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SYNTHESIS AND *In Vitro* ANTIMICROBIAL STUDY OF SCHIFF BASE AND THIAZOLIDINONE OF 1-CYCLOPROPYL-6-FLUORO-7-[4-(2,3-DICHLOROPHENYL)PIPERAZIN-1-YL]-4-QUINOLONE

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Abstract: The title compounds, 2-substituted phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(2,3-dichlorophenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones **6a-j**, have been synthesized after several structural variations viz. hydrazide **2** *via* acid chloride, Schiff base formation and cyclization of Schiff base followed by condensation with N-(2,3-dichlorophenyl)piperazine from the lead molecule 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acid **1.** The synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* against organisms viz. *S. aureus, S. pyogenes*, *E. coli, P. aeruginosa, C. albicans*, *A. niger* and *A. clavatus* taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. Compounds **4i**, **5i** and **6j** (2-Cl, 2-Cl and 4-Cl) demonstrated excellent activity compared with ampicillin.

Keywords: fluoroquinolone, thiazolidinone, N-(2,3-dichlorophenyl)piperazine, antibacterial, antifungal activity

Fluoroquinolones are widely used for treatment of numerous infections. They are investigated as broad-spectrum antibacterials (1). They act by the inactivation of bacterial enzymes: DNA gyrase and topoisomerase IV, which play a significant role in DNA-supercoiling, essential for DNA to occupy less space in the cell, otherwise DNA can no longer be contained within the cell and cause rapid bacterial death (2). They are also investigated as antidiabetic (3), anticancer (4), antiviral (5) and anti-HIV (6) agents.

Thiazolidinones possess antibacterial activity (7). They contain β-lactam ring with sulfur atom in it, and derivatives inhibit the biosynthesis of the peptidoglycan polymer essential for cell wall of bacteria on inactivation of MurB enzyme. MurB enzyme is a unique target for antibacterial activity of thiazolidinone (8). Thiazolidinones also have some significant activity, viz. antihyperglycemic (9), anti-inflammatory (10), antitubercular (11), anticancer (12), antitumor (13), anti-HIV (14), antifungal (15), anesthetic (16), anti-viral (17), anticonvulsant (18), diuretics (19), nematicidal (20), and antihistaminic activity (21).

From the literature survey we observed that some of the synthesized fluoroquinolones having hydrolysable group viz. amide and ester (22-25) were found active and henceforth we continued this work with Schiff base and synthesized thiazolidinones to study the effect of substituents on antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. The IR spectra were recorded on Perkin-Elmer-843 spectrometer, using KBr pellets. ^{1}H-NMR spectra were scanned on Bruker Avance II FT-NMR spectrometer at 400 MHz, using TMS as an internal standard and ($CDCl_3$: DMSO d_6) (2 : 1, v/v) as solvent (chemical shifts in δ ppm). The compounds gave satisfactory C, H and N analysis.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro -3-quinoline carbonyl chloride (**2**)

The mixture of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid **1** (0.01 mol), DMF (1 mL) and thionyl chloride (0.01 mol) was refluxed using benzene as a solvent on water bath at 80°C for 5-6 h. Anhydrous condition was maintained by using calcium chloride

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guard tube, till the HCl gas evolution was ceased. Solvent and thionyl chloride were removed by distillation. The solid of the title compound obtained was cooled and used in the next step.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro quinoline-3-carbohydrazide (**3**)

To a mixture of hydrazine hydrate (0.03 mol) in dry chloroform and triethyl amine (1 mL), acid chloride **2** (0.01 mol) in dry chloroform added dropwise in 45 min and temperature was maintained at 0-5^{o}C. The reaction mixture was further stirred at room temperature for 2 h, the solvent was distilled off and the solid product obtained was neutralized with $NaHCO_3$ (10%) and washed with distilled water. The product was filtered, dried and recrystallized from DMF. The reaction was monitored by TLC on silica gel using chloroform : methanol (9:1, v/v). M. p.: 324^{o}C, yield = 67%. IR (KBr, cm^{-1}): 3446 (NH), 3072, 2980 (C-H), 1750 (>C=O), 1627 (amide-I), 1533 (amide-II), 1220 (amide-III), 1361 (C-N), 1263 (C-F), 746 (C-Cl); ^{1}H NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.3 (s, 1H, H_2), 8.1 (s, 1H, H_8), 7.7 (s, 1H, H_5), 3.64 (m, 1H, >N-CH-), 1.11-1.41 (m, 4H, cyclopropyl), 8.8 (s, 1H, >CO.NH), 4.33 (s, 2H, -NH_2).

1-Cyclopropryl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-[-N-(benzal hydrazinyl)-carbonyl]quinoline **(4a)**

The mixture of **3** (0.01 mol) and benzaldehyde **a** (0.012 mol) in dry benzene was taken and was refluxed for 6-8 h maintained dry condition by using Dean Stark apparatus. Solvent was removed by distillation, solid product obtained was washed with distilled water, dried and recrystallized in benzene : acetone (9:1). The reaction was monitored by TLC on silica gel using chloroform: methanol (9:1). % Yield = 67. IR (KBr, cm^{-1}): 3450 (NH), 3010, 2980 (C-H), 1627 (amide-I), 1547 (amide-II), 1226 (amide-III), 1355 (C-N), 1627 (-N=CH-), 1261 (C-F), 1748 (>C=O), 750(C-Cl). ^{1}H NMR ($CDCl_3$: DMSO d_6 δ, ppm): 8.3 (s, 1H, H_2), 8.1 (s, 1H, H_8), 7.8 (s, 1H, H_5), 3.75 (m, 1H, >N-CH-), 1.25-1.48 (m, 4H, cyclopropyl), 8.9 (s, 1H, >CO.NH), 7.3 (s, 1H, -N=CH-).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(benzal hydrazinyl)-carbonyl]quinoline (**5a**)

The mixture of compound **4a** (0.01 mol) and N-(2,3-dichlorophenyl)piperazine (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). IR (KBr, cm^{-1}): 3435 (NH), 3020, 2832 (C-H), 1625 (amide-I), 1567 (amide-II), 1220 (amide-III), 1361 (C-N), 1037 (C-N, piperazine), 1619 (-N=CH-), 1260 (C-F), 1741 (>C=O), 744 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.7 (s, 1H, H_2), 8.6 (s, 1H, H_8), 8.1 (s, 1H, H_5), 3.82 (m, 1H, >N-CH-), 1.11-1.53 (m, 4H, cyclopropyl), 8.88 (s, 1H, >CO.NH), 5.85 (s, 1H, -N=CH-), 2.65-2.95 (m, 8H, piperazine), 6.75-8.46 (m, 8H, Ar-H).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(4-methoxybenzal hydrazinyl)-carbonyl]quinoline **(5b)**

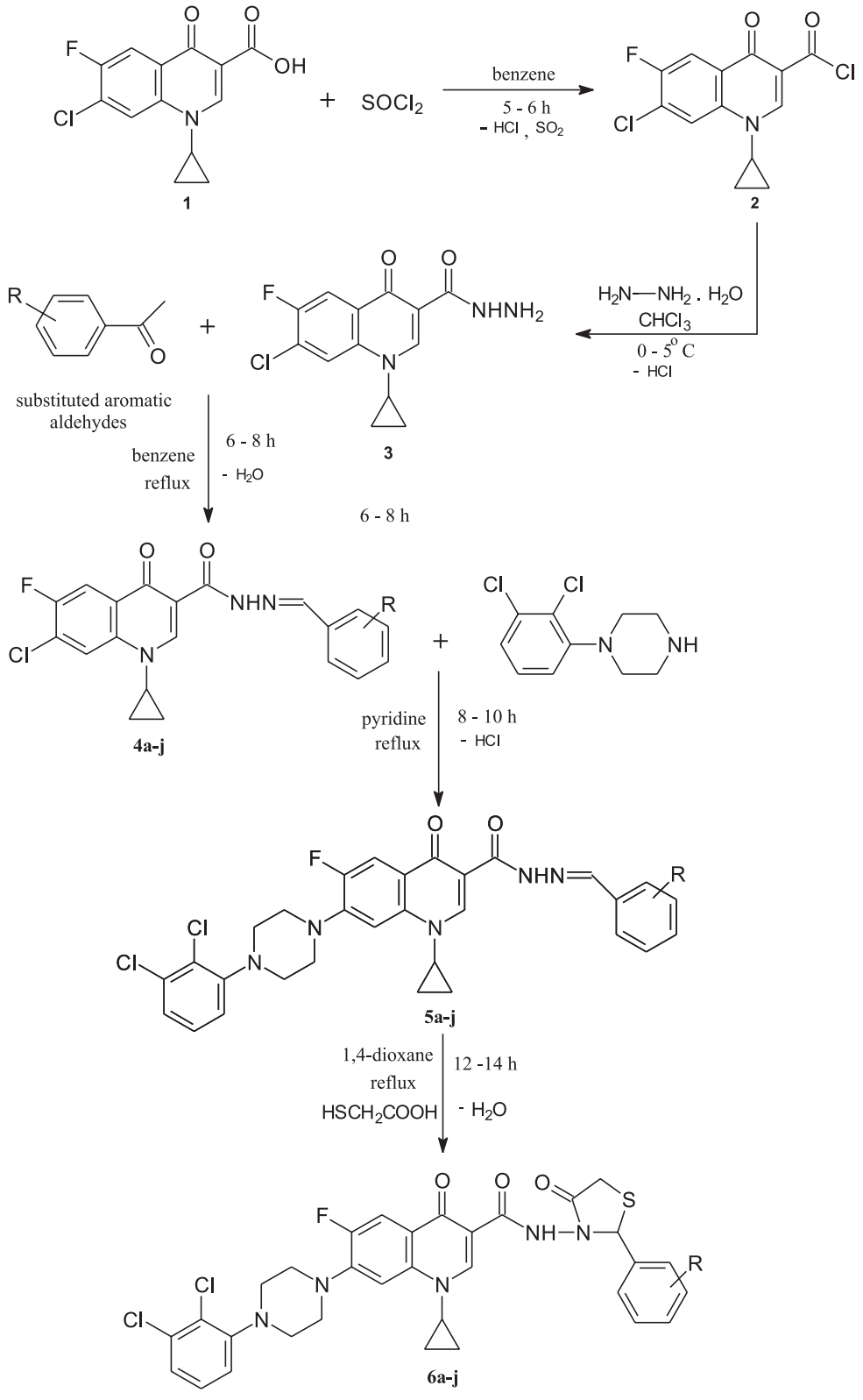
IR (KBr, cm^{-1}): 3452 (NH), 3010, 2825 (C-H), 1625 (amide-I), 1545 (amide-II), 1215 (amide-III), 1346 (C-N), 1035 (C-N, piperazine), 1610 (-N=CH-), 1258 (C-F), 1739 (>C=O), 747 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.56 (s, 1H, H_2), 8.35 (s, 1H, H_8), 8.11 (s, 1H, H_5), 3.35 (m, 1H, >N-CH-), 1.11-1.58 (m, 4H, cyclopropyl), 8.56 (s, 1H, >CO.NH), 7.47 (s, 1H, -N=CH-), 2.28-3.15 (m, 8H, piperazine), 6.66-8.35 (m, 7H, Ar-H), 4.1 (s, 3H, -OCH_3).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(2-hydroxy-4-methoxybenzal hydrazinyl)-carbonyl] quinoline **(5c)**

IR (KBr, cm^{-1}): 3440 (NH), 2915, 2825 (C-H), 1628 (amide-I), 1552 (amide-II), 1210 (amide-III), 1335 (C-N), 1041 (C-N, piperazine), 1609 (-N=CH-), 1245 (C-F), 1742 (>C=O), 3235 (O-H), 1025,1202 (C-O-C), 751 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.48 (s, 1H, H_2), 8.25 (s, 1H, H_8), 8.12 (s, 1H, H_5), 3.57 (m, 1H, >N-CH-), 1.11-1.63 (m, 4H, cyclopropyl), 8.37 (s, 1H, >CO.NH), 7.35 (s, 1H, -N=CH-), 1.97-2.93 (m, 8H, piperazine), 6.44-8.32 (m, 6H, Ar-H), 7.80 (s, 1H, -OH), 3.69 (s, 3H, -OCH_3).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(4-fluorobenzal hydrazinyl)-carbonyl]quinoline **(5d)**

IR (KBr, cm^{-1}): 3440 (NH), 2922, 2846 (C-H), 1628 (amide-I), 1540 (amide-II), 1218 (amide-III), 1352 (C-N), 1048 (C-N, piperazine), 1578 (-N=CH-), 1225, 1244 (C-F), 1737 (>C=O), 748 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.67 (s, 1H, H_2), 8.15 (s, 1H, H_8), 7.92 (s, 1H, H_5), 3.52 (m, 1H, >N-CH-), 1.00-1.62 (m, 4H, cyclopropyl), 8.47 (s, 1H,


benzene
5 - 6 h
- HCl , SO2
SOCl2
1
2
H2N—NH2 . H2O
CHCl3
0 - 5° C
- HCl
substituted aromatic aldehydes
benzene
reflux
6 - 8 h
- H2O
3
6 - 8 h
4a-j
pyridine
reflux
8 - 10 h
- HCl
5a-j
1,4-dioxane
reflux
HSCH2COOH
12 -14 h
- H2O
6a-j

Scheme 1

Table 1. Physical and analytical data of synthesized compounds

Compd.	R	Molecular Formula	M.p. (°C)	Yield %	C H N Analysis Calculated (found)		
					%C	%H	%N
5a	-H	$C_{30}H_{26}O_2N_5FCl_2$	315	61	62.29 (62.29)	04.53 (04.51)	12.11 (12.09)
5b	4-OCH_3	$C_{31}H_{28}O_3N_5FCl_2$	201	64	61.19 (61.17)	04.64 (04.68)	11.51 (11.54)
5c	4-OH, 3-OCH_3	$C_{31}H_{29}O_4N_5FCl_2$	235	59	59.53 (59.51)	04.67 (04.68)	11.20 (11.23)
5d	4-F	$C_{30}H_{25}O_2N_5F_2Cl_2$	273	58	60.41 (60.35)	04.22 (04.25)	11.74 (11.77)
5e	2-OH	$C_{30}H_{26}O_3N_5FCl_2$	197	65	60.61 (60.63)	04.41 (04.45)	11.78 (11.81)
5f	4-OH	$C_{30}H_{26}O_3N_5FCl_2$	301	62	60.61 (60.59)	04.41 (04.39)	11.78 (11.75)
5g	2-NO_2	$C_{30}H_{25}O_4N_6FCl_2$	239	69	57.79 (57.81)	04.04 (04.06)	13.48 (13.51)
5h	3-NO_2	$C_{30}H_{25}O_4N_6FCl_2$	267	61	57.79 (57.77)	04.04 (04.08)	13.48 (13.52)
5i	2-Cl	$C_{30}H_{25}O_3N_5FCl_3$	283	54	57.29 (57.29)	04.01 (04.03)	11.14 (11.17)
5j	4-Cl	$C_{30}H_{25}O_3N_5FCl_3$	296	57	57.29 (57.28)	04.01 (04.04)	11.14 (11.10)
6a	–H	$C_{32}H_{28}O_3N_5FCl_2S$	257	67	58.97 58.91	04.33 04.31	10.75 10.73
6b	4-OCH_3	$C_{33}H_{30}O_4N_5FCl_2S$	292	69	58.14 58.11	04.44 04.39	10.28 10.25
6c	4-OH, 3-OCH_3	$C_{33}H_{30}O_5N_5FCl_2S$	264	59	56.74 56.72	04.33 04.34	10.02 09.99
6d	4-F	$C_{33}H_{30}O_5N_5F_2Cl_2S$	297	58	57.39 57.32	04.07 04.09	10.46 10.48
6e	2-OH	$C_{32}H_{28}O_4N_5FCl_2S$	288	65	57.56 57.57	04.23 04.19	10.48 10.51
6f	4-OH	$C_{32}H_{28}O_4N_5FCl_2S$	223	62	57.49 57.52	04.22 04.24	10.50 10.47
6g	2-NO_2	$C_{32}H_{27}O_5N_6FCl_2S$	212	57	55.16 55.15	03.91 03.87	11.49 11.50
6h	3-NO_2	$C_{32}H_{27}O_5N_6FCl_2S$	245	61	55.16 55.12	03.91 03.90	11.49 11.48
6i	2-Cl	$C_{32}H_{27}O_3N_5FCl_3S$	296	69	56.05 56.04	03.97 03.93	11.22 11.20
6j	4-Cl	$C_{32}H_{27}O_3N_5FCl_3S$	247	59	56.05 56.08	03.97 03.92	11.22 11.20

>CO.NH), 7.25 (s, 1H, -N=CH-), 2.15-3.21 (m, 8H, piperazine), 6.43-8.22 (m, 7H, Ar-H).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(2-hydroxybenzal hydrazinyl)-carbonyl]quinoline **(5e)**

IR (KBr, cm^{-1}): 3452 (NH), 2925,2848 (C-H), 1625 (amide-I), 1535 (amide-II), 1209 (amide-III), 1347 (C-N), 1041 (C-N, piperazine), 1587 (-N=CH-), 1257 (C-F), 1748 (>C=O), 3225 (O-H), 748 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.42 (s, 1H, H_2), 8.32 (s, 1H, H_8), 7.75 (s, 1H, H_5), 3.68 (m, 1H, >N-CH-), 1.10-1.52 (m, 4H, cyclopropyl), 8.45 (s, 1H, >CO.NH), 7.29 (s, 1H, -N=CH-), 2.18-3.15 (m, 8H, piperazine), 6.35-8.20 (m, 7H, Ar-H), 7.77 (s, 1H, -OH).

Table 2. Antimicrobial activity of the synthesized compounds

Compd. no.	R	Minimum inhibitory concentration in µ/mL						
		Gram negative		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	4-OH, 3-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	200	200	250	250	1000	1000	>1000
5b	4-OCH_3	500	1000	1000	1000	500	1000	1000
5c	4-OH, 3-OCH_3	100	200	250	100	500	>1000	>1000
5d	4-F	500	500	500	500	250	500	500
5e	2-OH	500	1000	1000	1000	1000	1000	1000
5f	4-OH	100	200	500	500	100	500	1000
5g	2-NO_2	250	500	1000	1000	500	>1000	>1000
5h	3-NO_2	500	250	500	500	1000	500	500
5i	2-Cl	62.5	200	500	500	1000	1000	1000
5j	4-Cl	250	250	500	500	250	500	500
6a	-H	250	250	500	500	500	1000	1000
6b	4-OCH_3	500	500	250	500	1000	>1000	>1000
6c	4-OH, 3-OCH_3	100	150	200	250	1000	1000	1000
6d	4-F	500	500	1000	1000	1000	1000	1000
6e	2-OH	100	150	200	200	1000	1000	1000
6f	4-OH	100	150	200	200	500	1000	>1000
6g	2-NO_2	100	100	150	500	500	>1000	>1000
6h	3-NO_2	100	150	100	100	1000	500	500
6i	2-Cl	250	250	500	500	1000	1000	1000
6j	4-Cl	50	100	200	200	>1000	>1000	>1000
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
Griseofulvin		-	-	-	-	500	100	100

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(4-hydroxybenzal hydrazinyl)-carbonyl]quinoline **(5f)**

IR (KBr, cm^{-1}) 3433 (NH), 3022, 2845 (C-H), 1622 (amide-I), 1568 (amide-II), 1215 (amide-III), 1338 (C-N), 1058 (C-N piperazine), 1625 (-N=CH-), 1250 (C-F), 1745 (>C=O), 3235 (O-H), 758 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.75 (s, 1H, H_2), 8.56 (s, 1H, H_8), 8.05 (s, 1H, H_5), 3.77 (m, 1H, >N-CH-), 1.11-1.67 (m, 4H, cyclopropyl), 8.22 (s, 1H, >CO.NH), 7.56 (s, 1H, -N=CH-), 2.25-3.28 (m, 8H, piperazine), 6.22-8.25 (m, 7H, Ar-H), 7.67 (s, 1H, -OH).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(2-nitrobenzal hydrazinyl)-carbonyl]quinoline **(5g)**

IR (KBr, cm^{-1}): 3438 (NH), 2922, 2835 (C-H), 1625 (amide-I), 1525 (amide-II), 1215 (amide-III), 1335 (C-N), 1042 (C-N, piperazine), 1610 (-N=CH-), 1257 (C-F), 1742 (>C=O), 1342, 1562 (-NO_2 sym, asym), 756 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.78 (s, 1H, H_2), 8.25 (s, 1H, H_8), 8.19 (s, 1H, H_5), 3.52 (m, 1H, >N-CH-), 1.15-1.58 (m, 4H, cyclopropyl), 8.15 (s, 1H, >CO.NH), 7.45 (s, 1H, -N=CH-), 2.10-3.15 (m, 8H, piperazine), 6.27-8.25 (m, 7H, Ar-H).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(3-nitrobenzal hydrazinyl)-carbonyl]quinoline **(5h).**

IR (KBr, cm^{-1}): 3450 (NH), 3001, 2832 (C-H), 1648 (amide-I), 1541 (amide-II), 1237 (amide-III), 1351 (C-N), 1038 (C-N, piperazine), 1635 (-N=CH-), 1262 (C-F), 1734 (>C=O), 1360, 1525 (-NO_2 sym, asym), 759 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.57 (s, 1H, H_2), 8.26 (s, 1H, H_8), 7.87 (s, 1H, H_5), 3.77 (m, 1H, >N-CH-), 1.05-1.67 (m, 4H, cyclopropyl), 8.19 (s, 1H, >CO.NH), 7.77 (s, 1H, -N=CH-), 2.67-3.05 (m, 8H, piperazine), 6.22-8.39 (m, 7H, Ar-H).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(2-chlorobenzal hydrazinyl)-carbonyl]quinoline **(5i)**

IR (KBr, cm^{-1}): 3412 (NH), 3008, 2835 (C-H), 1629 (amide-I), 1533 (amide-II), 1223 (amide-III), 1358 (C-N), 1044 (C-N, piperazine), 1619 (-N=CH-), 1264 (C-F), 1734 (>C=O), 756, 744 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.42 (s, 1H, H_2), 8.22 (s, 1H, H_8), 7.82 (s, 1H, H_5), 3.67 (m, 1H, >N-CH-), 1.10-1.67 (m, 4H, cyclopropyl), 7.79 (s, 1H, >CO.NH), 7.54 (s, 1H, -N=CH-), 2.05-3.37 (m, 8H, piperazine), 6.15-8.25 (m, 7H, Ar-H).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-[N-(4-chlorobenzal hydrazinyl)-carbonyl]quinoline **(5j)**

IR (KBr, cm^{-1}): 3420 (NH), 3020, 2850 (C-H), 1629 (amide-I), 1528 (amide-II), 1232 (amide-III), 1351 (C-N), 1051 (C-N, piperazine), 1617 (-N=CH-), 1263 (C-F), 1753 (>C=O), 752, 744 (C-Cl); ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm) 8.45 (s, 1H, H_2), 8.34 (s, 1H, H_8), 7.77 (s, 1H, H_5), 3.52 (m, 1H, >N-CH-), 1.05-1.69 (m, 4H, cyclopropyl), 7.68 (s, 1H, >CO.NH), 7.25 (s, 1H, -N=CH-), 2.15-3.20 (m, 8H, piperazine), 6.28-8.25 (m, 7H, Ar-H).

2-Phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(2,3-dichlorophenyl)piperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones **(6a)**

The mixture of compound **5a** (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 into 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: ethyl acetate (9:1). IR (KBr, cm^{-1}): 3418 (NH), 3015, 2827 (C-H), 1619 (amide-I), 1561 (amide-II), 1205 (amide-III), 1348 (C-N), 1041 (C-N, piperazine), 1255 (C-F), 1735 (>C=O), 1717 (>C=O), 755 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.75 (s, 1H, H_2), 8.56 (s,1H, H_8), 8.19 (s, 1H, H_5), 3.37 (m, 1H, >N-CH-), 1.00-1.67 (m, 4H, Cyclopropyl), 8.67 (s, 1H, >CO.NH), 6.15 (s, 1H, -N-CH-), 3.68 (s, 2H, -CH_2-S), 2.15-3.23 (m, 8H, piperazine), 6.66-8.69 (m, 8H, Ar-H).

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

IR (KBr, cm^{-1}): 3441 (NH), 3015, 2835 (C-H), 1632 (amide-I), 1534 (amide-II), 1230 (amide-III), 1347 (C-N), 1046 (C-N, piperazine), 1265 (C-F), 1765 (>C=O), 1720 (>C=O), 741 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.5 (s, 1H, H_2), 8.3 (S, 1H, H_8), 8.1 (S, 1H, H_5), 3.5 (m, 1H, >N-CH-), 1.12-1.42 (m, 4H, cyclopropyl), 8.82 (s, 1H, >CO.NH), 5.82 (s, 1H, -N-CH-), 3.58 (s, 2H, -CH_2-S), 2.75-3.16 (m, 8H, piperazine), 6.75-8.22 (m, 7H, Ar-H), 3.85 (s, 3H, -OCH_3).

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

IR (KBr, cm^{-1}) 3452 (NH), 2915, 2816 (C-H), 1625 (amide-I), 1525 (amide-II), 1221 (amide-III),

1322 (C-N), 1052 (C-N, piperazine), 1235 (C-F), 1751 (>C=O), 1718 (>C=O), 1021,1208 (C-O-C), 3237 (O-H), 751 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.77 (s, 1H, H_2), 8.32 (s, 1H, H_8), 7.77 (s, 1H, H_5), 3.49 (m, 1H, >N-CH-), 1.11-1.63 (m, 4H, cyclopropyl), 8.42 (s, 1H, >CO.NH), 6.18 (s, 1H, -N-H-), 3.42 (s, 2H, -CH_2-S), 2.14-3.15 (m, 8H, piperazine), 6.34-8.58 (m, 7H, Ar-H), 7.52 (s, 1H, -OH), 4.11 (s, 3H, -OCH_3).

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

IR (KBr, cm^{-1}) 3451 (NH), 2910,2862 (C-H), 1630 (amide-I), 1542 (amide-II), 1210 (amide-III), 1357 (C-N), 1057 (C-N, piperazine), 1239 1262 (C-F), 1757 (>C=O), 1730 (>C=O), 741 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.61 (s, 1H, H_2), 8.29 (s, 1H, H_8), 8.02 (s, 1H, H_5), 3.77 (m, 1H, >N-CH-), 1.10-1.53 (m, 4H, cyclopropyl), 8.47 (s, 1H, >CO.NH), 6.02 (s, 1H, -N-CH-), 3.35 (s, 2H, -CH_2-S), 2.55-3.13 (m, 8H, piperazine), 6.43-8.22 (m, 7H, Ar-H).

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

IR (KBr, cm^{-1}) 3415 (NH), 2915, 2830 (C-H), 1620 (amide-I), 1522 (amide-II), 1210 (amide-III), 1350 (C-N), 1042 (C-N piperazine), 1257 (C-F), 1758 (>C=O), 1715 (>C=O), 3250 (O-H) 721 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.56 (s, 1H, H_2), 8.01 (s, 1H, H_8), 7.82 (s, 1H, H_5), 3.64 (m, 1H, >N-CH-), 1.05-1.49 (m, 4H, cyclopropyl), 8.42 (s, 1H, >CO.NH), 6.19 (s, 1H, -N-CH-), 3.97 (s, 2H, -CH_2-S), 2.15-3.15 (m, 8H, piperazine), 6.25-8.12 (m, 7H, Ar-H), 7.47 (s, 1H, -OH).

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

IR (KBr, cm^{-1}) 3422 (NH), 3022, 2845 (C-H), 1629 (amide-I), 1534 (amide-II), 1224 (amide-III), 1353 (C-N), 1034 (C-N piperazine), 1263 (C-F), 1734 (>C=O), 1718 (>C=O), 3250 (O-H), 744 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.78 (s, 1H, H_2), 8.62 (s, 1H, H_8), 7.81 (s, 1H, H_5), 3.35 (m, 1H, >N-CH-), 1.11-1.67 (m, 4H, cyclopropyl), 8.35 (s, 1H, >CO.NH), 6.12 (s, 1H, -N-CH-), 3.75 (s, 2H, -CH_2-S), 2.05-3.10 (m, 8H, pipreazine), 6.13-8.12 (m, 7H, Ar-H), 7.77 (s, 1H, -OH).

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

IR (KBr, cm^{-1}) 3546 (NH), 2990, 2867 (C-H), 1625 (amide-I), 1533 (amide-II), 1227 (amide-III), 1358 (C-N), 1038 (C-N, piperazine), 1257 (C-F), 1734 (>C=O), 1712 (>C=O), 1355, 1515 (-NO_2 sym, asym), 777 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.52 (s, 1H, H_2), 8.15 (s, 1H, H_8), 7.92 (s, 1H, H_5), 3.67 (m, 1H, >N-CH-), 1.11-1.57 (m, 4H, cyclopropyl), 8.22 (s, 1H, >CO.NH), 6.08 (s, 1H, -N-CH-), 3.57 (s, 2H, -CH_2-S), 2.01-2.96 (m, 8H, piperzine), 6.37-8.22 (m, 7H, Ar-H).

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

IR (KBr, cm^{-1}): 3431 (NH), 2915, 2825 (C-H), 1625 (amide-I), 1525 (amide-II), 1210 (amide-III), 1325 (C-N), 1051 (C-N, piperazine), 1252 (C-F), 1752 (>C=O), 1720 (>C=O), 1345, 1535 (-NO_2 sym, asym) 745 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.65 (s, 1H, H_2), 8.21 (s, 1H, H_8), 8.11 (s, 1H, H_5), 3.62 (m, 1H, >N-CH-), 1.05-1.68 (m, 4H, cyclopropyl), 8.12 (s, 1H, >CO.NH), 6.15 (s, 1H, -N-CH-), 3.62 (s, 2H, -CH_2-S), 2.08-3.11 (m, 8H, piperazine), 6.29 – 8.11 (m, 7H, Ar-H).

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

IR (KBr, cm^{-1}): 3422 (NH), 3015, 2845 (C-H), 1630 (amide-I), 1537 (amide-II), 1219 (amide-III), 1348 (C-N), 1047 (C-N, piperazine), 1261 (C-F), 1754 (>C=O), 1719 (>C=O), 761, 739 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.52 (s, 1H, H_2), 8.22 (s, 1H, H_8), 7.85 (s, 1H, H_5), 3.37 (m, 1H, >N-CH-), 1.11-1.67 (m, 4H, cyclopropyl), 7.85 (s, 1H, >CO.NH), 6.62 (s, 1H, -N-CH-), 3.77 (s, 2H, -CH_2-S), 2.10-3.19 (m, 8H, piperazine), 6.47-8.32 (m, 7H, Ar-H).

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

IR (KBr, cm^{-1}) 3447 (NH), 2925, 2840 (C-H), 1610 (amide-I), 1528 (amide-II), 1232 (amide-III), 1351 (C-N), 1041 (C-N, piperazine), 1261 (C-F), 1745 (>C=O), 1718 (>C=O), 763, 736 (C-Cl). ^{1}H-NMR ($CDCl_3$: DMSO d_6, δ, ppm): 8.71 (s, 1H, H_2),

8.31 (s, 1H, H_8), 8.08 (s, 1H, H_5), 3.62 (m, 1H, >N-CH-), 1.10-1.68 (m, 4H, cyclopropyl), 7.77 (s, 1H, >CO.NH), 6.11 (s, 1H, -N-CH-), 3.67 (s, 2H, -CH_2-S), 1.77-3.11 (m, 8H, piperazine), 6.42-8.20 (3, 7H, Ar-H).

Antimicrobial activity

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram positive bacteria *S. aureus* MTCC – 96*, S. pyogenes* MTCC – 443 and two Gram negative bacteria *E. coli* MTCC – 442*, P. aeruginosa* MTCC – 441 and fungi *C. albicans* MTCC – 227, *A. niger* MTCC – 282 and *A. clavatus* MTCC – 1323 organisms taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The strains were procured from Institute of Microbial Technology; Chandigarh (India). Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a diluent which not effected the growth of microbes.

RESULTS

Schiff base **(5a-j)**, prepared from the 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid **1,** on cyclization with thioglycolic acid potent thiazolidinones **(6a-j)** were synthesized. The whole conversion of compounds from **1** to **3**, **4a-j**, **5a-j** and **6a-j** is presented in Scheme 1. Physical data of **5a-j** and **6a-j** are given in Table 1. The structures of synthesized compounds **5a-j** and **6a-j** were confirmed by the ^{1}H-NMR and IR spectral data. The MIC values in µ/mL of the synthesized compounds are presented in Table 2.

DISCUSSION AND CONCLUSION

From the screening results, lead molecule **1** was found as potent as ampicillin against all the bacteria. Hydrazide **3** of compound **1** showed poor activity against all bacteria. Schiff base **4i** (R = 2-Cl) showed excellent activity when compared with ampicillin and chloramphenicol; while **5c**, **5f** and **5i** (4-OH, 3-OCH_3, 4-OH, 2-Cl) demonstrated good activity against *E. coli* and **4i** (R = 2-Cl) showed significant activity against *P. aeruginosa*; while **4c**, **4g**, **4i**, **5a** and **5c** (R = 4-OH, 3-OCH_3, 2-NO_2, -H and 4-OH, 3-OCH_3) showed good activity against *S. aureus* and **4i** and **5c** (R = 2-Cl and 4-OH and 3-OCH_3) demonstrated significant activity against *S. pyogenes* when compared with standard drug ampicillin.

The cyclized thiazolidinone **6j** (R = 4-Cl) was found equipotent to chloramphenicol. **6c**, **6e**, **6f**, **6g**, **6h** and **6j** (R = 4-OH, 3-OCH_3, 2-OH, 4-OH, 2-NO_2, 3-NO_2, 4-Cl) showed good activity against *E. coli*; while **6g** and **6j** (R = 2-NO_2 and 4-Cl) demonstrated significant activity against *P. aeruginosa*. **6b**, **6c**, **6e**, **6f**, **6g**, **6h** and **6j** (R = 4-OCH_3, 4-OH, 3-OCH_3, 2-OH, 4-OH, 2-NO_2, 3-NO_2 and 4-Cl) were found significantly active against *S. aureus* and **6h** (R = 3-NO_2) showed good activity against *S. pyogenes* when compared with standard drug ampicillin.

From the MIC results of fungal activity, the lead molecule and hydrazide demonstrated good activity against *C. albicans*. Schiff bases **4c** and **5f** (R = 4-OH, 3-OCH_3 and 4-OH) were found equipotent to nystatin; while **4a**, **4b**, **4c**, **4e**, **4f**, **4g**, **5b**, **5c**, **5d**, **5f**, **5g** and **5j** (R = -H, -OCH_3, 4-OH, 3-OCH_3, 2-OH, 4-OH, 2-NO_2, 4-OCH_3, 4-OH, 3-OCH_3, 4-F, 4-OH, 2-NO_2) demonstrated significant activity. The thiazolidinones **6a**, **6f** and **6g** (R = -H, 4-OH and 3-NO_2) demonstrated good activity against *C. albicans* when compared with greseofulvin. All remaining compounds demonstrated good to moderate activity against remaining fungal species.

Overall conclusions made for synthesized compounds are that most of the compounds were more active against *E. coli* and *S. aureus*. Most of the compounds were found equipotent to ampicillin and found less active than other standard drugs. Most of the compounds demonstrated antifungal activity for *C. albicans* similar to that of greseofulvin, found less active than other standard drugs and for other fungal species. In general, thiazolidinones demonstrated better antibacterial activity than Schiff bases and Schiff bases demonstrated comparatively good antifungal activity as thiazolidinones with some exception in both the cases. Especially, compounds **4i**, **5i** and **6j** (2-Cl, 2-Cl and 4-Cl) demonstrated excellent activity with reference to ampicillin.

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