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Synthesis and antimicrobial studies of some 4-Thiazolidinone containing Fluoroquinolones analogous

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Abstract

A series of broad spectrum antibacterial fluoroquinolone attached to thiazolidinone **6a-j** have been prepared and tested for their antibactial and antifungal *in vitro* activity against two Gram positive bacteria *S. aureus, S. pyogenes* and two Gram negative bacteria *E. coli, P. aeruginosa* and fungi *C. albicans*, *A. niger* and *A. clavatus* organisms by using Broth dilution method. Results indicated that the activity of fluroquinolones was not improved on incorporation of 4-thiazolidinone at C-3 and 4-methyl-2-phenylpiperazin-1-yl group at C-7.

Keywords: Fluoroquinolone, N-methyl-3-phenylpiperazine, thiazolidinone, antibacterial and antifungal activity

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Introduction

Fluoroquinolones are new class of antibacterial compounds developed after the discovery of nalidixic acid by Lesher 1962. The molecular structures of quinolones have been extensively modified to improve their antimicrobial properties and pharmacokinetic profile. Main modification was the introduction of a C-6 fluorine atom. Fluoroquinolones, clinically applied since the mid-1980s, are widely used for the treatment of various bacterial infections of the lower respiratory tract, urinary tract, and skin/soft tissue, as well as sexually transmitted diseases. Fluoroquinolones were investigated as inhibitors of DNA gyrase/topoisomerase IV enzyme [1]. Structure activity relation of fluoroquinolones has been studied in some reviews [2,3], which indicate that carboxylic acid group or any hydrolysable group viz. ester and amide at C-3 is essential for DNA gyrase binding. Basic group at C-7 position can influence the antibacterial activity and pharmacokinetics. They are extensively investigated as antidiabetic [4], anticancer [5] antiviral [6] and anti-HIV [7] agents.

4-Thiazolidinones demonstrated variety of pharmacological activities viz. anti-inflammatory [8] antitubercular [9], anticancer [10], antitumor [11], anti- HIV [12] antibacterial [13], antifungal [14], anesthetic [15], anti-viral [16], anticonvulsant [17], diuretics [18], nematicidal [19] and antihistaminic activity [20]. Its derivatives were found to interact with MurB enzyme and inhibited peptidoglycan biosynthesis, essential polymer for cell wall of bacteria [21] Pharmacological profile of 4-thiazolidinones proves its biological importance.

We have synthesized thiazolidinones and Schiff bases incorporated fluoroquinolones with n-[4-methoxyphenyl]piperazin-1-yl [22] and n-methylpiperazin-1-yl group [23] and also studied antimicrobial activity of amides [24-26] and esters [27] of fluoroquinolone, some of them showed significant activity with thiazolidinones, hence we have decided to observe the variation of antimicrobial activity in fuloroquinolone with 4-thiazolidinones via Schiff base through the hydrolysable amide linkage at C-3 and 4-methyl-2-phenylpiperazin-1-yl group at C-7.

Results & Discussion

Schiff bases of fluoroquinolone have taken as lead molecules, prepared from1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid via hydrazide, which converted to Schiff bases with substituted aromatic aldehydes [22, 23]; further n-methyl-3-phenyl piperazin-1-yl group was introduced and cyclized with thioglycolic acid. The ^{1}H NMR spectra of the lead molecule showed multiplet for N-CH proton at 3.55-3.68, a multiplet observed for cyclopropane protons at 1.02-1.21, and signal for three protons of the quinolones ring at 8.15-8.69. The –CH- proton of Schiff base at 6.42 – 6.58 and singlet of >CONH- at 8.58-8.67 was observed. A multiplet at 2.27-3.10 for piperazin-1-yl group and singlet for >N-CH_3 at 1.95-2.15 were observed; a singlet at 3.45 - 3.57 for –CH_2- and 6.12 – 6.45 for the proton at C-2 of the cyclized thiazolidinones were observed. The IR absorption band for >C=O of the quinolone ring at 1745 – 1752 cm^{-1}, 2845-2955 cm^{-1} for the cyclopropyl group, for amide at 1645 and for Schiff base >N=CH- at 1620 cm^{-1} were observed. In addition a band was observed at 1031-1052 cm^{-1} for N-CH for piperazin-1-yl group, for thiazolidinones the lactam >C=O band was observed at 1715 -1725 cm^{-1} with disappearance of the >N=CH- band.

Activity of all synthesized compounds are described in Table-I. Schiff base **1c** (R=2-OH, 4-OCH_3) demonstrated good activity against *E. coli* and excellent activity against *S. aureus*, **1i** (R=2-Cl) demonstrated excellent activity against *E. coli* as well as *S. aureus* and good activity against *P. aeruginosa* as well as *S. pyogenes*. **1g** (R = 2-NO_2) showed excellent activity against *S. aureus* when compared with ampicillin. Schiff base **1i** (R = 4-Cl) showed good activity against *E. coli* when compared with chloramphenicol. Piperazin-1-yl Schiff base **2a** (R = -H) showed good activity against *E. coli* as well as *S. pyogenes* and excellent activity against *S. aureus*, **2b** (4–OCH_3) showed good activity against *E. coli* and excellent activity against *S. aureus*. **2e** (R=2-OH) showed excellent activity against *E. coli* as well as *S. aureus* and good activity against *P. aeruginosa* as well *S. pyogenes*. **2f** (R = 4-OH) demonstrated good activity against *P. aeruginosa* and excellent activity against *S. aureus*. **2g** (R = 2-NO_2) demonstrated good activity against both Gram negative bacteria and *S. pyogenes*. **2h** (R = 2-Cl) showed good activity against *S. pyogenes* when compared with ampicillin. **2e** (R = 2-OH) demonstrated good activity against *E. coli* when compared with chloramphenicol.

Table (1) *In vitro* antimicrobial activity in µg/ml of 1a-j, 2a-j & 3a-j

Compd.	R	Antimicrobial activity in µ/ml						
		Gram positive		Gram negative		Fungal species		
		E. coli	*P. Aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
1		100	100	100	100	500	1000	1000
3		500	500	500	500	200	500	500
4a	-H	500	1000	500	1000	500	1000	1000
4b	4-OCH_3	200	500	500	1000	500	>1000	>1000
4c	2-OH, 4-OCH_3	100	200	200	500	100	500	1000
4d	4-F	500	500	500	500	1000	1000	1000
4e	2-OH	500	500	500	1000	500	500	500
4f	4-OH	500	500	500	500	500	500	500
4g	2-NO_2	500	200	100	200	500	1000	>1000
4h	3-NO_2	200	200	1000	1000	1000	1000	>1000
4i	2-Cl	50	100	200	100	1000	500	500
4j	4-Cl	1000	1000	1000	1000	1000	500	500
5a	-H	100	500	100	100	100	500	1000
5b	4-OCH_3	100	200	200	500	500	1000	1000
5c	2-OH, 4-OCH_3	1000	1000	1000	1000	1000	1000	1000
5d	4-F	250	500	500	500	1000	>1000	>1000
5e	2-OH	50	100	200	100	1000	>1000	>1000
5f	4-OH	500	100	200	500	1000	1000	1000
5g	2-NO_2	100	100	500	100	1000	500	500
5h	3-NO_2	1000	500	500	100	500	500	500
5i	2-Cl	500	200	500	1000	500	>1000	>1000
5j	4-Cl	500	500	500	500	500	>1000	>1000
6a	-H	500	1000	500	500	500	500	500
6b	4-OCH_3	150	200	500	500	1000	1000	1000
6c	2-OH, 4-OCH_3	500	500	500	500	1000	>1000	>1000
6d	4-F	1000	500	1000	1000	1000	1000	1000
6e	2-OH	100	100	500	100	1000	>1000	>1000
6f	4-OH	500	500	500	500	500	>1000	>1000
6g	2-NO_2	50	100	150	150	1000	1000	1000
6h	3-NO_2	500	500	500	1000	1000	1000	1000
6i	2-Cl	500	500	500	500	200	500	500
6j	4-Cl	50	100	200	100	200	500	500
Gentamycin		0.05	1	0.25	0.5	-	-	-
Ampicillin		100	100	250	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Ciprofloxacin		25	25	50	50	-	-	-
Norfloxacin		10	10	10	10	-	-	-
Nystatin		-	-	-	-	100	100	100
Greseofulvin		-	-	-	-	500	100	100

Thiazolidinones **3e** (R = 2-OH) showed good activity against both Gram negative bacteria and *S. pyogenes*. **3g** (R = 2-NO_2) showed excellent activity against *E. coli* as well *S. aureus* and good activity against *P aeruginosa*, **3j** (R = 4-Cl) demonstrated excellent activity against *E. coli* as well as *S. aureus* and good activity against *P. aeruginosa* as well *S. pyogenes*. **3g** and **3j** (2-NO_2 and 4-Cl) showed good activity against *E. coli* when compared with chloramphenicol. All other compounds demonstrated moderate activity when compared all standard drugs.

Antifungal activity of all synthesized compounds was evaluated against fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 using nystatin and greseofulvin as standard drugs. All compounds demonstrated significant activity against *C. albicans*. Schiff base **1a, 1b, 1e, 1f** and **1g** (R = -H, 4-OCH_3, 2-OH, 4-OH and 2-NO_2) showed good activity and **1c** (R = 2-OH, 4-OCH_3) showed excellent activity when compared greseofulvin and **1c** (R = 2-OH, 4-OCH_3) showed good activity when compared with nystatin. Piperazin-1-yl Schiff base **2b**, **2h**, **2i** and **2j** (R = 4-OCH_3, 3-NO_2, 2-Cl and 4-Cl) showed good activity and **2a** (R = -H) showed excellent activity when compared greseofulvin and good activity when compared with nystatin. Thiazolidinones **3a** and **3f** (R = -H and 4-OH) showed good activity and **6i** and **6j** (R = 2-Cl and 4-Cl) showed excellent activity when compared with greseaofulvin. All other compounds demonstrated good to moderate activity when compared with both standard drugs.

Materials and Methods

Experimental

Melting points were determined in open capillaries and were left uncorrected. The IR spectra were recorded on Shimadzu FTIR spectrophotometer, using potassium bromide pallets. ^{1}H-NMR spectra were scanned on Bruker Avance II FT-NMR spectrometer at 400 MHz, using TMS as the internal standard and ($CDCl_3$: DMSO-d_6) (2:1) as solvent. All the chemical shift were reported as δ (ppm) values. The elemental analyses (C, H and N) of compounds were performed on Carlo Erba 1108. The compounds gave satisfactory C, H and N analysis. The purity of the compounds were controlled with Merck precoated TLC plates and spots were visualized with ultraviolet light.

Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-[-N-(benzalhydrazinyl)-carbonyl]quinoline (1a-j)

The title compound have synthesized from 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid via hydrazide on condensation with substituted aromatic aldehydes [22,23].

Synthesis of 1-cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(benzal hydrazinyl)carbonyl]quinoline (2a-j)

The mixture of compound **1a-j** (0.01 mol) and N-methyl-3-phenylpiperazine (0.05 mol) in pyridine was refluxed for 8-10 h, poured in to crushed ice and neutralized with diluted HCl, stirred the product for half an hour, filtered, dried and recrystlized from DMF. The reaction was monitored by TLC on silica gel plate using benzene : acetone (9:1).

Synthesis of 2-phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-2-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3a-j)

The mixture of compound **2a-j** (0.01 mol) and thioglycolic acid (0.015 mol) was taken in dry 1,4 dioxane, added pinch of anhydrous $ZnCl_2$ and refluxed the mixture for 12-14 h and cooled to rt, poured in to crushed ice. The solid product was filtered, neutralized with distilled water, dried and recrystlized from DMF. The reaction was monitored on TLC on silica gel using toluene : ethylacetate (9:1).

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(benzal hydrazinyl)carbonyl]quinoline (2a)

Yield 65%. Mp 255-252 ˚C. IR (KBr): 3452 (NH), 2915, 2835 (C-H), 1747 (>C=O), 1625 (amide-I), 1615 (-N=CH-), 1535 (amide-II), 1337 (C-N), 1257 (C-F), 1222 (amide-III), 1051 (C-N, piperazine). PMR: δ 8.67 (1H, s, H_2), 8.42 (1H, s, H_8), 8.21 (1H, s, H_5), 3.68 (1H, m, >N-CH-), 1.05-1.65 (4H, m, Cyclopropyl), 8.58 (1H, s, >CO.NH), 6.42 (1H, s, -N=CH-), 2.27-3.10 (7H, m, piperazine), 6.78-8.48 (10H, m, Ar-H), 2.10 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{30}N_5O_2F$: C, 71.10; H, 05.78; N, 13.38 % Found: C, 71.06; H, 05.75; N, 13.33 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(4-methoxybenzal hydrazinyl)carbonyl]quinoline (2b)

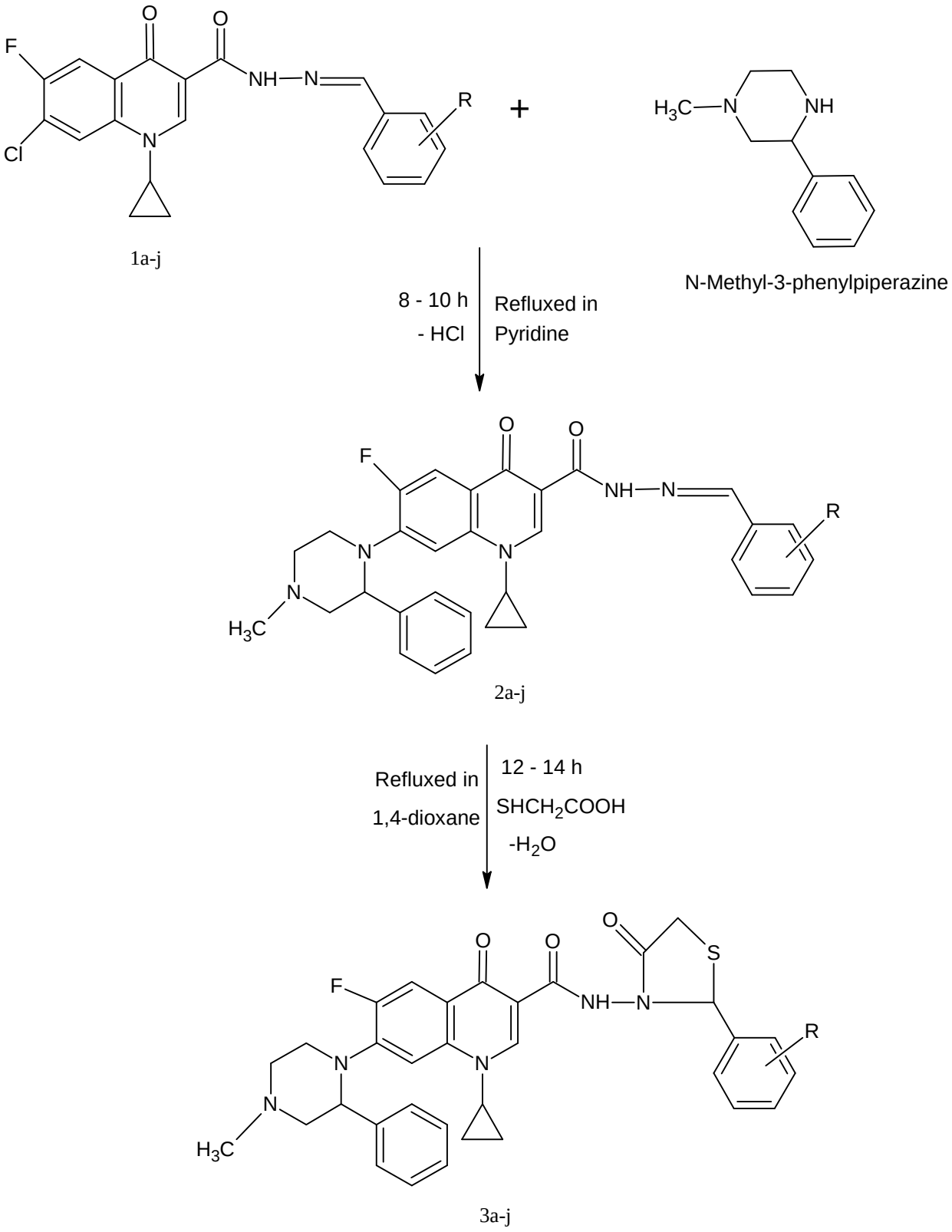
Yield 61%. Mp 294-296 ˚C. IR (KBr): 3446 (NH), 2919, 2828 (C-H), 1739 (>C=O), 1625 (amide-I), 1610 (-N=CH-), 1545 (amide-II), 1346 (C-N), 1258 (C-F), 1215 (amide-III), 1035 (C-N, piperazine). PMR: δ 8.56 (1H, s, H_2), 8.35 (1H, s, H_8), 8.11 (1H, s, H_5), 3.65 (1H, m, >N-CH-), 1.11-1.58 (4H, m, cyclopropyl), 8.56 (1H, s, >CO.NH), 6.52 (1H, s, -N=CH-), 2.28-3.15 (7H, m, piperazine), 6.66-8.35 (9H, m, Ar-H), 2.00 (3H, s, >N-CH_3). Anal. Cald. for $C_{32}H_{32}N_5O_3F$: C, 69.41; H, 05.83; N, 12.66 % Found: C, 69.43; H, 05.83; N, 12.64 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(2-hydroxy-4-methoxybenzal hydrazinyl)carbonyl]quinoline (2c)

Yield 55%. Mp 261-263 ˚C. IR (KBr): 3440 (NH), 3235 (O-H), 2915, 2825 (C-H), 1742 (>C=O), 1628 (amide-I), 1609 (-N=CH-), 1552 (amide-II), 1335 (C-N), 1245 (C-F), 1210 (amide-III), 1041 (C-N, piperazine), 1025,1202 (C-O-C). PMR: δ 8.48 (1H, s, H_2), 8.25 (1H, s, H_8), 8.12 (1H, s, H_5), 3.77 (1H, m, >N-CH-), 1.11-1.63 (4H, m, cyclopropyl), 8.67 (1H, s, >CO.NH), 6.25 (1H, s, -N=CH-), 1.97-2.93 (7H, m, piperazine), 6.44-8.32 (8H, m, Ar-H), 1.95 (3H, s, >N-CH_3), 7.15 (1H, s, -OH), 3.69 (3H, s, -OCH_3). Anal. Cald. for $C_{32}H_{32}N_5O_4F$: C, 67.46; H, 05.67; N, 12.30 % Found: C, 67.42; H, 05.61; N, 12.27 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(4-fluorobenzal hydrazinyl)carbonyl]quinoline (2d)

Yield 68%. Mp 304-306 ˚C. IR (KBr): 3440 (NH), 2922, 2846 (C-H), 1737 (>C=O), 1628 (amide-I), 1610 (-N=CH-), 1540 (amide-II), 1352 (C-N), 1225, 1244 (C-F), 1218 (amide-III), 1048 (C-N, piperazine). PMR: δ 8.67 (1H, s, H_2), 8.15 (1H, s, H_8), 7.92 (1H, s, H_5), 3.78 (1H, m, >N-CH-), 1.10-1.57 (4H, m, cyclopropyl), 8.78 (1H, s, >CO.NH), 7.25 (1H, s, -N=CH-), 1.87-3.21 (7H, m, piperazine), 6.43-8.22 (9H, m, Ar-H), 1.90 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{29}N_5O_2F_2$: C, 68.75; H, 05.40; N, 12.93 % Found: C, 68.71; H, 05.39; N, 12.91 %.



Scheme 1 Synthesis of the compounds 1a-j, 2a-j and 3a-j

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(2-hydroxybenzal hydrazinyl)carbonyl]quinoline (2e)

Yield 55%. Mp 310-312 ˚C. IR (KBr): 3452 (NH), 3225 (O-H), 2925, 2848 (C-H), 1748 (>C=O), 1625 (amide-I), 1612 (-N=CH-), 1535 (amide-II), 1347 (C-N), 1257 (C-F), 1209 (amide-III), 1041 (C-N, piperazine). PMR: δ 8.32 (1H, s, H_2), 8.25 (1H, s, H_8), 8.01 (1H, s, H_5), 3.77 (1H, m, >N-CH-), 1.12-1.65 (4H, m, cyclopropyl), 8.62 (1H, s, >CO.NH), 6.20 (1H, s, -N=CH-), 2.55-3.01 (7H, m, piperazine), 7.43-8.32 (9H, m, Ar-H), 1.75 (3H, s, >N-CH_3), 7.02 (1H, s, -OH). Anal. Cald. for $C_{31}H_{30}N_5O_3F$: C, 69.00; H, 05.60; N, 12.98 % Found: C, 69.01; H, 05.57; N, 12.95 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(4-hydroxybenzal hydrazinyl)carbonyl]quinoline (2f)

Yield 52%. Mp 285-287 ˚C. IR (KBr): 3415 (NH), 3245 (O-H), 2910, 2825 (C-H), 1758 (>C=O), 1628 (amide-I), 1600(-N=CH-), 1525 (amide-II), 1347 (C-N), 1259 (C-F) 1220 (amide-III), 1040 (C-N piperazine). PMR: δ 8.42 (1H, s, H_2), 8.32 (1H, s, H_8), 7.75 (1H, s, H_5), 3.87 (1H, m, >N-CH-), 1.22-1.57 (4H, m, cyclopropyl), 8.82 (1H, s, >CO.NH), 6.35 (1H, s, -N=CH-), 2.65-3.00 (7H, m, piperazine), 7.44-8.42 (9H, m, Ar-H), 6.98 (1H, s, -OH), 1.85 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{30}N_5O_3F$: C, 69.00; H, 05.60; N, 12.98 %. Found: C, 69.02; H, 05.56; N, 12.95 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(2-nitrobenzal hydrazinyl)carbonyl]quinoline (2g)

Yield 59%. Mp 291-294 ˚C. IR (KBr): 3438 (NH), 2922, 2835 (C-H), 1742 (>C=O), 1625 (amide-I), 1610 (-N=CH-),1342, 1562 (-NO_2 sym, asym), 1525 (amide-II), 1335 (C-N), 1257 (C-F), 1215 (amide-III), 1042 (C-N, piperazine). PMR: δ 8.78 (1H, s, H_2), 8.25 (1H, s, H_8), 8.19 (1H, s, H_5), 3.67 (1H, m, >N-CH-), 1.15-1.67 (4H, m, cyclopropyl), 8.78 (1H, s, >CO.NH), 6.45 (1H, s, -N=CH-), 2.10-3.15 (7H, m, piperazine), 6.27-8.25 (9H, m, Ar-H), 1.78 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{29}N_6O_4F$: C, 65.48; H, 05.14; N, 14.78 %. Found: C, 65.42; H, 05.11; N, 14.81 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(3-nitrobenzal hydrazinyl)carbonyl]quinoline (2h)

Yield 65%. Mp 288-291 ˚C. IR (KBr): 3442 (NH), 2925, 2851 (C-H), 1746 (>C=O), 1632 (amide-I), 1618 (-N=CH-),1335, 1545 (-NO_2 sym, asym), 1515 (amide-II), 1228 (amide-III), 1337 (C-N), 1037 (C-N, piperazine), 1257 (C-F). PMR: δ 8.57 (1H, s, H_2), 8.26 (1H, s, H_8), 7.87 (1H, s, H_5), 3.77 (1H, m, >N-CH-), 1.05-1.67 (4H, m, cyclopropyl), 8.71 (1H, s, >CO.NH), 7.77 (1H, s, -N=CH-), 2.67-3.05 (7H, m, piperazine), 6.22-8.39 (9H, m, Ar-H), 2.10 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{29}N_6O_4F$: C, 65.48; H, 05.14; N, 14.78 %. Found: C, 65.47; H, 05.13; N, 14.77 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(2-chlorobenzal hydrazinyl)carbonyl]quinoline (2i)

Yield 59%. M.p 247-249 ˚C. IR (KBr): 3438 (NH), 2939, 2815 (C-H), 1749 (>C=O), 1635 (amide-I), 1610 (-N=CH-), 1515 (amide-II), 1315 (C-N), 1245 (C-F), 1222 (amide-III), 1051 (C-N, piperazine), 767 (C-Cl). PMR: δ 8.42 (1H, s, H_2), 8.22 (1H, s, H_8), 7.82 (1H, s, H_5), 3.67 (1H, m, >N-CH-), 1.10-1.69 (4H, m, cyclopropyl), 8.85 (1H, s, >CO.NH), 6.55 (1H, s, -N=CH-),

2.05-3.37 (7H, m, piperazine), 6.15-8.25 (9H, m, Ar-H), 1.75 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{29}O_3N_5FCl$: C, 64.86; H, 05.09; N, 12.20 %. Found: C, 64.88; H, 05.12; N, 12.24 %.

1-Cylopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-methyl-2-phenylpiperazin-1-yl]-3-[N-(4-chlorobenzal hydrazinyl)carbonyl]quinoline (2j)

Yield 57%. M.p. 225-230 ˚C. IR (KBr): 3452 (NH), 2942, 2822 (C-H), 1625 (amide-I), 1515 (amide-II), 1209 (amide-III), 1310 (C-N), 1058 (C-N, piperazine), 1620 (-N=CH-), 1265 (C-F), 1742 (>C=O), 747 (C-Cl). PMR: δ 8.45 (1H, s, H_2), 8.34 (1H, s, H_8), 7.77 (1H, s, H_5), 3.52 (1H, m, >N-CH-), 1.05-1.69 (4H, m, cyclopropyl), 8.82 (1H, s, >CO.NH), 6.25 (1H, s, -N=CH-), 2.15-3.20 (7H, m, piperazine), 6.28-8.25 (9H, m, Ar-H), 1.90 (3H, s, >N-CH_3). Anal. Cald. for $C_{31}H_{29}O_3N_5FCl$: C, 64.86; H, 05.09; N, 12.20 %. Found: C, 64.86; H, 05.11; N, 12.26 %.

2-Phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydro-quinoline}carboxamido-3-thiazolidin-4-ones (3a)

Yield 65%. Mp. 233-235 ˚C. IR (KBr): 3442 (NH), 2935, 2815 (C-H), 1632 (amide-I), 1749 (>C=O of quinolone), 1721 (>C=O of thiazolidinone), 1525 (amide-II), 1345 (C-N), 1254 (C-F), 1242 (amide-III), 1042 (C-N, piperazine). PMR: δ 8.75 (1H, s, H_2), 8.56 (1H, s, H_8), 8.19 (1H, s, H_5), 3.85 (1H, m, >N-CH-), 1.07-1.58 (4H, m, Cyclopropyl), 8.80 (1H, s, >CO.NH), 6.15 (1H, s, -N-CH-), 3.60 (2H, s, -CH_2-S), 2.30-2.90 (7H, m, piperazine), 7.05-8.19 (10H, m, Ar-H), 1.95 (3H, s, >N-CH_3). Anal. Cald. for $C_{33}H_{32}N_5O_3FS$: C, 66.31; H, 05.40; N, 11.72 %. Found: C, 66.30; H, 05.42; N, 11.16%.

2-(4-Methoxyphenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3b)

Yield 61%. Mp. 221-224 ˚C. IR (KBr): 3441 (NH), 2930, 2812 (C-H), 1745 (>C=O of quinolone), 1720 (>C=O of thiazolidinone), 1632 (amide-I), 1534 (amide-II), 1347 (C-N), 1265 (C-F), 1230 (amide-III), 1046 (C-N, piperazine). PMR: δ 8.67 (1H, s, H_2), 8.48 (1H, s, H_8), 8.15 (1H, s, H_5), 3.77 (1H, m, >N-CH-), 1.00 -1.62 (4H, m, cyclopropyl), 8.72 (1H, s, >CO.NH), 6.11 (1H, s, -N-CH-), 3.53 (2H, s, -CH_2-S), 2.72-3.10 (7H, m, piperazine), 6.56-8.75 (9H, m, Ar-H), 1.79 (3H, s, >N-CH_3). Anal. Cald. for $C_{34}H_{34}N_5O_4FS$: C, 65.05; H, 05.46; N, 11.16 %. Found: C, 65.03; H, 05.43 N, 11.16 %.

2-(2-Hydroxy-4-methoxyphenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenyl piperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3c)

Yield 55%. Mp. 267-269 ˚C. IR (KBr): 3452 (NH), 3237 (O-H), 2915, 2816 (C-H), 1751 (>C=O of quinolone), 1718 (>C=O of thiazolidinone), 1625 (amide-I), 1322 (C-N), 1525 (amide-II), 1255 (C-F), 1221 (amide-III), 1052 (C-N, piperazine). PMR : 8.77 (1H, s, H_2), 8.32 (1H, s, H_8), 7.77 (s, 1H, H_5), 3.59 (1H, m, >N-CH-), 1.11-1.63 (4H, m, cyclopropyl), 8.72 (1H, s, >CO.NH), 6.18 (1H, s, -N-CH-), 3.42 (2H, s, -CH_2-S), 1.67-3.15 (7H, m, piperazine), 6.34-8.58 (8H, m, Ar-H), 1.87 (3H, s, >N-CH_3), 7.52 (1H, s, -OH), 4.11 (3H, s, -OCH_3). Anal. Cald. for $C_{34}H_{34}N_5O_5FS$: C, 63.43; H, 05.33; N, 10.89 %. Found: C, 63.42; H, 05.29; N, 10.88 %.

2-(4-Fluorophenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3d)

Yield 68%. Mp. 302-306 ˚C. IR (KBr): 3451 (NH), 2910,2862 (C-H), 1747 (>C=O of quinolone), 1730 (>C=O of thiazolidinone), 1630 (amide-I), 1542 (amide-II), 1357 (C-N), 1239

1262 (C-F), 1210 (amide-III), 1057 (C-N, piperazine); PMR: δ 8.61 (1H, s, H_2), 8.29 (1H, s, H_8), 8.02 (1H, s, H_5), 3.77 (1H, m, >N-CH-), 1.10-1.63 (4H, m, cyclopropyl), 8.77 (1H, s, >CO.NH), 6.02 (1H, s, -N-CH-), 3.45 (2H, s, -CH_2-S), 1.83-3.13 (7H, m, piperazine), 6.43-8.22 (9H, m, Ar-H), 1.64 (3H, s, >N-CH_3). Anal. Cald. for $C_{33}H_{31}N_5O_3F_2S$: C, 64.37; H, 05.08; N, 11.38 %. Found: C, 64.35; H, 05.08; N, 11.40 %.

2-(2-Hydroxyphenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3e)

Yield 55%. Mp. 310-312 ˚C. IR (KBr): 3415 (NH), 2915, 2830 (C-H), 3250 (O-H), 1742 (>C=O of quinolone), 1715 (>C=O of thiazolidinone), 1620 (amide-I), 1522 (amide-II), 1350 (C-N), 1257 (C-F), 1210 (amide-III), 1042 (C-N piperazine). PMR: δ 8.56 (1H, s, H_2), 8.01 (1H, s, H_8), 7.82 (1H, s, H_5), 3.64 (1H, m, >N-CH-), 1.05-1.69 (4H, m, cyclopropyl), 8.92 (1H, s, >CO.NH), 6.19 (1H, s, -N-CH-), 3.87 (2H, s, -CH_2-S), 1.82-3.15 (7H, m, piperazine), 6.25-8.12 (9H, m, Ar-H), 1.75 (3H, s, >N-CH_3), 7.47 (1H, s, -OH). Anal. Cald. for $C_{33}H_{32}N_5O_4FS$: C, 64.58; H, 05.26; N, 11.42 %. Found: C, 64.57; H, 05.29; N, 11.41 %.

2-(4-Hydroxyphenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3f)

Yield 52%. Mp. 243-245 ˚C. IR (KBr): 3422 (NH), 3242 (O-H), 2915, 2816 (C-H), 1752 (>C=O quinolone), 1715 (>C=O of thiazolodinone), 1620 (amide-I), 1510 (amide-II), 1347 (C-N), 1262 (C-F), 1215 (amide-III), 1025 (C-N piperazine). PMR: δ 8.78 (1H, s, H_2), 8.62 (1H, s, H_8), 8.48 (1H, s, H_5), 3.55 (1H, m, >N-CH-), 1.11-1.67 (4H, m, cyclopropyl), 8.75 (1H, s, >CO.NH), 6.12 (1H, s, -N-CH-), 3.75 (2H, s, -CH_2-S), 2.05-3.10 (7H, m, pipreazine), 6.13-8.12 (9H, m, Ar-H), 1.75 (3H, s, >N-CH_3), 7.77 (1H, s, -OH). Anal. Cald. for $C_{33}N_5H_{32}O_4FS$: C, 64.58; H, 05.26; N, 11.42 %. Found: C, 64.56; H, 05.27; N, 11.42 %.

2-(2-Nitrophenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3g)

Yield 59%. Mp. 284-287 ˚C; IR (KBr): 3452 (NH), 2945, 2856 (C-H), 1748 (>C=O of quinolone), 1719 (>C=O of thiazolidinone), 1630 (amide-I), 1552, 1345 (-NO_2 sym, asym) 1552 (amide-II), 1325 (C-N), 1265 (C-F), 1210 (amide-III), 1025 (C-N, piperazine). PMR: δ 8.52 (1H, s, H_2), 8.15 (1H, s, H_8), 7.92 (1H, s, H_5), 3.67 (1H, m, >N-CH-), 1.11-1.79 (4H, m, cyclopropyl), 8.79 (1H, s, >CO.NH), 6.08 (1H, s, -N-CH-), 3.57 (2H, s, -CH_2-S), 2.01-2.96 (7H, m, piperzine), 6.37-8.22 (9H, m, Ar-H), 1.67 (3H, s, >N-CH_3). Anal. Cald. for $C_{33}H_{31}N_6O_5FS$: C, 61.67; H, 04.81; N, 13.08 %. Found: C, 61.63; H, 04.81; N, 13.07 %.

2-(3-Nitrophenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3h)

Yield 65%. Mp. 293-295˚C. IR (KBr): 3431 (NH), 2915, 2825 (C-H), 1752 (>C=O of quinlone), 1720 (>C=O of thiazolidinone), 1625 (amide-I), 1535, 1345(-NO_2 sym, asym) 1525 (amide-II), 1325 (C-N), 1252 (C-F), 1210 (amide-III), 1051 (C-N, piperazine). PMR: δ 8.65 (1H, s, H_2), 8.21 (1H, s, H_8), 8.11 (1H, s, H_5), 3.62 (1H, m, >N-CH-), 1.05-1.71 (4H, m, cyclopropyl), 8.89 (1H, s, >CO.NH), 6.15 (1H, s, -N-CH-), 3.62 (2H, s, -CH_2-S), 2.08-3.11 (7H, m, piperazine), 6.29-8.11 (9H, m, Ar-H), 1.79 (3H, s, >N-CH_3). Anal. Cald. for $C_{33}H_{31}N_6O_5FS$: C, 61.67; H, 04.86; N, 13.08 %. Found: C, 61.68; H, 04.79; N, 13.06 %.

2-(2-Chlorophenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3i)

Yield 59%. Mp : 232-234 ˚C. IR (KBr): 3435 (NH), 2910, 2815 (C-H), 1742 (>C=O of quinolone), 1732 (>C=O of thiazolidinone), 1625 (amide-I), 1535 (amide-II), 1315 (C-N), 1262 (C-F), 1218 (amide-III), 1052 (C-N, piperazine), 742 (C-Cl). PMR: δ 8.52 (1H, s, H_2), 8.22 (1H, s, H_8), 7.85 (1H, s, H_5), 3.77 (1H, m, >N-CH-), 1.11-1.79 (4H, m, cyclopropyl), 8.86 (1H, s, >CO.NH), 6.19 (1H, s, -N-CH-), 3.77 (2H, s, -CH_2-S), 2.10-3.19 (7H, m, piperazine), 6.47-8.32 (9H, m, Ar-H), 1.92 (3H, s, >N-CH_3). Anal. Cald. For $C_{33}H_{31}N_5O_3FClS$: C, 62.74; H, 04.95; N, 11.09 %. Found: C, 62.72; H, 04.93; N, 11.09 %.

2-(4-Chlorophenyl)-3-{1-cyclopropyl-6-fluoro-7-[4-methyl-3-phenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-3-thiazolidin-4-ones (3j)

Yield 57%. Mp. 299-301˚C. IR (KBr): 3449 (NH), 2937, 2808 (C-H), 1737 (>C=O of quinolone), 1712 (>C=O of thiazolidinone), 1625 (amide-I), 1537 amide-II), 1357 (C-N), 1256 (C-F), 1207 (amide-III), 1042 (C-N, piperazine), 771 (C-Cl). PMR: δ 8.71 (1H, s, H_2), 8.31 (1H, s, H_8), 8.08 (1H, s, H_5), 3.62 (1H, m, >N-CH-), 1.10-1.68 (4H, m, cyclopropyl), 8.79 (1H, s, >CO.NH), 6.11 (1H, s, -N-CH-), 3.67 (2H, s, -CH_2-S), 1.77-3.11 (7H, m, piperazine), 6.42-8.20 (9H, m, Ar-H), 1.75 (3H, s, >N-CH_3) Calculated for $C_{33}H_{31}N_5O_3FClS$: C, 62.74; H, 04.95; N, 11.09 %. Found: C, 62.70; H, 04.93; N, 11.10 %.

Antimicrobial activity

All the synthesized compounds were evaluated for antibacterial activity against Gram positive bacterial *S. aureus* MTCC 96, *S. pyogenes* MTCC 443 and Gram negative *E. coli* MTCC 442 and *P. aeruginosa* MTCC 441 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin as standard drugs. The activity of compounds was evaluated by using broth dilution method [28]. Muller Hinton broth was used as nutrient medium to grow and dilution the drug suspension for test. DMSO was used as diluents which not effect the growth of microbes.

Conclusion

Compounds demonstrated antibacterial activity close to ampicillin. All of them were found poorly active on compassion with standard fluoroquinolones ciprofloxacin and norfloxacin. Activity was not improved on Introduction of 4-thiazolidinone through the hydrolysable amide linkage at C-3 and 4-methyl-2-phenylpiperazin-1-yl group at C-7, which suggested that C-3 carboxylic group is essential for better activity. Present work provides more information about SAR of fluoroquinolones. Significant activity observed against *C. albicans* but compounds were found poor active for other fungal species.

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