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Synthesis and Antibacterial Activity of Thioureido Amide of Fluoroquinolone

N.B. Patel, S.D. Patel, J.N. Patel, J.C. Patel and Y.S. Gorgamwala
Department of Chemistry, Veer Narmad South Gujarat University, Surat-395007, India

Corresponding Author: Navin B. Patel, Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, Gujarat, India Tel: +91-0261-2264746 Fax: +91-0261-2256012

ABSTRACT

We have synthesized thioureido amide of fluoroquinolone to study the variation in biological activity. All the compounds were synthesized from simple condensation of acid chloride with phenyl thiourea to give thioureido amides, which further condensed with substituted piperazines, structure of the compounds were conformed from IR and ^{1}H-NMR spectra and elemental analysis. All the compounds evaluated for antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* using cup-plate method. Significant improvement in biological activity was observed.

Key words: Cup plate method, ciprofloxacin, piperazine, significant activity

INTRODUCTION

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 (Emani *et al*., 2005). Structure activity relation of fluoroquinolones has been studied in some reviews (Mitscher, 2005; Bhanot *et al*., 2001; Sharma *et al*., 2009) 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 (Edmont *et al*., 2000), antitumor (Shaharyar *et al*., 2007), antiviral (Lucero *et al*., 2006), antifilarial (Srivastava *et al*., 2000) and anti-HIV (Tabarrini *et al*., 2008) agents.

Phenyl thiourea derivatives possess significant pharmacological importance viz., antiviral (Yan *et al*., 2009), antimicrobial (Turan-Zitouni *et al*., 2002), antidiabetics (Maruyama *et al*., 2009), anti-HIV (Ravichandran *et al*., 2009), anti cancer (Figueiredo *et al*., 2006), antiviral (Clikla *et al*., 2010).

We have observed that the structural and biological variation at C-3 position of fluroquinolones with thiazolidinones from Schiff base (Patel and Patel, 2009, 2010), amides (Patel *et al*., 2007) from simple substituted anilines and esters (Sharma and Jain, 2008) from long chain alcohols. Significant activity observed for both the cases. Structure activity relationship study of fluoroquinolones and biological importance of phenyl thiourea provided scope to synthesize the thioureido amides of fluoroquinolones and study the variation in antibacterial activity, like whether it increase or decrease on addition of different piperazin-1-yl groups and effect of different functional groups on antibacterial activity.

MATERIALS AND METHODS

All melting points were determined by using open capillary method and are uncorrected. The IR spectra were recorded on Perkin-Elmer-838 FT-IR spectrophotometer using Kbr pellet. The PMR spectra were recorded in $DMSOd_6$ on Bruker DRX-300 (300 MHz FT NMR) instrument and chemical shifts were expressed in δ ppm against TMS as internal reference. Purity of compounds was checked by TLC using silica gel. Antibacterial activity of all the synthesized compounds have been screened against four different strains viz., two gram positive *S. aureus*, *B. subtilis* and two gram negative *E. coli*, *P. aeruginosa* bacteria by cup plate method (Collee *et al.*, 1996) at 100 μg mL^{-1} concentrations, compared with standard drug ciprofloxacin. Phenyl thiourea derivatives synthesized from reported methods (Venkatesh and Pandeya, 2009).

Synthesis of 7-Chloro-1-Cyclopropyl-6-Fluoro-4-Oxo-1,4-Dihydro-Quinoline-3-Carbonyl Chloride (2): Compound was prepared from acid (1) on reaction with thionyl chloride (Patel and Bhagat, 2006).

Synthesis of 1-(7-Chloro-1-Cyclopropyl-6-Fluoro-4-Oxo-1,4-DIhydro-Quinoline-3-Carbonyl)-3-Phenylthiourea (3a-3l)

General procedure: Aryl thioureas (a-*l*) (0.005 mole) were dissolved in dry pyridine, add solution of acid chloride and (0.005 mole) in pyridine drop wise in 1.5 h with constant stirring at 0-5°C. The reaction mixture was further refluxed for 8 h. The whole content was pour into acidic crushed ice with gentle shaking. The resultant solid was filtered and washed thoroughly with aqueous $NaHCO_3$ (10%) solution. The purity of the compounds were checked by TLC on silica gel plate using benzene:ethylacetate (1:1). All the compounds were recrystallised from Ethanol:DMSO (1:2).

Spectral data of 1-Phenyl-3-(1-Cyclopropyl-6-Fluoro-7-Chloro-1,4-Dihydro-Quinoline-3-Carbonyl) Thiourea 3a

- IR (KBr ν_{max} in cm^{-1}): 3440, 3120 (NH), 2930 (C-H), 1645 (amide-I), 1540 (amide-II), 1310 (C-N), 1265 (C-F), 1230 (amide-III), 1210 (>C=S), 750 (C-Cl)
- ^1H NMR (DMSO d_6, δ ppm): 1.15-1.52 (m, 4H, cyclopropyl), 3.77 (m, 1H, >N-CH-), 6.24-7.20 (m, 5H, Ar-H), 8.10 (s, 1H, H_2), 8.41 (d, 1H, H_5), 8.35 (s, 1H, H_8), 9.07 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH)

1-Phenyl-3-(1-Cyclopropyl-6-Fluoro-7-Piperazin-1-yl-1,4-Dihydro-Quinoline-3-Carbonyl) Thiourea (4a-4*l*)

General procedure: The mixture of 1-(7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carbonyl)-3-phenylthioureas (3a-3*l*) (0.001 mole), N-piperazine (0.001 mole), CH_3CN (10 mL), DMSO (5 mL) and Et_3N was refluxed at 135°C for 14 h and cool at room temperature. The resultant mass was pour in to crushed ice and neutralized with 50% HCl. The solid product was filtered, dried and recrystallised from absolute alcohol:DMSO (1:2) mixture.

Synthesis of 1-Phenyl-3-[1-Cyclopropyl-6-Fluoro-7-(4-Methylpiperazin-1-yl)-4-Oxo-1,4-Dihydro-Quinoline-3-Carbonyl]thiourea (5a-5l)

General procedure: Compounds were synthesized similarly to (4a-4*l*), from (3a-3*l*) on condensation with N-methylpiperazine.

Synthesis of 1-Phenyl-3-{1-Cylcopropyl-6-Fluoro-7-[4-(2-Hydroxyethyl) Piperazin-1-yl]-4-oxo-1,4-Dihydro-Quinoline-3-Cabonyl} Thiourea (6a-6l)

General procedure: Compounds were synthesized similarly to (4a-4*l*), from (3a-3*l*) on condensation with N-(2-hydroxyethyl)piperazine.

RESULTS AND DISCUSSION

Compounds were evaluated for antibacterial activity against four bacteria using cup plate method and compared with reference drug ciprofloxacin. Spectral data of the newly prepared compounds are shown in Table 1. 5e, 5f, 5h and 5k demonstrated good activity (AI = 0.5), while 5g and 6d found highly active (AI = 0.8) against *S. aureus*. 4b, 4i, 4j, 4k, 4*l*, 5a, 5b, 5i, 5j, 6b, 6d, 6i, 6j, 6k and 6*l* showed good activity (AI = 0.5), 4h, 6c, 6g and 6h found highly active (AI = 0.8), while 4a and 5*l* found strongest (AI = 1) against *B. subtlis*. 4b, 4c, 4d, 4e, 4f, 4h, 4i, 4k, 4*l*, 5b, 5d, 5h, 5i, 5*l*, 6c, 6f and 6g demonstrated good activity (AI = 0.5), 5k showed strong activity (AI = 0.8), while 4a and 5j found strongest (AI = 1) against *E. coli*. 4a, 4b, 4c, 4d, 4h, 4i, 4j, 4k, 4*l*, 5b, 5e, 5f, 5h, 5j, 5k, 5*l*, 6c, 6f, 6h, 6j and 6*l* showed good activity (AI = 0.5) against *P. aeruginosa*. Antibacterial activity of compounds described in form of Zone of Inhibition (ZI) in mm and Activity Index (AI) in Table 2.

We have synthesized thioureido amides of fluoroquinolones with substituted piperazine derivatives. Acid chloride was synthesize from reported method, which on condensation with

Table 1: Spectral data of the newly prepared compounds

Compound	IR (cm^{-1})	^{1}H-NMR (δ ppm)
4a	3435, 3125 (NH), 2927 (C-H), 1631 (amide-I), 1533 (amide-II), 1315 (C-N), 1262 (C-F), 1232 (amide-III), 1208 (>C=S), 1038 (C-N piperazine)	1.05-1.48 (m, 4H, cyclopropyl), 3.62 (m, 1H, >N-CH-), 6.14-7.15 (m, 5H, Ar-H), 8.05 (s, 1H, H_2), 8.35 (d, 1H, H_5), 8.18 (s, 1H, H_8), 2.20-3.30 (m, 9H, piperazine), 9.05 (s, 1H, Ar-NH), 9.45 (s, 1H, CONH)
4b	3431, 3122 (NH), 2930 (C-H), 1626 (amide-I), 1535 (amide-II), 1320 (C-N), 1260 (C-F),1225 (amide-III), 1210 (>C=S), 1045 (C-N piperazine)	1.15-1.41 (m, 4H, cyclopropyl), 3.68 (m, 1H, >N-CH-), 6.04-7.25 (m, 4H, Ar-H), 8.11 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.20 (s, 1H, H_8), 2.15-3.15 (m, 9H, piperazine), 9.15 (s, 1H, Ar-NH), 9.42 (s, 1H, CONH), 1.95 (s, 3H, $-CH_3$)
4e	3428, 3112 (NH), 2932 (C-H), 1632 (amide-I), 1525 (amide-II), 1345, 1545 ($-NO_2$ sym, asym), 1315 (C-N), 1258 (C-F), 1215 (amide-III), 1205 (>C=S), 1040 (C-N piperazine)	1.05-1.35 (m, 4H, cyclopropyl), 3.70 (m, 1H, >N-CH-), 6.14-7.05 (m, 4H, Ar-H), 8.05 (s, 1H, H_2), 8.32 (d, 1H, H_5), 8.18 (s, 1H, H_8), 2.05-3.20 (m, 9H, piperazine), 9.08 (s, 1H, Ar-NH), 9.55 (s, 1H, CONH)
4h	3442, 3110 (NH), 2920 (C-H), 1633 (amide-I), 1520 (amide-II), 1305 (C-N), 1267 (C-F), 1205 (amide-III), 1210 (>C=S), 1035 (C-N piperazine), 1011, 1221 (C-O-C)	1.15-1.47 (m, 4H, cyclopropyl), 3.62 (m, 1H, >N-CH-), 6.04-7.15 (m, 4H, Ar-H), 8.00 (s, 1H, H_2), 8.25 (d, 1H, H_5), 8.15 (s, 1H, H_8), 2.15-3.25 (m, 9H, piperazine), 9.18 (s, 1H, Ar-NH), 9.45 (s, 1H, CONH), 4.10 (s, 3H, $-OCH_3$)
4j	3440, 3115 (NH), 2915 (C-H), 1638 (amide-I), 1515 (amide-II), 1315 (C-N), 1260 (C-F), 1215 (amide-III), 1205 (>C=S), 1040 (C-N piperazine), 760 (C-Cl)	1.05-1.41 (m, 4H, cyclopropyl), 3.58 (m, 1H, >N-CH-), 6.15-7.10 (m, 4H, Ar-H), 8.08 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.19 (s, 1H, H_8), 2.05-3.28 (m, 9H, piperazine), 9.20 (s, 1H, Ar-NH), 9.52 (s, 1H, CONH)
5a	3440, 3120 (NH), 2925 (C-H), 1625 (amide-I), 1532 (amide-II), 1320 (C-N), 1267 (C-F), 1225 (amide-III), 1210 (>C=S), 1042 (C-N piperazine)	1.15-1.45 (m, 4H, cyclopropyl), 3.65 (m, 1H, >N-CH-), 6.14-7.15 (m, 5H, Ar-H), 8.12 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.18 (s, 1H, H_8), 2.12-3.20 (m, 8H, piperazine), 9.15 (s, 1H, Ar-NH), 9.38 (s, 1H, CONH), 1.95 (s, 3H, $-CH_3$)

Table 1: Continued

Compound	IR (cm^{-1})	^{1}H-NMR (δ ppm)
5b	3432, 3115 (NH), 2920 (C-H), 1645 (amide-I), 1535 (amide-II), 1315 (C-N), 1260 (C-F), 1220 (amide-III), 1205 (>C=S), 1042 (C-N piperazine)	1.05-1.55 (m, 4H, cyclopropyl), 3.68 (m, 1H, >N-CH-), 6.14-7.10 (m, 4H, Ar-H), 8.10 (s, 1H, H_2), 8.30 (d, 1H, H_5), 8.20 (s, 1H, H_8), 2.02-3.15 (m, 8H, piperazine), 9.20 (s, 1H, Ar-NH), 9.50 (s, 1H, CONH), 1.95 (s, 3H, >N-CH_3), 1.85 (s, 3H, -CH_3)
5e	3440, 3120 (NH), 2925 (C-H), 1630 (amide-I), 1532 (amide-II), 1335, 1535 (-NO_2 sym, asym), 1320 (C-N), 1265 (C-F), 1215 (amide-III), 1210 (>C=S), 1045 (C-N piperazine)	1.15-1.60 (m, 4H, cyclopropyl), 3.61 (m, 1H, >N-CH-), 6.04-7.15 (m, 4H, Ar-H), 8.12 (s, 1H, H_2), 8.22 (d, 1H, H_5), 8.15 (s, 1H, H_8), 2.12-3.10 (m, 8H, piperazine), 9.15 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH), 1.85 (s, 3H, >N-CH_3)
5h	3435, 3115 (NH), 2920 (C-H), 1625 (amide-I), 1545 (amide-II), 1315 (C-N), 1261 (C-F), 1210 (amide-III), 1202 (>C=S), 1040 (C-N piperazine), 1011, 1221 (C-O-C)	1.05-1.65 (m, 4H, cyclopropyl), 3.61 (m, 1H, >N-CH-), 6.14-7.10 (m, 4H, Ar-H), 8.10 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.20 (s, 1H, H_8), 2.10-3.23 (m, 8H, piperazine), 9.10 (s, 1H, Ar-NH), 9.55 (s, 1H, CONH), 4.20 (s, 3H, -OCH_3)
5j	3440, 3120 (NH), 2928 (C-H), 1630 (amide-I), 1542 (amide-II), 1320 (C-N), 1265 (C-F), 1215 (amide-III), 1205 (>C=S), 1043 (C-N piperazine), 766 (C-Cl)	1.15-1.60 (m, 4H, cyclopropyl), 3.68 (m, 1H, >N-CH-), 6.04-7.15 (m, 4H, Ar-H), 8.14 (s, 1H, H_2), 8.30 (d, 1H, H_5), 8.18 (s, 1H, H_8), 2.15-3.20 (m, 8H, piperazine), 9.15 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH)
5*l*	3442, 3125 (NH), 2930 (C-H), 1725 (-COOH), 1625 (amide-I), 1535 (amide-II), 1315 (C-N), 1260 (C-F), 1220 (amide-III), 1210 (>C=S), 1039 (C-N piperazine)	1.05-1.55 (m, 4H, cyclopropyl), 3.62 (m, 1H, >N-CH-), 6.15-7.10 (m, 4H, Ar-H), 8.10 (s, 1H, H_2), 8.25 (d, 1H, H_5), 8.12 (s, 1H, H_8), 2.05-3.18 (m, 8H, piperazine), 9.20 (s, 1H, Ar-NH), 9.55 (s,1H, CONH), 13.50 (s, 1H,-COOH)
6a	3450, 3130 (NH), 3235 (O-H), 2925 (C-H), 1634 (amide-I), 1523 (amide-II), 1320 (C-N), 1266 (C-F), 1215 (amide-III), 1205 (>C=S), 1040 (C-N piperazine)	1.02-1.60 (m, 4H, cyclopropyl), 3.65 (m, 1H, >N-CH-), 6.20-7.14 (m, 5H, Ar-H), 2.10 (m, 4H, -CH_2-CH_2-), 4.15 (s, 1H, -OH) 8.15 (s, 1H, H_2), 8.21 (d, 1H, H_5), 8.10 (s, 1H, H_8), 2.19-3.30 (m, 8H, piperazine), 9.15 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH)
6b	3445, 3125 (NH), 3230 (O-H), 2930 (C-H), 1630 (amide-I), 1520 (amide-II), 1315 (C-N), 1260 (C-F), 1210 (amide-III), 1200 (>C=S), 1035 (C-N piperazine)	1.12-1.61 (m, 4H, cyclopropyl), 3.61 (m, 1H, >N-CH-), 6.15-7.10 (m, 4H, Ar-H), 2.02 (m, 4H, -CH_2-CH_2-), 4.10 (s, 1H, -OH) 8.10 (s, 1H, H_2), 8.20 (d, 1H, H_5), 8.15 (s, 1H, H_8), 2.10-3.15 (m, 8H, piperazine), 9.10 (s, 1H, Ar-NH), 9.55 (s, 1H, CONH), 1.85 (s, 3H, -CH_3)
6e	3440, 3115 (NH), 3220 (O-H), 2925 (C-H), 1638 (amide-I), 1325, 1538 (-NO_2 sym, asym), 1515 (amide-II), 1320 (C-N), 1258 (C-F), 1220 (amide-III), 1208 (>C=S), 1041 (C-N piperazine)	1.02-1.49 (m, 4H, cyclopropyl), 3.69 (m, 1H, >N-CH-), 6.20-7.15 (m, 4H, Ar-H), 2.00 (m, 4H, -CH_2-CH_2-), 4.15 (s, 1H, -OH) 8.15 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.05 (s, 1H, H_8), 2.16-3.22 (m, 8H, piperazine), 9.15 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH)
6h	3435, 3117 (NH), 3228 (O-H), 2930 (C-H), 1640 (amide-I), 1520 (amide-II), 1325 (C-N), 1260 (C-F), 1223 (amide-III), 1210 (>C=S), 1040 (C-N piperazine), 1015, 1200 (C-O-C)	1.02-1.49 (m, 4H, cyclopropyl), 3.69 (m, 1H, >N-CH-), 6.20-7.15 (m, 4H, Ar-H), 2.05 (m, 4H, -CH_2-CH_2-), 4.15 (s, 1H, -OH) 8.15 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.05 (s, 1H, H_8), 2.16-3.22 (m, 8H, piperazine), 9.15 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH), 4.00 (s, 3H, -OCH_3)
6j	3435, 3117 (NH), 3228 (O-H), 2930 (C-H), 1640 (amide-I), 1520 (amide-II), 1325 (C-N), 1260 (C-F), 1223 (amide-III), 1210 (>C=S), 1040 (C-N piperazine), 765 (C-Cl)	1.12-1.51 (m, 4H, cyclopropyl), 3.61 (m, 1H, >N-CH-), 6.10-7.10 (m, 4H, Ar-H), 2.00 (m, 4H, -CH_2-CH_2-), 4.10 (s, 1H, -OH) 8.10 (s, 1H, H_2), 8.22 (d, 1H, H_5), 8.02 (s, 1H, H_8), 2.10-3.12 (m, 8H, piperazine), 9.05 (s, 1H, Ar-NH), 9.55 (s, 1H, CONH)
6*l*	3435, 3115 (NH), 2930 (C-H), 1725 (-COOH), 1630 (amide-I), 1533 (amide-II), 1315 (C-N), 1260 (C-F), 1220 (amide-III), 1215 (>C=S), 1035 (C-N piperazine)	1.15-1.60 (m, 4H, cyclopropyl), 3.65 (m, 1H, >N-CH-), 6.05-7.15 (m, 4H, Ar-H), 8.05 (s, 1H, H_2), 8.28 (d, 1H, H_5), 8.15 (s, 1H, H_8), 2.15-3.20 (m, 8H, piperazine), 9.55 (s, 1H, Ar-NH), 9.60 (s, 1H, CONH), 13.40 (s, 1H,-COOH)

Table 2: Antibacterial synthesized compounds (4a-*l*, 5a-*l*, 6a-*l*) zone of inhibition (mm)

		S. aureus		*B. subtlis*		*E. coli*		*P. aeruginosa*	
Compound	R	ZI	AI	ZI	AI	ZI	AI	ZI	AI
4a	-H	08	0.30	38	1.20	37	1.40	15	0.70
4b	2-CH_3	10	0.35	16	0.50	20	0.75	12	0.55
4c	3-CH_3	08	0.30	13	0.40	17	0.65	15	0.70
4d	4-CH_3	08	0.30	10	0.33	14	0.50	11	0.50
4e	2-NO_2	09	0.32	14	0.45	16	0.60	10	0.45
4f	3-NO_2	09	0.32	09	0.30	13	0.50	09	0.40
4g	4-NO_2	10	0.35	09	0.30	12	0.45	09	0.40
4h	2-OCH_3	12	0.40	24	0.80	14	0.50	15	0.70
4i	4-OCH_3	09	0.32	21	0.70	13	0.50	11	0.50
4j	3-Cl	08	0.30	19	0.60	12	0.45	13	0.60
4k	4-Cl	08	0.30	16	0.50	15	0.55	16	0.70
4*l*	4-COOH	10	0.35	18	0.60	13	0.50	14	0.60
5a	-H	09	0.32	20	0.65	09	0.35	10	0.45
5b	2-CH_3	10	0.35	18	0.60	16	0.60	12	0.55
5c	3-CH_3	09	0.32	13	0.40	11	0.40	09	0.40
5d	4-CH_3	13	0.45	11	0.35	13	0.50	09	0.40
5e	2-NO_2	15	0.50	12	0.40	09	0.35	13	0.60
5f	3-NO_2	19	0.65	31	1.00	12	0.45	11	0.50
5g	4-NO_2	24	0.85	14	0.45	10	0.40	09	0.40
5h	2-OCH_3	14	0.50	11	0.35	14	0.50	13	0.60
5i	4-OCH_3	09	0.32	22	0.70	18	0.70	12	0.55
5j	3-Cl	11	0.40	21	0.70	30	1.15	09	0.40
5k	4-Cl	18	0.65	09	0.30	25	1.00	11	0.50
5*l*	4-COOH	09	0.32	36	1.20	25	1.00	14	0.60
6a	-H	09	0.32	13	0.40	09	0.35	09	0.40
6b	2-CH_3	11	0.40	17	0.55	11	0.40	09	0.40
6c	3-CH_3	12	0.40	29	1.00	13	0.50	16	0.70
6d	4-CH_3	22	0.80	18	0.60	09	0.35	10	0.45
6e	2-NO_2	10	0.35	11	0.35	11	0.40	09	0.40
6f	3-NO_2	11	0.40	12	0.40	13	0.50	15	0.70
6g	4-NO_2	09	0.32	30	1.00	17	0.65	10	0.45
6h	2-OCH_3	13	0.45	25	0.80	09	0.35	11	0.50
6i	4-OCH_3	14	0.50	17	0.55	11	0.40	09	0.40
6j	3-Cl	11	0.40	16	0.50	12	0.45	12	0.55
6k	4-Cl	09	0.32	20	0.65	10	0.40	10	0.45
6*l*	4-COOH	11	0.40	19	0.60	09	0.35	15	0.70
Ciprofloxacin		28	-	30	-	26	-	22	-

ZI: Zone of inhibition in mm, AI: Activity index, AI: Zone of inhibition of compounds/Zone of inhibition of standard drug

substituted phenyl thiourea derivatives gave amide, further addition of substituted piperazin-1-yl group furnished target compounds. All the conversion and condition shown in Fig. 1 and Table 3. The structures of synthesized compounds 3a-l were confirmed by elemental analysis and IR-spectra (cm^{-1}) absorption bands at 3452 (NH), 2915, 2832 (C-H), 1748 (>C=O for quinolone), 1638 (amide-I), 1530 (amide-II), 1340 (C-N), 1268 (C-F), 1225 (amide-III), 1045 (C-N, piperazine), 1210 (>C=S), some additional peaks appear due to substitution in aromatic ring showing absorption band at 3235 (O-H), 1730 (-COOH), 1356, 1550 (-NO_2 sym, asym), 756 (C-Cl). In ^{1}H-NMR spectra common

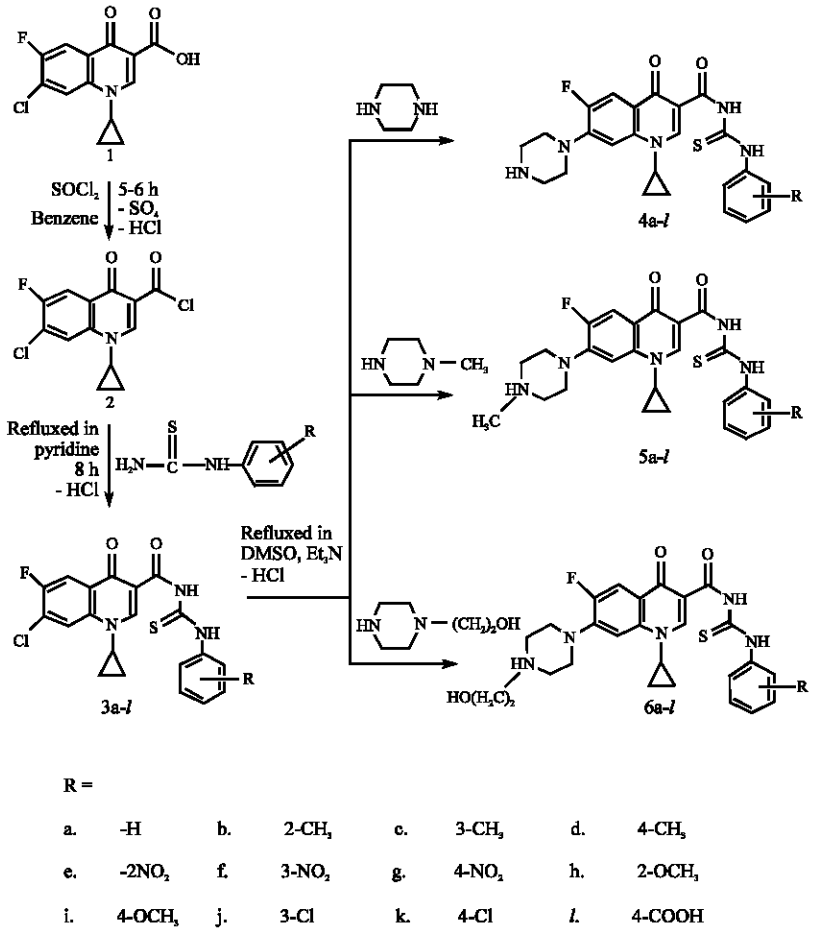

Fig. 1: Scheme of reactions

Table 3: Characterization data of compounds (4a-4*l*, 5a-5*l* and 6a-6*l*)

Compound No.	R	Yield (%)	M.p (°C)	Mol. formula (Mol. weight)	Elemental analysis (%) Calcd./found		
					C	H	N
4a	-H	55	195-197	$C_{24}H_{25}FN_5O_2S$	61.73	5.35	15.05
				(466.17)	61.72	5.32	15.00
4b	2-CH_3	65	203-204	$C_{25}H_{27}FN_5O_2S$	62.43	5.61	14.56
				(480.18)	62.46	5.59	14.55
4c	3-CH_3	67	173-175	$C_{25}H_{27}FN_5O_2S$	62.43	5.61	14.56
				(480.18)	62.39	5.64	14.52
4d	4-CH_3	51	156-158	$C_{25}H_{27}FN_5O_2S$	62.43	5.61	14.56
				(480.18)	62.42	5.62	14.58
4e	2-NO_2	67	187-189	$C_{24}H_{24}FN_6O_4S$	56.30	4.69	16.42
				(511.15)	56.31	4.65	16.40
4f	3-NO_2	45	155-157	$C_{24}H_{24}FN_6O_4S$	56.30	4.69	16.42
				(511.15)	56.29	4.71	16.38
4g	4-NO_2	56	152-154	$C_{24}H_{24}FN_6O_4S$	56.30	4.69	16.42
				(511.15)	56.27	4.73	16.37
4h	2-OCH_3	70	161-163	$C_{25}H_{27}FN_5O_3S$	60.42	5.43	14.09
				(496.18)	60.40	5.47	14.11

Table 3: Continued

Compound No.	R	Yield (%)	M.p (°C)	Mol. formula (Mol. weight)	Elemental analysis (%) Calcd./found C	H	N
4i	4- OCH_3	67	177-179	$C_{25}H_{27}FN_5O_3S$	60.42	5.43	14.09
				(496.18)	60.39	5.41	14.14
4j	3-Cl	72	145-147	$C_{24}H_{24}FClN_5O_2S$	57.48	4.79	13.97
				(500.13)	57.45	4.75	13.95
4k	4-Cl	80	132-134	$C_{24}H_{24}FClN_5O_2S$	57.48	4.79	13.97
				(500.13)	57.44	4.81	13.95
4*l*	4-COOH	82	215-218	$C_{25}H_{25}FN_5O_4S$	58.76	4.89	13.71
				(510.16)	58.75	4.92	13.69
5a	-H	85	139-141	$C_{25}H_{26}FN_5O_2S$	62.56	5.42	14.59
				(479.17)	62.55	5.44	14.56
5b	2-CH_3	75	147-149	$C_{26}H_{28}FN_5O_2S$	63.22	5.67	14.18
				(493.19)	63.20	5.64	14.14
5c	3-CH_3	61	151-153	$C_{26}H_{28}FN_5O_2S$	63.22	5.67	14.18
				(493.19)	63.25	5.70	14.22
5d	4-CH_3	59	165-166	$C_{26}H_{28}FN_5O_2S$	63.22	5.67	14.18
				(493.19)	63.26	5.65	14.16
5e	2-NO_2	60	129-132	$C_{25}H_{25}FN_6O_4S$	57.19	4.76	16.01
				(524.16)	57.21	4.75	15.97
5f	3-NO_2	64	118-120	$C_{25}H_{25}FN_6O_4S$	57.19	4.76	16.01
				(524.16)	57.22	4.74	16.06
5g	4-NO_2	60	154-156	$C_{25}H_{25}FN_6O_4S$	57.19	4.76	16.01
				(524.16)	57.22	4.80	16.03
5h	2-OCH_3	67	160-162	$C_{26}H_{28}FN_5O_3S$	63.47	5.69	14.24
				(509.18)	63.43	5.71	14.22
5i	4-OCH_3	76	155-156	$C_{26}H_{28}FN_5O_3S$	63.47	5.69	14.24
				(509.18)	63.51	5.73	14.27
5j	3-Cl	79	171-173	$C_{25}H_{25}FClN_5O_2S$	58.36	4.86	13.61
				(513.14)	58.40	4.89	13.58
5k	4-Cl	73	181-183	$C_{25}H_{25}FClN_5O_2S$	58.36	4.86	13.61
				(513.14)	58.32	4.91	13.57
5*l*	4-COOH	80	199-201	$C_{26}H_{26}FN_5O_4S$	59.59	4.96	13.37
				(523.16)	59.62	4.92	13.32
6a	-H	83	205-208	$C_{26}H_{28}FN_5O_2S$	62.56	5.67	14.18
				(493.19)	62.55	5.65	14.24
6b	2-CH_3	82	211-214	$C_{27}H_{30}FN_5O_2S$	63.22	5.91	13.79
				(507.21)	63.20	5.89	13.75
6c	3-CH_3	83	205-207	$C_{27}H_{30}FN_5O_2S$	63.22	5.91	13.79
				(507.21)	63.27	5.92	13.81
6d	4-CH_3	72	168-170	$C_{27}H_{30}FN_5O_2S$	63.22	5.91	13.79
				(507.21)	63.19	5.90	13.76
6e	2-NO_2	73	123-125	$C_{26}H_{27}FN_6O_4S$	57.19	5.01	15.59
				(538.17)	57.23	4.98	15.61
6f	3-NO_2	75	133-135	$C_{26}H_{27}FN_6O_4S$	57.19	5.01	15.59
				(538.17)	57.23	5.03	15.63
6g	4-NO_2	76	120-122	$C_{26}H_{27}FN_6O_4S$	57.19	5.01	15.59
				(538.17)	57.22	5.04	15.65

Table 3: Continued

Compound No.	R	Yield (%)	M.p (°C)	Mol. formula (Mol. weight)	Elemental analysis (%) Calcd./found C	H	N
6h	2-OCH_3	84	118-120	$C_{27}H_{30}FN_5O_3S$	63.47	5.73	13.37
				(523.20)	63.45	5.70	13.39
6i	4-OCH_3	85	176-178	$C_{27}H_{30}FN_5O_3S$	63.47	5.73	13.37
				(523.20)	63.51	5.69	13.41
6j	3-Cl	89	179-181	$C_{26}H_{27}FClN_5O_2S$	58.36	5.11	13.28
				(527.15)	58.34	5.10	13.31
6k	4-Cl	85	140-142	$C_{26}H_{27}FClN_5O_2S$	58.36	5.11	13.28
				(527.15)	58.38	5.09	13.30
6l	4-COOH	84	151-153	$C_{27}H_{28}FN_5O_4S$	59.59	5.20	13.02
				(537.18)	59.63	5.15	13.00

signals appears are: δ_H (ppm): singlet signals at δ 8.05, 8.18 corresponding to H_2, H_8 and doublet at δ 8.30 corresponding to H_5 of quinolone ring, a multiplet at δ 3.68 corresponding to >N-CH-, a multiplet at δ 1.05 to 1.62 corresponding to cyclopropyl, a singlet at δ 9.60 corresponding to >CO. NH, singlet signal at δ 9.55 also appeared corresponding to Ar-NH and due to substitution on phenyl ring singlet single signal appeared at δ 1.95, 4.10 and 13.50 corresponding to -CH_3, -OCH_3 and -COOH, on addition of different piperazin-1-yl group multiplet at δ 2.37-3.15 observed corresponding to piperazine, multiplet at δ 2.05 due to hydroxy ethyl group, a multiplet at δ 6.15-7.20 corresponding to aromatic proton.

Over all conclusions are that significant improvement in activity for thioureido amide of fluoroquinolone when compared with previously synthesized ester and amides. Activity of piperazin-1-yl and N-methy pieprazin-1-yl group is similar and increased with 1-(2-hydroxyethyl)piperazin-1-yl. Activity against *S. aureus* was not increased.

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