacillus subtilis (clinical



Scheme 1.Synthesis of Precursor 4 starting from Compound 1

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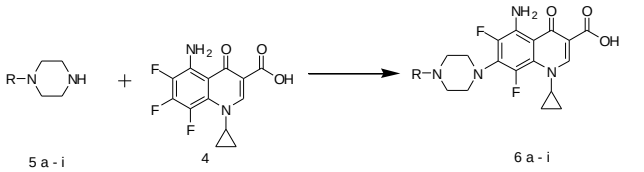

No	R
a	2-FC_6H_4
b	4-FC_6H_4
c	2-MeC_6H_4
d	2-CNC_6H_4
e	C_6H_5
f	2-Cl,3-ClC_6H_3
g	$C_6H_5CH_2$
h	$(C_6H_5)_2CH$
i	2-$OMeC_6H_4$

Scheme 2.Nucleophilic substitution at C-7 position of precursor **4**

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