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Synthesis of amide derivatives of quinolone and their antimicrobial studies

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A series of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[chloro/1-piperazinyl/4-methyl-1-piperazinyl/4-ethyl-1-piperazinyl/ 4-hydroxyethyl-1-piperazinyl/imidazolyl/morpholinyl]-3[*N*-(substituted phenyl amino) carbonyl]quinoline **5-11a-j** have been prepared by using substituted arylamine at C-3 position and 1-piperazine/4-methyl-1-piperazine/4-ethyl-1-piperazine/4-hydroxyethyl-1-piperazine/imidazole/morpholine at C-7 position of newly synthesized quinolone **3**. Biological profile like antibacterial activity against four different strain *viz. S. aureus* and *B. subtilis* (gram-positive bacteria) and *E. coli* and *P. aeruginosa* (gram-negative bacteria) and *C. albicans* (fungi) by cup plate method have been studied.

Keywords: Amide, antimicrobial activity, cyclopropyl, imidazole, morpholine, piperazine, quinolone

IPC: Int.Cl.[8] C07D

Heterocyclic compounds have different types of pharmacological properties in which fluoroquinolones are most widely useful as antibacerial agents. Several quinolones are released in clinical world, which are ciprofloxacin, pefloxacin, levofloxacin, norfloxacin, ofloxacin, enoxacin, lomefloxacin, sparfloxacin *etc*. which are widely used in the treatment of conjuctivitis and other opthalmological diseases like gonorrhea and syphilis. Structure activity relationships (SAR) for quinolones have confirmed that the 7-position is largely responsible for the controlling the spectrum of antibacterial activity.

Several methods have been reported for the synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylicacid **3** (ref. 1-7). The method of Srinivasu *et al.*[8] for the synthesis of **3** via 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylate **2 (Scheme I)** has been modified and used for amide derivatives to study their biological activities.

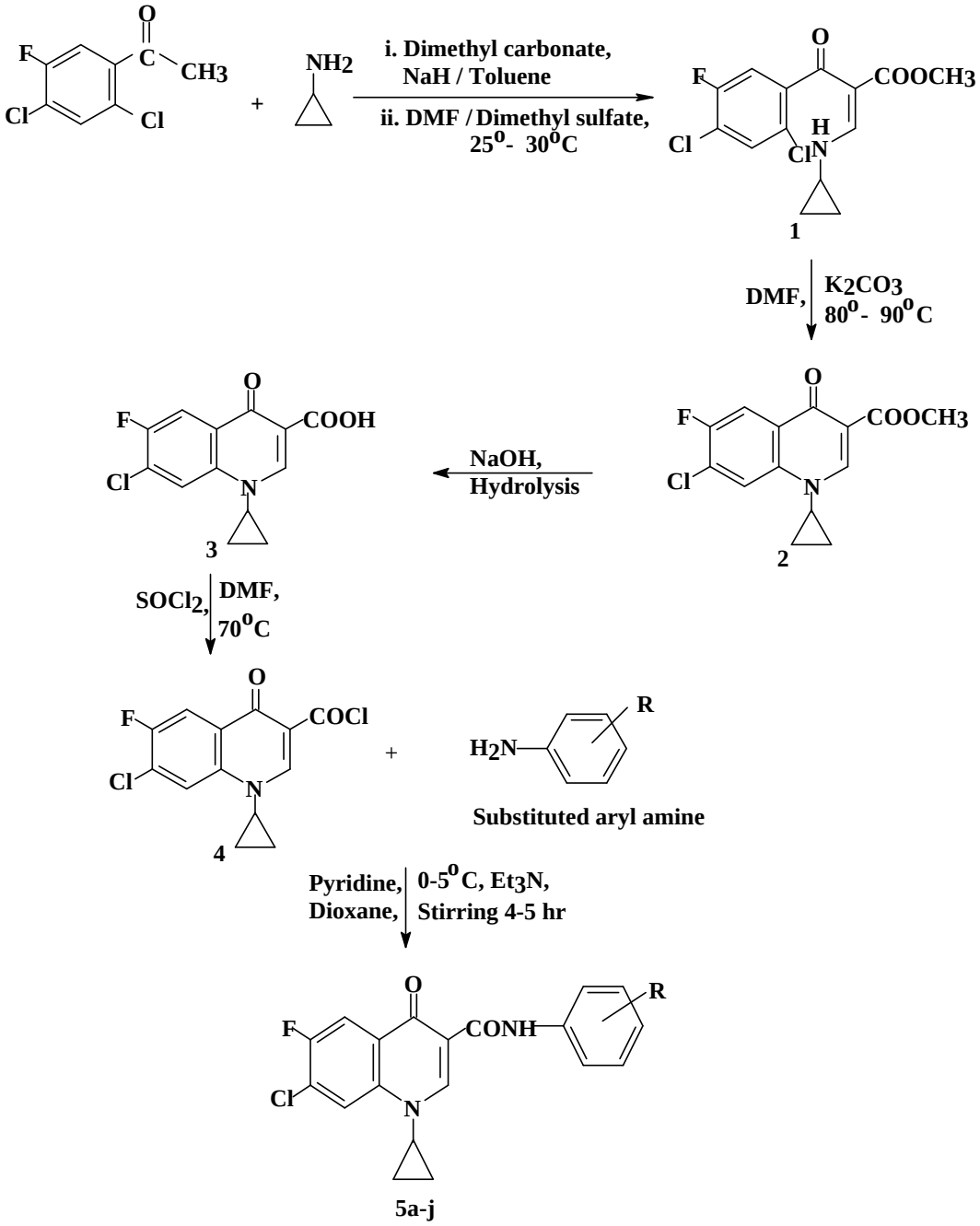
Literature survey of quinolone reveals that the several research workers[2,9,10] have studied antibacterial activity of quinolones substituted with piperazine at C-7 and carboxylic acid group at C-3 position. In addition to reports on compounds containing amide linkage at C-3 and their microbial study[11,12], we have synthesized 70 amide derivatives **(Scheme II**, **Table I)** of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid with ten different arylamines at C-3 and variation of 1-piperazine, 4-methyl-1-piperazine, 4-ethyl-1-piperazine, 4-hydroxyethyl-1-piperazine, imidazole, morpholine at C-7 position, to elaborate the SAR study. These compounds are identified from their IR and ^{1}H NMR spectra (**Table II**)

Results and Discussion

Minimum inhibitory concentration (MIC) for all the synthesized compounds have been tested against gram-positive bacteria *viz. B. subtilis* & *S. aureus* and gram-negative *viz. E. coli* & *P. aeruginosa* by cup plate method[13,14] using DMF as solvent at 100 µg/mL concentration in comparison with standard drug amofax, ofloxacin and tetracycline. The results of activity are summarized in **Table III**.

The compounds **5b**,**d**,**e**,**h**, **6a**, **8a**,**e**,**g**, **9f**,**j**, **10g**,**i**,**j**, **11d**,**g** reflected significant antibacterial activity against *B. subtilis* and compounds **5b**,**d**,**e**,**h**, **6a**,**d**, **7e**, **8e**, **9e**, **10e**, **11e** showed significant antibacterial activity against *S. aureus*. The compounds **6j**, **8j**, **10b**, exhibited better antibacterial activity against *E. coli*, whereas no significant activity was observed against *P. aeruginosa*. Other compounds exhibited moderate to least actions against both species.

No significant antifungal activity was reflected by the prepared compounds. In general, the compounds were found to possess better bactericidal and not the fungicidal properties.



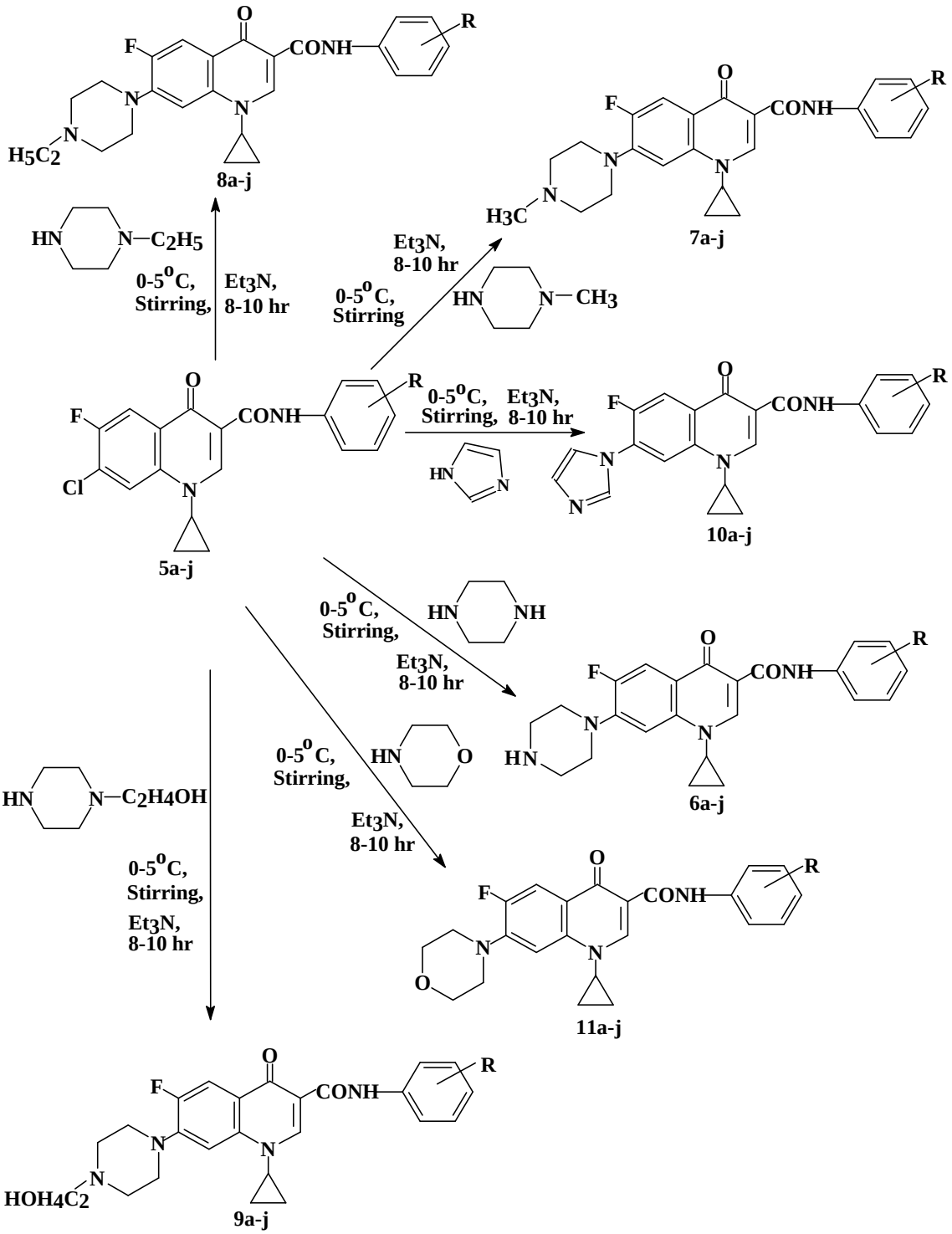
Scheme I

Experimental Section

3-Cyclopropylaminomethylene-2-(2,4-dichloro-5-fluorobenzoyl)carboxylate 1. Compound **1** was prepared in following two steps **A** and **B**.

Step A. To a mixture of 1.2 liter toluene and dimethyl carbonate (10 g) added sodium hydride (4 g) and carefully heated at 70-72°C under N_2 atmosphere, then 2,4 dichloro-5-fluoro acetophenone (0.5 mole) in toluene was added in at 70-80°C and forwarded the reaction for more 3 hr. The reaction was allowed to cool at 20°C. The compound was checked by TLC on silica gel using mobile phase, chloroform and methanol; 50:50, UV-V is at 254 nm.

Step B. **Dimethyl sulphate and dimethyl-formamide complex**. In a dry flask, dimethyl formamide (25 mL) and dimethyl sulphate (10 g) was added at 55 -60°C during 1 hr. The temperature was maintained 60-65°C for 3 hr and cooled to 20°C.



Scheme II

After completion of **A** and **B**, **B** was added into **A** at 25-30°C during 1-3 hr and the temp. was maintained at 33-35°C for 3 hr. The reaction was checked by TLC on silica gel, UV-Vis is 254 nm. Water (500 mL) was added with continuous stirring of the mixture and the *p*H was adjusted to 7 by acetic acid and the toluene (about 50%) was distilled out, cooled to 5°C. Cyclopropyl amine (25 g, 0.43 mole) mixture in toluene was added at 5-10°C, the temperature was raised to 15-20°C in 3 hr duration, purity was checked by TLC on silica gel, UV-Vis is 254 nm. The product was cooled 5°C, filtered and washed with toluene, m.p. 151°C.

Table I— Characterization data of **5 - 11a-j**

Compd	R	Mol. formula	m.p. °C	Yield (%)	Found (required) %		
					C	H	N
5a	H	$C_{19}H_{13}O_2N_2ClF$	208	78	63.96 (64.04	3.95 4.02	7.86 7.96)
5b	*o*- CH_3	$C_{20}H_{15}O_2N_2F$	240	79	64.84 (64.86	4.35 4.44	7.86 7.68)
5c	*m*- CH_3	$C_{20}H_{15}O_2N_2F$	246	76	64.87 (64.86	4.35 4.46	7.56 7.64)
5d	*p*- CH_3	$C_{20}H_{15}O_2N_2F$	221	72	64.89 (64.86	4.35 4.48	7.56 7.69)
5e	*o*- OCH_3	$C_{20}H_{15}O_3N_2F$	230	68	62.20 (62.17	4.17 4.28	7.25 7.36)
5f	*p*- OCH_3	$C_{20}H_{15}O_3N_2F$	212	70	62.22 (62.17	4.17 4.26	7.25 7.38)
5g	*o*- Cl	$C_{19}H_{12}O_2N_2ClF$	216	69	58.45 (58.38	3.35 3.46	7.17 7.28)
5h	*m*-Cl	$C_{19}H_{12}O_2N_2ClF$	209	64	58.41 (58.38	3.35 3.39	7.17 7.24)
5i	*o*-NO_2	$C_{19}H_{12}O_4N_3ClF$	196	58	56.91 (56.85	3.26 3.40	10.46 10.59)
5j	*p*-NO_2	$C_{19}H_{12}O_4N_3ClF$	226	63	56.89 (56.85	3.26 3.38	10.47 10.57)
6a	H	$C_{23}H_{22}O_2N_4F$	201	74	67.08 (68.14	5.70 5.81	13.90 13.82)
6b	*o*- CH_3	$C_{24}H_{24}O_2N_4F$	210	72	68.68 (68.73	5.99 6.13	13.45 13.36)
6c	*m*- CH_3	$C_{24}H_{24}O_2N_4F$	204	78	68.64 (68.73	5.99 6.08	13.42 13.36)
6d	*p*- CH_3	$C_{24}H_{24}O_2N_4F$	224	70	68.69 (66.73	5.99 6.16	13.40 13.36)
6e	*o*- OCH_3	$C_{24}H_{24}O_3N_4F$	198	75	66.18 (66.20	5.77 5.89	12.96 12.87)
6f	*p*- OCH_3	$C_{24}H_{24}O_3N_4F$	208	72	66.15 (66.20	5.77 5.87	12.90 12.87)
6g	*o*- Cl	$C_{23}H_{21}O_2N_4FCl$	236	68	62.75 (62.79	5.03 5.15	12.84 12.74)
6h	*m*-Cl	$C_{23}H_{21}O_2N_4FCl$	226	66	62.80 (62.79	5.03 5.16	12.81 12.74)
6i	*o*-NO_2	$C_{23}H_{21}O_4N_5F$	204	56	61.29 (61.33	4.91 5.03	15.64 15.85)
6j	p-NO_2	$C_{23}H_{21}O_4N_5F$	216	52	61.32 (61.33	4.91 5.01	15.62 15.85)
7a	H	$C_{24}H_{24}O_2N_4F$	216	63	68.66 (68.73	5.99 6.11	13.45 13.36)
7b	*o*- CH_3	$C_{25}H_{26}O_2N_4F$	240	71	69.19 (69.28	6.26 6.39	12.98 12.93)
7c	*m*- CH_3	$C_{25}H_{26}O_2N_4F$	258	68	69.21 (69.28	6.26 6.37	12.99 12.93)
7d	p- CH_3	$C_{25}H_{26}O_2N_4F$	208	76	69.24 (69.28	6.26 6.41	13.02 12.93)

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Table I— Characterization data of **5 - 11a-j**—*Contd*

Compd	R	Mol. formula	m.p. °C	Yield (%)	Found (required) %		
					C	H	N
7e	*o*- OCH_3	$C_{25}H_{26}O_3N_4F$	218	68	66.76 (66.81	6.04 6.16	12.56 12.47)
7f	*p*- OCH_3	$C_{25}H_{26}O_3N_4F$	210	67	66.74 (66.81	6.04 6.10	12.69 12.47)
7g	*o*- Cl	$C_{24}H_{23}O_2N_4FCl$	226	65	63.45 (63.53	5.32 5.41	12.46 12.34)
7h	*m*-Cl	$C_{24}H_{23}O_2N_4FCl$	214	63	63.49 (63.53	5.32 5.44	12.41 12.34)
7i	*o*-NO_2	$C_{24}H_{23}O_4N_5F$	212	55	62.05 (62.06	5.20 5.33	15.16 15.08)
7j	*p*-NO_2	$C_{24}H_{23}O_4N_5F$	248	59	61.99 (62.06	5.20 5.35	15.15 15.08)
8a	H	$C_{25}H_{26}O_2N_4F$	232	65	69.21 (69.28	6.26 6.36	12.98 12.93)
8b	*o*- CH_3	$C_{26}H_{28}O_2N_4F$	280	73	69.69 (69.79	6.52 6.62	12.60 12.52)
8c	*m*- CH_3	$C_{26}H_{28}O_2N_4F$	256	70	69.74 (69.79	6.52 6.59	12.58 12.52)
8d	*p*- CH_3	$C_{26}H_{28}O_2N_4F$	310	76	69.72 (69.79	6.52 6.66	12.63 12.52)
8e	*o*- OCH_3	$C_{26}H_{28}O_3N_4F$	210	68	67.32 (67.38	6.29 6.40	12.15 12.09)
8f	*p*- OCH_3	$C_{26}H_{28}O_3N_4F$	232	63	67.34 (67.38	6.29 6.42	12.19 12.09)
8g	*o*- Cl	$C_{25}H_{25}O_3N_4FCl$	208	64	64.14 (64.17	5.59 5.73	12.04 11.97)
8h	*m*-Cl	$C_{25}H_{25}O_3N_4FCl$	245	62	64.12 (64.17	5.59 5.70	12.06 11.97)
8i	*o*-NO_2	$C_{25}H_{24}O_4N_5F$	202	58	62.76 (62.76	5.46 5.59	14.71 14.64)
8j	*p*-NO_2	$C_{25}H_{24}O_4N_5F$	232	61	62.72 (62.76	5.46 5.57	14.73 14.64)
9a	H	$C_{25}H_{26}O_3N_4F$	220	63	69.43 (69.81	6.04 6.14	12.54 12.47)
9b	*o*- CH_3	$C_{26}H_{28}O_3N_4F$	236	71	67.32 (67.38	6.29 6.39	12.17 12.09)
9c	*m*- CH_3	$C_{26}H_{28}O_3N_4F$	204	75	67.29 (67.38	6.29 6.37	12.15 12.09)
9d	*p*- CH_3	$C_{26}H_{28}O_3N_4F$	306	70	67.31 (67.38	6.29 6.42	12.14 12.09)
9e	*o*- OCH_3	$C_{26}H_{28}O_4N_4F$	310	68	65.08 (65.13	6.08 6.18	11.76 11.69)
9f	*p*- OCH_3	$C_{26}H_{28}O_4N_4F$	262	66	64.11 (65.13	6.08 6.16	11.79 11.69)
9g	*o*- Cl	$C_{25}H_{25}O_3N_4FCl$	266	71	61.81 (62.04	5.40 5.51	11.67 11.58)
9h	*m*-Cl	$C_{25}H_{25}O_3N_4FCl$	296	69	61.02 (62.04	5.40 5.49	11.64 11.58)

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Table I— Characterization data of **5 - 11a-j**—*Contd*

Compd	R	Mol. formula	m.p. °C	Yield (%)	Found (required) % C	H	N
9i	*o*-NO_2	$C_{25}H_{25}O_5N_5F$	160	56	60.01 (60.72	5.29 5.39	14.27 14.17)
9j	*p*-NO_2	$C_{25}H_{25}O_5N_5F$	192	61	59.90 (60.72	5.29 5.38	14.22 14.17)
10a	H	$C_{22}H_{16}O_2N_2F$	202	63	73.50 (73.53	4.42 4.50	7.58 7.79)
10b	*o*- CH_3	$C_{23}H_{18}O_2N_2F$	230	71	71.25 (71.31	4.77 4.90	7.42 7.50)
10c	*m*- CH_3	$C_{23}H_{18}O_2N_2F$	278	69	71.29 (71.31	4.77 4.88	7.52 7.50)
10d	*p*- CH_3	$C_{23}H_{18}O_2N_2F$	216	70	71.25 (71.31	4.77 4.86	7.48 7.50)
10e	*o*- OCH_3	$C_{23}H_{18}O_3N_2F$	258	65	68.25 (68.38	4.59 4.70	7.16 7.19)
10f	*p*- OCH_3	$C_{23}H_{18}O_3N_2F$	208	61	68.11 (68.38	4.59 4.73	7.19 7.19)
10g	o- Cl	$C_{22}H_{15}O_2N_2FCl$	242	58	67.10 (67.09	3.82 3.93	7.10 7.01)
10h	*m*-Cl	$C_{22}H_{15}O_2N_2FCl$	230	66	67.00 (67.09	3.82 3.89	7.11 7.01)
10i	*o*-NO_2	$C_{22}H_{15}O_4N_3F$	208	60	65.28 (65.34	3.73 3.82	6.77 6.93)
10j	*p*-NO_2	$C_{22}H_{15}O_4N_3F$	214	55	65.30 (65.34	3.73 3.89	6.80 6.93)
11a	H	$C_{23}H_{21}O_3N_3F$	198	70	67.91 (67.78	5.44 5.53	10.41 10.34)
11b	*o*- CH_3	$C_{24}H_{23}O_3N_3F$	206	68	68.49 (68.57	5.74 5.87	10.06 10.00)
11c	*m*- CH_3	$C_{24}H_{23}O_3N_3F$	218	66	68.48 (68.57	5.74 5.85	10.09 10.00)
11d	*p*- CH_3	$C_{24}H_{23}O_3N_3F$	206	72	68.53 (68.57	5.74 5.84	10.12 10.00)
11e	*o*- OCH_3	$C_{24}H_{23}O_4N_3F$	210	68	65.99 (66.05	5.53 5.64	9.73 9.63)
11f	*p*- OCH_3	$C_{24}H_{23}O_4N_3F$	218	69	65.97 (66.05	5.53 5.62	9.71 9.63)
11g	*o*- Cl	$C_{23}H_{20}O_3N_3FCl$	230	66	62.66 (62.65	4.79 4.94	9.65 9.53)
11h	*m*-Cl	$C_{23}H_{20}O_3N_3FCl$	246	70	62.64 (62.66	4.79 4.92	9.64 9.53)
11i	*o*-NO_2	$C_{23}H_{20}O_5N_4F$	298	61	61.19 (61.15	4.68 4.82	12.49 12.41)
11j	*p*-NO_2	$C_{23}H_{20}O_5N_4F$	288	64	61.17 (61.15	4.68 4.80	12.50 12.41)

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylate 2. A mixture of 1, 10 g (0.05 mole), DMF (25 mL) and potassium carbonate (2 g), was refluxed on a heating mental to 95-110°C about 3 hr. DMF was distilled out below 80°C by vacuum. The *p*H 7 was adjusted by acetic acid, filtered and washed with water. The compound was checked by TLC on silica gel using mobile phase chloroform and methanol (50:50), UV-Vis is at 254 nm, m.p. 256°C, yield: 92%.

Table II—Spectral data

Compd	IR (cm^{-1})	^1H NMR (δ, ppm)
3	3440 (-OH), 3040 (cyclopropyl), 2936, 2830 (-CH), 1730 (-COOH), 1330 (C-N), 1260 (C-F), 750 (C-Cl)	8.61 (s, 1H, H_2), 8.44 (d, 1H, H_8), 8.15 (d, 1H, H_5), 3.85 (m, 1H, >N-CH-), 1.16-1.33 (m, 4H, cyclopropyl)
5a	3180 (N-H), 2940, 2820 (-CH), 1680 (amide-I), 1540 (amide-II), 1350 (C-N), 1260 (C-F), 1230 (amide-III), 760 (C-Cl)	9.22 (s, 1H, -CONH-), 8.70 (s, 1H, H_2), 8.48 (d, 1H, H_8), 8.15 (d, 1H, H_5), 7.30-7.91 (m, 5H, Ar-H), 3.81 (m, 1H, >N-CH-), 1.13-1.35 (m, 4H, cyclopropyl)
6j	3440 (N-H), 2930, 2860 (-CH), 1630 (amide-I), 1550 (amide-II), 1480, 1310 (N=O), 1350 (C-N), 1260 (C-F), 1240 (amide-III), 1040 (C-N piperazine) 760 (C-Cl)	9.78 (s, 1H, -CONH-), 8.75 (s, 1H, H_2), 8.35 (d, 1H, H_8), 8.13 (d, 1H, H_5), 6.85-7.84 (m, 4H, Ar-H), 3.82 (m, 1H, >N-CH-), 2.51-3.06 (m, 9H, piperazine), 1.18-1.38 (m, 4H, cyclopropyl)
7d	3440 (N-H), 2950, 2840 (-CH), 1670 (amide-I), 1550 (amide-II), 1340 (C-N), 1260 (C-F), 1230 (amide-III), 1040 (C-N piperazine)	9.62 (s, 1H, -CONH-), 8.70 (s, 1H, H_2), 8.50 (d, 1H, H_8), 8.20 (d, 1H, H_5), 7.30-7.81 (m, 4H, Ar-H), 3.89 (m, 1H, >N-CH-), 2.52-3.35 (m, 8H, piperazine), 1.13-1.43 (m, 4H, cyclopropyl)
8f	3440 (N-H), 2930, 2840 (-CH), 1680 (amide-I), 1550 (amide-II), 1340 (C-N), 1260 (C-F), 1240 (amide-III), 1240-1030 (C-O-C), 1080 (C-N piperazine)	9.27 (s, 1H, -CONH-), 8.75 (s, 1H, H_2), 8.35 (d, 1H, H_8), 8.12 (d, 1H, H_5), 6.92-7.70 (m, 4H, Ar-H), 4.23 (m, 1H, >N-CH-), 3.91 (s, 3H, $-OCH_3$), 2.52-3.40 (m, 8H, piperazine), 1.12-1.32 (m, 4H, cyclopropyl)
9e	3400 (N-H), 2950, 2840 (-CH), 1680 (amide-I), 1540 (amide-II), 1340 (C-N), 1270 (C-F), 1230 (amide-III), 1230-1030 (C-O-C), 1070 (C-N piperazine)	9.68 (s, 1H, -CONH-), 8.75 (s, 1H, H_2), 8.38 (d, 1H, H_8), 8.18 (d, 1H, H_5), 7.30-7.89 (m, 4H, Ar-H), 3.82 (m, 1H, >N-CH-), 3.65 (s, 3H, $-OCH_3$), 2.50-3.25 (m, 8H, piperazine), 1.12-1.27 (m, 4H, cyclopropyl)
10h	3400 (N-H), 2960, 2840 (-CH), 1680 (amide-I), 1540 (amide-II), 1340 (C-N), 1260 (C-F), 1230 (amide-III), 1100 (C-N imidazole), 810 (C-Cl)	9.16 (s, 1H, -CONH-), 8.78 (s, 1H, H_2), 8.32 (d, 1H, H_8), 8.09 (d, 1H, H_5), 7.28-7.90 (m, 7H, Ar-H, imidazole), 4.10 (m, 1H, >N-CH-), 1.18-1.36 (m, 4H, cyclopropyl)

Table III—Characterization data of **5-11a-j**

Compd	R	Antibacterial activity (Zone of inhibition in mm) 100μg/mL				Antifungal activity (Zone of inhibition in mm) 100μg/mL
		Gram-positive		Gram-negative		Fungi
		S. aureus	*B. subtlis*	*E. coli*	*P. aeruginosa*	*S. aureus*
5a	H	14	13	8	7	7
5b	*o*- CH_3	17	18	11	8	8
5c	*m*- CH_3	12	10	9	7	7
5d	*p*- CH_3	20	20	8	7	8
5e	*o*- OCH_3	20	19	7	8	7
5f	*p*- OCH_3	13	14	9	9	8
5g	*o*- Cl	14	12	8	7	7
5h	*m*-Cl	18	19	7	7	9
5i	*o*-NO_2	14	15	7	9	8
5j	*p*-NO_2	12	13	8	8	8
6a	H	13	12	8	7	7
6b	o- CH_3	7	11	7	7	7
6c	*m*- CH_3	12	9	9	8	8
6d	*p*- CH_3	13	8	9	7	8
6e	*o*- OCH_3	9	13	9	8	7
6f	*p*- OCH_3	8	13	8	7	7
6g	*o*- Cl	7	12	9	7	7
6h	*m*-Cl	12	9	8	7	8
6i	*o*-NO_2	8	12	8	8	7
6j	p-NO_2	7	8	12	8	7
7a	H	8	9	9	7	7
7b	*o*- CH_3	9	8	8	8	8
7c	*m*- CH_3	7	13	13	7	8
7d	*p*- CH_3	7	9	7	8	8
7e	*o*- OCH_3	13	7	7	9	8
7f	p- OCH_3	9	8	8	8	7

—Contd

Table III—Characterization data of **5-11a-j**—*Contd*

Compd	R	Antibacterial activity (Zone of inhibition in mm) 100µg/mL				Antifungal activity (Zone of inhibition in mm) 100µg/mL
		Gram-positive		Gram-negative		Fungi
		S. aureus	*B. subtlis*	*E. coli*	*P. aeruginosa*	*S. aureus*
7g	*o*- Cl	7	13	8	7	7
7h	*m*-Cl	7	8	9	7	7
7i	*o*-NO_2	8	7	7	8	7
7j	*p*-NO_2	8	9	8	8	7
8a	H	9	13	11	8	8
8b	*o*- CH_3	9	14	8	7	7
8c	*m*- CH_3	13	9	8	9	7
8d	*p*- CH_3	12	9	9	7	8
8e	*o*- OCH_3	8	9	8	9	8
8f	*p*- OCH_3	12	8	7	7	8
8g	*o*- Cl	7	9	9	8	7
8h	*m*-Cl	9	12	8	8	7
8i	*o*-NO_2	8	8	12	8	8
8j	p-NO_2	8	8	9	8	8
9a	H	8	8	7	7	7
9b	*o*- CH_3	7	8	9	8	8
9c	*m*- CH_3	8	9	8	7	7
9d	*p*- CH_3	7	8	8	8	8
9e	*o*- OCH_3	12	9	7	7	7
9f	*p*- OCH_3	8	12	7	8	8
9g	*o*- Cl	7	10	8	7	8
9h	*m*-Cl	7	9	8	8	7
9i	*o*-NO_2	7	9	8	8	7
9j	*p*-NO_2	8	13	7	7	8
10a	H	10	8	8	7	7
10b	*o*- CH_3	8	9	12	7	7
10c	*m*- CH_3	9	7	7	7	8
10d	*p*- CH_3	13	9	8	8	7
10e	*o*- OCH_3	7	13	9	8	8
10f	*p*- OCH_3	12	9	8	7	8
10g	*o*- Cl	9	14	7	8	8
10h	m-Cl	7	12	11	8	8
10i	*o*-NO_2	8	12	8	7	7
10j	*p*-NO_2	10	8	8	7	7
11a	H	9	13	8	8	7
11b	*o*- CH_3	7	8	7	8	7
11c	*m*- CH_3	8	9	8	8	7
11d	*p*- CH_3	14	13	7	7	7
11e	*o*- OCH_3	8	8	7	8	7
11f	*p*- OCH_3	9	14	11	7	8
11g	*o*- Cl	8	9	11	7	7
11h	*m*-Cl	13	7	8	7	7
11i	*o*-NO_2	12	7	8	8	8
11j	*p*-NO_2	9	10	7	7	8
Amofax		26	23	30	11	-
Ofloxacin		14	29	27	17	-
Tetracyclin		26	28	22	21	-
Greisofulvin		-	-	-	-	23

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carboxylic acid 3. The mixture of ester **2** (0.04 mole), water (100 mL) and sodium hydroxide (4 g) was refluxed at 80-90°C for 3 hr. The reaction mixture was cooled to room temp. and the *p*H 7 was adjusted by acetic acid. The compound was checked by TLC on silica gel, UV-Vis is at 254 nm, m.p. 236°C, yields: 92%. Purity of the compound was checked by HPLC.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-quinoline carbonyl chloride 4 (ref. 15,16). The mixture of **3** (0.035 mole), DMF (2 mL) and thionyl chloride (0.05 mole) was refluxed using benzene or toluene as solvent on a waterbath at 80°C about 5-6 hr in anhydrous condition with the help of calcium chloride guard tube until HCl evolution was ceased. The excess of thionyl chloride was removed over first by vacuum distillation and last portion of reagent was eliminated by repeated vacuum distillation with small portion of dried benzene. The solid material of the title compound obtained was cooled and used in next step.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-chloro-3-[*N*-(phenyl amino) carbonyl quinoline 5a (ref. 17,18). To a mixture of aniline (0.035 mole) in dry toluene and triethyl amine (4 mL), acid chloride 4 (0.035 mole) in toluene was added during 1.5 hr. The reaction was performed in salted ice bath at 0-5°C. The reaction mixture was further stirred for 4 hr at room temp. The reaction mixture was poured into acidic crushed ice with gentle shaking. The resultant solid compound **5**, was neutralized with aqueous $NaHCO_3$ (10%) solution, filtered, dried and recrystallised from DMF. The compound was checked by TLC on silica gel plate using chloroform:methanol (9:1).

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[piperazinyl]-3-[*N*-(substituted phenyl amino)-carbonyl]quinoline 6a-j (ref. 17,18). The mixture of compound **5** (0.005 mole), piperazine (0.01 mole), pyridine (10 mL) and triethyl amine (3 mL) was refluxed for 10 hr. After completion of reaction, the reaction mixture was cooled to room temp. The solid product was poured into crushed ice and neutralized with dilute HCl. The solid product was filtered dried and recrystallised from DMF and alcohol (2:1).

Similarly all the compounds **7-11a-j** were prepared by the same method using various substituted piperazine/imidazole/morpholine.

Characterization and spectral data are described in **Tables I** and **II** respectively.

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