Med Chem Res
DOI 10.1007/s00044-012-0394-2

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of new *N*-substituted amino methyl-[1,2,3] triazolyl moieties of fluoroquinolones as antibacterial agents

G. Govinda Rajulu · Halehatty S. Bhojya Naik · Abhilash Viswanathan · Devesh S. Agarwal · Ganesh Sambasivam · Kesavan Poonimangadu Koppolu

Received: 11 August 2012 / Accepted: 4 December 2012

Abstract A series of twenty new *N*-substituted amino methyl-[1,2,3] triazolyl derivatives at C-7 position of fluoroquinolones were designed and synthesized through multistep synthesis. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, ESI–MS, and IR. The antibacterial activities of these new fluoroquinolones were evaluated using a standard broth micro dilution technique. Out of the twenty derivatives, aryl substituted amino derivatives (**6m** to **6q**) exhibited very good potency in inhibiting the growth of Methicillin-sensitive *Staphylococcus aureus* (MSSA), Methicillin-resistant *Staphylococcus aureus* (MRSA), and Vancomycin-Resistant *Enterococcus faecalis* (VRE *faecalis*) (MIC: 0.25–4.00 μg/mL) as compared to the marketed drugs Linezolid and Ciprofloxacin.

Keywords Synthesis · [1,2,3] triazolyl derivatives · Fluoroquinolones · Antibacterial activity

Introduction

Fluoroquinolones are class of quinolone compounds and known as first made broad-spectrum antibiotics. The fluoroquinoles such as Ciprofloxacin and Norfloxacin are extremely successful antibiotics that are potent, broad-spectrum antibacterial activity, and have relatively few side effects (Mitscher, 2005). These antibiotics exert their antimicrobial activity by binding to two type II bacterial topoisomerase enzymes, DNA gyrase (subunits encoded by gyrA and gyrB) and topoisomerase IV (subunits encoded by grlA and grlB for Staphylococcus aureus). This binding induces permanent double-stranded DNA breaks, and results in cell death (De Souza, 2005; Hooper, 2001).

Most of the quinolones currently in the market or under development are generally characterized by a broad antibacterial spectrum, but their activity against clinically important Gram-positive cocci, including *Staphylococci*, *Streptococci*, and *Enterococci*, is relatively moderate. This insufficient activity has not only limited their use in infections caused by these organisms, but has also contributed to the rapidly developing quinolone resistance. Thus, recent efforts have been directed toward the synthesis of new quinolones that can provide improved Gram-positive antibacterial activity, while retaining the Gram-negative activity of early fluoroquinolones, such as ciprofloxacin (Piddock et al, 1994).

Structure–activity relationship (SAR) studies of quinolone antibacterial agents showed that the basic group at the C-7 position is the most adaptable site for chemical change and an area that greatly influences their potency, spectrum, and safety (Bryskier and Chantot, 1995; Koga et al, 1980). In general, 5- and 6-membered nitrogen heterocycles have been proven to be the optimal substituents (Domagala, 1994).

As part of an ongoing program to identify novel, potent, and broad-spectrum antibacterial agents, we have introduced 5-memebered nitrogen containing heterocycle such as [1,2,3] triazole derivatives at C-7 position of fluoroquinolones. Also, the [1,2,3] triazoles are known to be

G. Govinda Rajulu (✉) · A. Viswanathan · D. S. Agarwal · G. Sambasivam · K. P. Koppolu
Anthem Biosciences Pvt. Ltd., 49 Bommasandra Industrial Area, Bangalore 560099, Karnataka, India
e-mail: govinda_iitd@yahoo.com; govindarajulu.g@anthembio.com

H. S. Bhojya Naik
Department of PG Studies and Research in Industrial Chemistry, School of Chemical Sciences, Kuvempu University, Shankaraghatta, Karnataka 577451, India

Published online: 13 December 2012

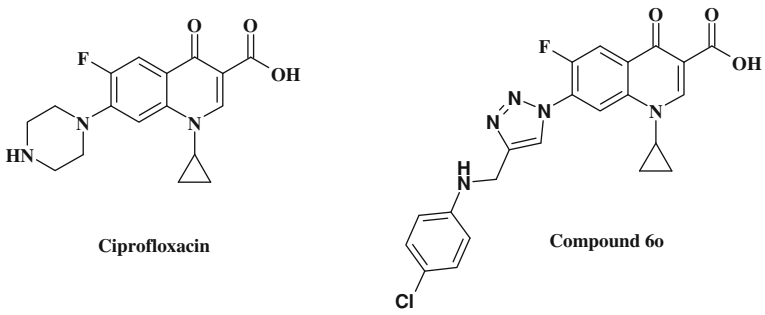


Fig. 1 Chemical structure of **Ciprofloxacin** and compound **6o**

good building blocks in antimicrobial drug discovery (Patpi et al., 2012; Shanmugavelan et al., 2011; Sumangala et al., 2010). To the best of our knowledge, there is no literature available to reveal the effect of [1,2,3] triazole group at C-7 position of fluoroquinolones on their antibacterial activity. The design strategy of [1,2,3] triazolyl derivative with a representative example (compound **6o**) is shown in Fig. 1.

Experimental

Chemistry

Chemicals were obtained from Sigma-Aldrich Co. Final purifications were carried out using Merck silica gel 230–400 mesh. TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and $KMnO_4$. Melting points were determined using Buchi B-540 and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR), Bruker BioSpin Corp., Germany. Molecular weights of unknown compounds were checked by LCMS 6200 series Agilent Technology. Chemical shifts are reported in ppm (δ) with reference to internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet. IR Spectra were recorded using a Bruker Alpha FTIR spectrometer using a diamond ATR single reflectance module (24 scans).

*Procedure for the synthesis of 7-azido-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**2**)*

To a solution of compound **1** (2.5 g, 8.5 mmol) in *N, N*-dimethylformamide (25 mL) sodium azide (0.6 g, 9.3 mmol) was added at room temperature (25 °C) under nitrogen atmosphere. Then reaction mixture was allowed to stir at 50 °C over a period of 16 h. The resulting reaction mass was allowed to reach room temperature and poured into crushed ice to obtain pale yellow precipitate. The precipitate formed was filtered and dried to give compound **2** as off-white solid 2.3 g (85 %).

MP: 237.0–238.0 °C; IR (ATR, cm^{-1}) υ: 3089 (ArH), 2119 ($-N_3$), 1718 (ester –C=O), 1615 (quinolone –C=O), 1594 (–C=C), 1478 (ester –C–O), 1050 (–C–F); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.11–1.13 (2H, m, cyclopropyl), 1.21–1.24 (2H, m, cyclopropyl), 1.27 (3H, t, J =6.0 Hz, OCH_2CH_3), 3.64–3.69 (1H, m, cyclopropyl), 4.22 (2H, q, J = 6.0 Hz, OCH_2CH_3), 7.79 (1H, d, J = 6.9 Hz, ArH), 7.90 (1H, d, J = 11.4 Hz, ArH), 8.45 (1H, s, C_2–H); LC–MS (ESI, *m/z*): 317.2 (M+H).

*Procedure for the synthesis of 1-cyclopropyl-6-fluoro-7-(4-hydroxymethyl-[1,2,3] triazol-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**3**)*

To a solution of compound **2** (3.0 g, 9.48 mmol) in *N, N*-dimethylformamide (20.0 mL) propargyl alcohol (632 mg, 11.02 mmol), sodium ascorbate (586 mg, 2.3 mmol), copper iodide (893 mg, 4.7 mmol), and *N*-ethyl diisopropyl amine (3.2 mL, 18.9 mmol) were added at ice bath temperature under nitrogen atmosphere. After stirring at ice bath temperature for 10 min, the reaction mixture was allowed to stir at room temperature over a period of 2 h. After completion of reaction, the reaction mass was quenched with 5 % aqueous ammonia (2 mL), poured into crushed ice, and the precipitate formed was filtered and dried to obtain product **3** as off-white solid 2.4 g (68 %).

MP: 237.0–238.0 °C; IR (ATR, cm^{-1}) υ: 3474 (–OH); 3042 (ArH), 1668 (ester –C=O), 1614 (quinolone –C=O), 1477 (ester –C–O), 1025 (–C–F); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.17–1.18 (2H, m, cyclopropyl), 1.24–1.32 (5H, m, cyclopropyl and OCH_2CH_3), 3.72–3.78 (1H, m, cyclopropyl), 4.25 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.67 (2H, d, J = 5.7 Hz, CH_2OH), 5.42 (1H, t, J = 5.7 Hz, CH_2OH), 8.16 (1H, d, J = 10.8 Hz, ArH), 8.53 (1H, d, J = 6.0 Hz, ArH), 8.56 (1H, s, triazole H), 8.62 (1H, d, J = 2.4 Hz, ArH); LC–MS (ESI, *m/z*): 373.1 (M+H).

*Procedure for the synthesis of 7-(4-Chloromethyl-[1,2,3] triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**4**)*

To a solution of compound **3** (3.0 g, 8.02 mmol) in dichloromethane (15.0 mL) pyridine (0.79 mL, 12.08 mmol) and thionyl chloride (0.70 mL, 9.6 mmol) were added at ice bath temperature. After stirring at ice bath temperature for 10 min, then reaction mixture was allowed to stir at room temperature over a period of 2 h. After completion of the reaction, the reaction mixture was diluted with dichloromethane (50 mL), washed with water (2 × 20 mL), and dried over sodium sulfate. The residue obtained upon evaporation of the solvent was washed with diethyl ether to obtain product **4** as a pale yellow solid 3.0 g (96 %).

MP: 217.3–218.0 °C; IR (ATR, cm^{-1}) υ: 3183 (ArH), 1733 (ester –C=O), 1620 (quinolone –C=O), 1500 (–C=C), 1477 (ester –C–O), 1027 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.16–1.18 (2H, m, cyclopropyl), 1.25–1.32 (5H, m, cyclopropyl and OCH_2CH_3), 3.72–3.78 (1H, m, cyclopropyl), 4.25 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 4.99 (2H, s, CH_2Cl), 8.17 (1H, d, $J = 10.8$ Hz, ArH), 8.56–8.58 (2H, m, ArH and triazole H), 8.87 (1H, d, $J = 2.4$ Hz, ArH); LC–MS (ESI, *m/z*): 391.0 (M+H).

*General procedure for the synthesis of 1-cyclopropyl-7-(4-substituted aminomethyl-[1,2,3] triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl esters (**5a**–**t**)*

To a solution of compound **4** (200 mg, 0.48 mmol) in *N, N*-dimethylformamide (5.0 mL) triethylamine (230 µL, 1.60 mmol), potassium iodide (42.5 mg, 0.25 mmol), and the corresponding amine (0.69 mmol) were added at ice bath temperature. After stirring at ice bath temperature for 10 min, the reaction mass was allowed to stir at room temperature over a period 4–6 h. After completion of reaction, reaction mass was diluted with ethyl acetate (500 mL), washed with water (3 × 25 mL), and dried over sodium sulfate. The residue obtained upon evaporation of the solvent was further purified by silica gel column chromatography using methanol/chloroform as the eluent.

*1-Cyclopropyl-7-(4-dimethylaminomethyl-[1,2,3] triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5a**)*

Compound **5a** was obtained as off-white solid; MP: 187.1–188.6 °C; IR (ATR, cm^{-1}) υ: 2925 (ArH), 1725 (ester –C=O), 1698 (quinone –C=O), 1615 (–C=C), 1480 (ester –C–O), 1024 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.16–1.32 (7H, m, cyclopropyl & OCH_2CH_3), 2.22 (6H, s, dimethyl amine-NCH_3), 3.64 (2H, s, $–CH_{2–}$), 3.76 (1H, bs, cyclopropyl), 4.25 (2H, q, $J = 6.6$ Hz, OCH_2CH_3), 8.15 (1H, d, $J = 10.8$ Hz, ArH), 8.53–8.56 (2H, m, ArH & triazole H), 8.63 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.51, 36.86, 42.81, 53.62, 60.24, 108.27, 113.22, 115.82, 126.70, 129.56, 138.12, 138.58, 149.79, 150.41, 153.51, 165.21, 172.29; LC–MS (ESI, *m/z*): 400.0 (M+H).

*1-Cyclopropyl-7-(4-diethylaminomethyl-[1,2,3]triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5b**)*

Compound **5b** was obtained as white solid; MP: 171.8–172.1 °C; IR (ATR, cm^{-1}) υ: 2968 (ArH), 1726 (ester –C=O), 1699 (quinone –C=O), 1617 (–C=C), 1481 (ester –C–O), 1034 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.06–1.08 (6H, m, diethyl amine–CH_3), 1.16–1.32 (7H, m, cyclopropyl & OCH_2CH_3), 2.50–2.57 (4H, m, diethyl amine-NCH_2), 3.76 (2H, s, $–CH_{2–}$), 3.89 (1H, bs, cyclopropyl), 4.24 (2H, q, $J = 6.9$ Hz, OCH_2CH_3), 8.15 (1H, d, $J = 11.1$ Hz, ArH), 8.53-8.56 (2H, m, ArH & triazole H), 8.65 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.52, 14.71, 35.57, 60.24, 60.48, 110.44, 113.72, 115.85, 125.05, 128.87, 137.91, 145.40, 147.36, 149.79, 153.51, 164.51, 170.10; LC–MS (ESI, *m/z*): 428.2 (M+H).

*1-Cyclopropyl-7-(4-dipropylaminomethyl-[1,2,3] triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5c**)*

Compound **5c** was obtained as off-white solid; MP: 117.7–118.8 °C; IR (ATR, cm^{-1}) υ: 2959 (ArH), 1724 (ester –C=O), 1695 (quinone –C=O), 1616 (–C=C), 1481 (ester –C–O), 1024 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 0.86 (6H, t, $J = 7.2$ Hz, dipropyl amine–CH_3), 1.16–1.32 (7H, m, cyclopropyl & OCH_2CH_3), 1.50 (4H, bs, dipropyl amine–CH_2), 2.40 (4H, bs, dipropyl amine-NCH_2), 3.88 (3H, m, $–CH_{2–}$ & cyclopropyl), 4.24 (2H, q, $J = 6.9$ Hz, OCH_2CH_3), 8.15 (1H, d, $J = 11.1$ Hz, ArH), 8.53–8.56 (3H, m, ArH & triazole H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.24, 11.41, 14.55, 17.18, 36.84, 45.84, 53.90, 60.25, 108.84, 113.51, 115.86, 126.72, 129.54, 138.09, 138.58, 149.84, 150.41, 153.48, 164.52, 172.11; LC–MS (ESI, *m/z*): 456.2 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-pyrrolidin-1-ylmethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5d**)*

Compound **5d** was obtained as off-white solid; MP: 214.4–214.9 °C; IR (ATR, cm^{-1}) υ: 3182 (ArH), 3022 (ArH), 1730 (ester –C=O), 1617 (–C=C), 1475 (ester –C–O), 1023 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm):

1.16–1.32 (7H, m, cyclopropyl & OCH_2CH_3), 1.74 (4H, bs, pyrrolidine–CH_2), 2.65 (4H, bs, pyrrolidine-NCH_2), 3.76 (1H, bs, cyclopropyl), 3.91 (2H, s, –CH_2–), 4.25 (2H, q, $J = 6.9$ Hz, OCH_2CH_3), 8.16 (1H, d, $J = 10.8$ Hz, ArH), 8.53–8.56 (2H, m, ArH & triazole H), 8.68 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.24, 14.54, 25.61, 36.79, 53.89, 60.25, 108.27, 113.55, 115.87, 126.70, 129.59, 138.12, 138.61, 149.85, 150.39, 153.54, 165.49, 172.21; LC–MS (ESI, *m/z*): 426.1 (M+H);

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-piperidin-1-ylmethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5e**)*

Compound **5e** was obtained as pale yellow solid; MP: 182.4–183.7 °C; IR (ATR, cm^{-1}) υ: 2935 (ArH), 1700 (ester –C=O), 1640 (quinone –C=O), 1617 (–C=C), 1475 (ester –C–O), 1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.16–1.40 (9H, m, cyclopropyl, OCH_2CH_3 & piperadine–CH_2), 1.52–1.53 (4H, m, pyrrolidine–CH_2), 2.55–2.56 (4H, bs, pyrrolidine-NCH_2), 3.72-3.76 (3H, m, cyclopropyl & –CH_2–), 4.24 (2H, q, $J = 6.9$ Hz, OCH_2CH_3), 8.16 (1H, d, $J = 10.8$ Hz, ArH), 8.54–8.56 (2H, m, ArH & triazole H), 8.65 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.52, 25.41, 27.70. 36.80, 49.70, 54.31, 60.28, 109.10, 113.58, 115.80, 126.72, 129.54, 138.21, 138.61, 149.10, 150.43, 153.45, 165.51, 172.13; LC–MS (ESI, *m/z*): 440.1 (M+H).

*1-Cyclopropyl-6-fluoro-7-(4-morpholin-4-ylmethyl-[1,2,3]triazol-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5f**)*

Compound **5f** was obtained as pale yellow solid; MP: 192.6–193.5 °C; IR (ATR, cm^{-1}) υ: 2914 (ArH), 1693 (ester –C=O), 1641 (quinolone –C=O), 1617 (–C=C), 1482 (ester –C–O), 1005 (–C–F); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.22–1.23 (2H, m, cyclopropyl), 1.41–1.48 (5H, m, cyclopropyl and OCH_2CH_3), 2.68 (4H, bs, morpholine-NCH_2), 3.55-3.59 (1H, m, cyclopropyl), 3.80 (4H, t, $J = 4.5$ Hz, morpholine–OCH_2), 3.88 (2H, s, –CH_2–), 4.43 (2H, q, $J = 6.9$ Hz, OCH_2CH_3), 8.34 (1H, d, $J = 2.7$ Hz, ArH), 8.39 (1H, d, $J = 11.0$ Hz, ArH), 8.67 (1H, s, triazole H), 8.72 (1H, d, $J = 6.0$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.55, 36.89, 53.62, 55.81, 60.28, 72.24, 108.27, 113.55, 115.85, 126.71, 129.50, 138.27, 138.57, 149.80, 150.44, 153.51, 164.82, 172.12; LC–MS (ESI, *m/z*): 442.3 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-piperazin-1-ylmethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5g**)*

Compound **5g** was obtained as yellow solid; MP: 192.6–193.5 °C; IR (ATR, cm^{-1}) υ: 2919 (ArH), 1717 (ester –C=O), 1694 (quinone –C=O), 1615 (–C=C), 1482 (ester –C–O), 1028 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.08–1.33 (7H, m, cyclopropyl & –OCH2CH3), 2.63 (4H, m, piperazine), 2.98 (4H, bs, piperazine), 3.76 (3H, bs, cyclopropyl & –CH_2–), 4.24 (2H, q, $J = 7.2$ Hz, –OCH2CH3), 8.17 (1H, d, $J = 10.8$ Hz, ArH), 8.51–8.54 (2H, m, ArH & triazole H), 8.71 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.54, 36.83, 47.41, 49.62, 60.27, 108.31, 113.61, 116.22, 126.86, 129.70, 137.62, 138.56, 149.92, 150.38, 153.28, 164.82, 172.12; LC–MS (ESI, *m/z*): 441.3 (M+H).

*1-Cyclopropyl-6-fluoro-7-[4-(isopropylamino-methyl)-[1,2,3]triazol-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5h**)*

Compound **5h** was obtained as yellow solid; MP: 186.2-187.1 °C; IR (ATR, cm^{-1}) υ: 2964 (ArH), 1726 (ester –C=O), 1696 (quinone –C=O), 1616 (–C=C), 1482 (ester –C–O), 1021 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.07 (6H, d, $J = 6.3$ Hz, isopropyl–CH_3), 1.17–1.32 (7H, m, cyclopropyl & –OCH_2CH_3), 2.85-2.89 (1H, m, isopropyl –CH), 3.76 (1H, m, cyclopropyl), 3.95 (2H, s, –CH_2–), 4.24 (2H, q, $J = 6.9$ Hz, –OCH_2CH_3), 8.16 (1H, d, $J = 10.8$ Hz, ArH), 8.53 (1H, d, $J = 6.3$ Hz, ArH), 8.56 (1H, s, triazole H), 8.63 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.54, 18.95, 36.77, 49.65, 60.26, 60.54, 108.30, 113.50, 113.80, 115.89, 128.13, 138.60, 140.58, 149.85, 150.37, 153.21, 164.84, 172.11; LC–MS (ESI, *m/z*): 414.2 (M+H).

*1-Cyclopropyl-7-(4-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5i**)*

Compound **5i** was obtained as off-white solid; MP: 214.9–215.0.6 °C; IR (ATR, cm^{-1}) υ: 2966 (ArH), 1722 (ester –C=O), 1692 (quinone –C=O), 1617 (–C=C), 1484 (ester –C–O), 1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 0.66–0.73 (4H, m, cyclopropyl), 1.69–1.32 (7H, m, cyclopropyl & –OCH_2CH_3), 2.63 (1H, bs, –NH), 3.06–3.08 (1H, m, cyclopropyl), 3.76 (1H, m, cyclopropyl), 4.25 (2H, q, $J = 6.6$ Hz, –OCH_2CH_3), 4.34 (2H, s, –CH_2–), 8.19 (1H, d, $J = 10.8$ Hz, ArH), 8.53–8.57 (2H, m, ArH & triazole H), 8.83 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 4.04, 8.22, 14.53, 30.01, 35.61, 60.24, 60.52, 110.48, 113.72, 114.01, 115.21, 128.39, 137.96, 141.24, 149.36, 149.90, 152.71, 164.23, 170.82; LC–MS (ESI, *m/z*): 412.2 (M+H).

*7-(4-Cyclopentylaminomethyl-[1,2,3]triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5j**)*

Compound **5j** was obtained as off-white solid; MP: 193.3–194.2 °C; IR (ATR, cm^{-1}) υ: 3306 (–NH), 2955 (ArH),

1727 (ester –C=O), 1695 (quinone –C=O), 1615 (–C=C), 1482 (ester –C–O), 1024 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.17–1.32 (7H, m, cyclopropyl & $-OCH_2CH_3$), 1.46-1.49 (4H, m, cyclopentyl), 1.66 (2H, bs, cyclopentyl), 1.81–1.83 (2H, m, cyclopentyl), 3.05 (1H, bs, cyclopentyl), 3.76 (1H, bs, cyclopropyl), 4.00 (2H, s, $-CH_2-$), 4.24 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 8.16 (1H, d, $J = 11.1$ Hz, ArH), 8.53–8.56 (2H, m, ArH & triazole H), 8.67 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.54, 24.07, 29.45, 31.15, 36.78, 58.38, 60.52, 108.30, 113.52, 113.80, 115.88, 128.17, 138.58, 140.52, 149.81, 150.39, 153.19, 164.25, 172.12; LC–MS (ESI, *m/z*): 440.2 (M+H).

*7-(4-Cyclohexylaminomethyl-[1,2,3]triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5k**)*

Compound **5k** was obtained as pale yellow solid; MP: 154.4–154.9 °C; IR (ATR, cm^{-1}) υ: 3311 (–NH), 2932 (ArH), 1727 (ester –C=O), 1694 (quinone –C=O), 1613 (–C=C), 1481 (ester –C–O), 1023 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.07–1.32 (13H, m, cyclopropyl, cyclohexyl & $-OCH_2CH_3$), 1.56–1.58 (1H, m, cyclohexyl), 1.68 (2H, bs, cyclohexyl), 1.88-1.92 (2H, m, cyclohexyl), 3.76 (1H, bs, cyclopropyl), 3.96 (2H, s, $-CH_2-$), 4.25 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 8.15 (1H, d, $J = 11.1$ Hz, ArH), 8.53-8.60 (3H, m, ArH & triazole H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.54, 24.40, 25.22, 28.80, 36.78, 38.29, 56.11, 60.51, 108.40, 113.52, 113.80, 115.87, 128.20, 138.60, 140.60, 149.85, 150.44, 153.20, 164.24, 172.13; LC–MS (ESI, *m/z*): 454.2 (M+H).

*7-(4-Cycloheptylaminomethyl-[1,2,3]triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5l**)*

Compound **5l** was obtained as pale yellow solid; MP: 229.3–230.5 °C; IR (ATR, cm^{-1}) υ: 2921 (ArH), 1726 (ester –C=O), 1694 (quinone –C=O), 1617 (–C=C), 1483 (ester –C–O), 1010 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.27–1.63 (18H, m, cyclopropyl, cycloheptyl & $-OCH_2CH_3$), 1.84–1.88 (2H, m, cycloheptyl), 2.71 (1H, bs, cycloheptyl), 3.76 (1H, bs, cyclopropyl), 3.91 (2H, s, $-CH_2-$), 4.24 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 8.15 (1H, d, $J = 11.1$ Hz, ArH), 8.52-8.63 (3H, m, ArH & triazole H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.53, 24.08, 28.53, 34.20, 39.20, 41.79, 57.80, 60.51, 110.38, 113.72, 114.97, 128.70, 137.89, 147.98, 149.34, 149.78, 152.66, 164.11, 170.10; LC–MS (ESI, *m/z*): 468.2 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-phenylaminomethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5m**)*

Compound **5m** was obtained as yellow solid; MP: 260.6–261.2 °C; IR (ATR, cm^{-1}) υ: 3060 (ArH), 1715 (ester –C=O & quinone –C=O), 1612 (–C=C), 1490 (ester –C–O), 1023 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.15–1.35 (7H, m, cyclopropyl & –OCH2CH3), 3.75 (1H, bs, cyclopropyl), 4.24 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 4.43 (2H, d, $J = 5.7$ Hz, $-CH_2-$), 6.21 (1H, t, $J = 5.7$ Hz, –NH–), 6.55 (1H, t, $J = 7.2$ Hz, ArH), 6.70 (2H, t, $J = 7.5$ Hz, ArH), 7.08 (2H, t, $J = 7.5$ Hz, ArH), 8.14 (1H, d, $J = 10.8$ Hz, ArH), 8.52–8.55 (2H, m, ArH & triazole H), 8.64 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.53, 38.31, 58.22, 60.50, 108.30, 113.52, 113.81, 115.78, 128.18, 129.31, 132.42, 132.55, 138.60, 140.60, 142.32 149.85, 150.44, 153.20, 164.54, 172.11; LC–MS (ESI, *m/z*): 448.5 (M+H).

*1-Cyclopropyl-6-fluoro-7-{4-[(4-fluoro-phenylamino)-methyl]-[1,2,3]triazol-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5n**)*

Compound **5n** was obtained as yellow solid; MP: 255.3–256.2 °C; IR (ATR, cm^{-1}) υ: 2939 (ArH), 1720 (ester –C=O), 1695 (quinone –C=O), 1611 (–C=C), 1491 (ester –C–O), 1026 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.09–1.31 (7H, m, cyclopropyl & –OCH2CH3), 3.75 (1H, bs, cyclopropyl), 4.24 (2H, q, $J = 7.2$ Hz, $-OCH_2CH_3$), 4.41 (2H, d, $J = 5.4$ Hz, $-CH_2-$), 6.14 (1H, t, $J = 5.4$ Hz, –NH–), 6.70 (2H, d, $J = 4.5$ Hz, ArH), 6.93 (2H, t, $J = 8.7$ Hz, ArH), 8.15 (1H, d, $J = 10.8$ Hz, ArH), 8.51–8.55 (2H, m, ArH & triazole H), 8.64 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.24, 14.61, 38.87, 57.02, 60.48, 108.31, 113.56, 113.81, 115.75, 117.80, 121.41, 128.20, 138.61, 140.59, 142.64, 149.83, 150.44, 153.20, 154.98, 164.53, 172.11; LC–MS (ESI, *m/z*): 466.1 (M+H).

*7-{4-[(4–Chloro-phenylamino)-methyl]-[1,2,3]triazol-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5o**)*

Compound **5o** was obtained as pale yellow solid; MP: 261.4–262.0 °C; IR (ATR, cm^{-1}) υ: 3060 (ArH), 1716 (ester –C=O & quinone –C=O), 1612 (–C=C), 1490 (ester –C–O), 1023 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.15–1.31 (7H, m, cyclopropyl & –OCH2CH3), 3.75 (1H, bs, cyclopropyl), 4.23 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 4.43 (2H, d, $J = 4.8$ Hz, $-CH_2-$), 6.45 (1H, bs, –NH–), 6.70 (2H, d, $J = 8.4$ Hz, ArH), 7.10 (2H, d, $J = 8.1$ Hz, ArH), 8.14 (1H, d, $J = 10.8$ Hz, ArH), 8.51–8.55 (2H, m, ArH & triazole H), 8.66 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.62, 38.87, 57.04, 60.49, 108.30, 113.51, 113.81,

115.72, 117.81, 121.42, 128.20, 138.65, 140.58, 141.66, 149.86, 150.44, 152.26, 154.91, 164.52, 172.11; LC–MS (ESI, *m/z*): 482.3 (M+H).

*1-Cyclopropyl-6-fluoro-7-{4-[(4-methoxy-phenylamino)-methyl]-[1,2,3]triazol-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5p**)*

Compound **5p** was obtained as white solid; MP: 261.5–262.6 °C; IR (ATR, cm^{-1}) υ: 3058 (ArH), 2978 (ArH), 1716 (ester –C=O & quinone –C=O), 1612 (–C=C), 1490 (ester –C–O), 1024 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.16-1.29 (7H, m, cyclopropyl & –OCH2CH3), 3.63 (3H, s, –OMe), 3.75 (1H, bs, cyclopropyl), 4.24 (2H, q, $J = 6.3$ Hz, $-OCH_2CH_3$), 4.38 (2H, d, $J = 4.8$ Hz, $-CH_{2-}$), 5.80 (1H, bs, –NH–), 6.69 (4H, d, $J = 12.0$ Hz, ArH), 8.15 (1H, d, $J = 10.5$ Hz, ArH), 8.51–8.55 (2H, m, ArH & triazole H), 8.62 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.63, 38.30, 56.22, 57.25, 60.50, 108.31, 113.54, 113.80, 115.75, 118.12, 121.29, 128.22, 138.64, 140.60, 141.66, 143.51, 149.86, 150.45, 153.21, 164.52, 172.10; LC–MS (ESI, *m/z*): 478.1 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-[4-(p-tolylamino-methyl)-[1,2,3]triazol-1-yl]-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5q**)*

Compound **5q** was obtained as off-white solid; MP: 211.2–211.7 °C; IR (ATR, cm^{-1}) υ: 3333 (–NH)), 2936 (ArH), 1721 (ester –C=O), 1684 (quinone –C=O), 1608 (–C=C), 1478 (ester –C–O), 1021 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.16–1.31 (7H, m, cyclopropyl & –OCH2CH3), 2.14 (3H, s, –ArMe), 3.75 (1H, bs, cyclopropyl), 4.24 (2H, q, $J = 6.3$ Hz, $-OCH_2CH_3$), 4.40 (2H, d, $J = 6.0$ Hz, $-CH_{2-}$), 5.96 (1H, t, $J = 5.7$ Hz, –NH–), 6.61 (2H, d, $J = 8.1$ Hz, ArH), 6.90 (2H, d, $J = 10.8$ Hz, ArH), 8.14 (1H, d, $J = 10.8$ Hz, ArH), 8.52 (1H, d, $J = 6.0$ Hz, ArH), 8.55 (1H, s, triazole H), 8.61 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.64, 23.26, 38.30, 56.12, 60.52, 108.30, 113.53, 113.81, 114.78, 115.82, 126.82, 127.96, 130.21, 138.61, 140.52, 140.92, 149.86, 150.40, 153.22, 164.51, 172.12; LC–MS (ESI, *m/z*): 462.2 (M+H).

*7-[4-(Benzylamino-methyl)-[1,2,3]triazol-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5r**)*

Compound **5r** was obtained as off-white solid; MP: 120.2–121.9 °C; IR (ATR, cm^{-1}) υ: 3324 (–NH), 3044 (ArH), 1710 (ester –C=O), 1691 (quinone –C=O), 1611 (–C=C), 1479 (ester –C–O), 1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.16-1.35 (7H, m, cyclopropyl & –OCH2CH3), 3.77 (2H, bs, cyclopropyl & $-CH_{2-}$), 3.87 (2H, s, $-CH_{2-}$), 4.24 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 7.21–7.39 (5H, m, ArH), 8.16 (1H, d, $J = 11.1$ Hz, ArH), 8.53–8.56 (2H, m, ArH & triazole H), 8.62 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.23, 14.64, 36.79, 56.32, 57.20, 60.50, 108.27, 113.50, 113.81, 115.84, 128.11, 128.34, 129.46, 129.52, 138.25, 139.66, 140.52, 149.84, 150.39, 153.22, 164.52, 172.12; LC–MS (ESI, *m/z*): 462.1 (M+H).

*1-Cyclopropyl-6-fluoro-7-{4-[(4-fluoro-benzylamino)-methyl]-[1,2,3]triazol-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5s**)*

Compound **5s** was obtained as white solid; MP: 156.7–157.3 °C; IR (ATR, cm^{-1}) υ: 3322 (–NH), 3041 (ArH), 1725 (ester –C=O), 1695 (quinone –C=O), 1612 (–C=C), 1482 (ester –C–O), 1023 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.16–1.32 (7H, m, cyclopropyl & –OCH2CH3), 2.93 (bs, 1H), 3.76 (1H, bs, cyclopropyl & $-CH_{2-}$), 3.86 (2H, s, $-CH_{2-}$), 4.24 (2H, q, $J = 6.6$ Hz, $-OCH_2CH_3$), 7.14 (2H, t, $J = 7.0$ Hz, –ArH), 7.40 (2H, t, $J = 7.8$ Hz, –ArH), 8.16 (1H, d, $J = 10.8$ Hz, ArH), 8.53–8.56 (2H, m, ArH & triazole H), 8.61 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 14.64, 36.77, 56.32, 58.12, 60.51, 108.28, 113.54, 113.77, 115.86, 128.21, 128.70, 129.72, 138.57, 139.42, 140.48, 149.82, 150.41, 153.21, 154.53, 164.49, 171.99; LC–MS (ESI, *m/z*): 480.2 (M+H).

*1-Cyclopropyl-6-fluoro-7-(4-imidazol-1-ylmethyl-[1,2,3]triazol-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (**5t**)*

Compound **5t** was obtained as white solid; MP: 178.4–179.8 °C; IR (ATR, cm^{-1}) υ: 2979 (ArH), 1720 (ester –C=O & quinone –C=O), 1614 (–C=C), 1482 (ester –C–O), 1032 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.15-1.13 (7H, m, cyclopropyl & –OCH2CH3), 3.73 (1H, bs, cyclopropyl), 4.24 (2H, q, $J = 6.9$ Hz, $-OCH_2CH_3$), 5.44 (2H, s, $-CH_2$-), 6.92 (1H, s, Imidazole H), 7.29 (1H, s, Imidazole H), 7.80 (1H, s, Imidazole H), 8.16 (1H, d, $J = 11.1$ Hz, ArH), 8.54-8.56 (2H, m, ArH & triazole H), 8.80 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.22, 14.65, 36.80, 54.64, 60.50, 108.24, 113.54, 115.84, 124.52, 126.72, 128.51, 129.54, 138.14, 138.57, 140.25, 149.82, 150.34, 153.50, 164.51, 172.11; LC–MS (ESI, *m/z*): 423.2 (M+H).

*General procedure for the synthesis of 1-cyclopropyl-7 -(4- substituted amino methyl-[1,2,3]triazol-1-yl)-6-fluoro-4 -oxo-1,4-dihydro-quinoline-3-carboxylic acids (**6a–t**)*

To a solution of 6N hydrochloric acid (10.0 mL) substituted ester **5a–t** (0.5 mmol) was added at room temperature. The resulting suspension was allowed to stir at 60 °C over a period of 12 h. The completion of the reaction was monitored by TLC. The solid obtained upon evaporation of the volatiles under reduced pressure was washed with diethyl ether (2 × 5 mL).

*1-Cyclopropyl-7-(4-dimethylaminomethyl-[1,2,3]triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6a**)*

Compound 6**a** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2942 (ArH), 2537 (acid –OH), 1722 (acid –C=O & quinolone –C=O), 1617 (–C=C), 1479 (acid –C–O), 1024 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.26–1.32 (4H, m, cyclopropyl), 2.80 (6H, s, dimethyl amine–CH_3), 3.95 (1H, bs, cyclopropyl), 4.56 (2H, s, –CH_2–), 8.41 (1H, d, $J = 9.0$ Hz, ArH), 8.83–8.85 (2H, m, ArH & triazole H), 9.08 (1H, s, ArH), 11.16 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.19, 36.87, 42.81, 53.62, 108.27, 113.64, 115.85, 126.69, 129.56, 138.12, 138.58, 149.82, 150.42, 153.51, 165.77, 177.29; LC–MS (ESI, *m/z*): 372.1 (M+H).

*1-Cyclopropyl-7-(4-diethylaminomethyl-[1,2,3]triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6b**)*

Compound **6b** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2942 (ArH), 2538 (acid –OH), 1720 (acid –C=O & quinolone –C=O), 1617 (–C=C), 1479 (acid –C–O), 1030 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.16–1.27 (4H, m, cyclopropyl), 1.34 (6H, t, $J = 6.9$ Hz, diethyl amine–CH_3), 3.14 (4H, q, $J = 6.9$ Hz, diethyl amine-NCH_2), 3.95 (1H, bs, cyclopropyl), 4.57 (2H, s, –CH_2–), 8.41 (1H, d, $J = 10.8$ Hz, ArH), 8.81 (1H, d, $J = 6.0$ Hz, ArH), 8.84 (1H, s, triazole H), 9.13 (1H, s, ArH), 11.03 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.08, 14.72, 35.57, 60.49, 110.44, 113.72, 115.85, 125.00, 128.88, 137.93, 145.39, 147.36, 149.80, 153.51, 164.56, 171.81; LC–MS (ESI, *m/z*): 400.1 (M+H).

1-Cyclopropyl-7-(4-dipropylaminomethyl-[1,2,3]triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (6c)

Compound **6c** was obtained as yellow solid; IR (ATR, cm^{-1}) υ: 2968 (ArH), 2492 (acid –OH), 1718 (acid –C=O & quinolone –C=O), 1611 (–C=C), 1452 (acid –C–O), 1043 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.92 (6H, t, $J = 7.2$ Hz, dipropyl amine–CH_3), 1.27–1.35 (4H, m, cyclopropyl), 1.82–1.83 (4H, bs, dipropyl amine–CH_2), 3.02 (4H, bs, dipropyl amine-NCH_2), 3.95 (1H, bs, cyclopropyl), 4.59 (2H, s, –CH_2–), 8.42 (1H, d, $J = 10.5$ Hz, ArH), 8.82–8.85 (2H, m, ArH & triazole H), 9.13 (1H, s, ArH), 10.92 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.20, 11.41, 17.16, 36.80, 45.80, 53.91, 108.26, 113.55, 115.85, 126.77, 129.55, 138.09, 138.58, 149.80, 150.41, 153.51, 165.71, 177.01; LC–MS (ESI, *m/z*): 428.1 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-pyrrolidin-1-ylmethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid (**6d**)*

Compound **6d** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 3168 (–OH), 2923 (ArH), 2544 (acid –OH), 1707 (acid –C=O & quinolone –C=O), 1611 (–C=C), 1486 (acid –C–O), 1021 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.27–1.35 (4H, m, cyclopropyl), 1.91–2.03 (4H, m, pyrrolidine–CH_2), 3.19 (2H, bs, pyrrolidine-NCH_2), 3.48 (2H, bs, pyrrolidine-NCH_2), 3.95 (1H, bs, cyclopropyl), 4.64 (2H, s, –CH_2–), 8.41 (1H, d, $J = 10.8$ Hz, ArH), 8.80 (1H, d, $J = 5.7$ Hz, ArH), 8.84 (1H, s, triazole H), 9.08 (1H, s, ArH), 11.45 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.17, 25.62, 36.80, 53.89, 108.27, 113.56, 115.88, 126.69, 129.58, 138.12, 138.61, 149.81, 150.41, 153.54, 165.69, 177.22; LC–MS (ESI, *m/z*): 398.1 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-piperidin-1-ylmethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid (**6e**)*

Compound **6e** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2942 (ArH), 2541 (acid –OH), 1725 (acid –C=O & quinolone –C=O), 1611 (—C=C), 1494 (acid –C–O), 1033 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.07–1.15 (9H, m, cyclopropyl, OCH_2CH_3 & piperadine–CH_2), 1.74–1.81 (4H, m, pyrrolidine–CH_2), 2.96–2.99 (2H, m, pyrrolidine-NCH_2), 3.37–3.46 (2H, m, pyrrolidine–NCH_2), 3.94 (1H, m, cyclopropyl), 4.54 (2H, s, –CH_2–), 8.41 (1H, d, $J = 10.2$ Hz, ArH), 8.80–8.85 (2H, m, ArH & triazole H), 9.08 (1H, s, ArH), 10.85 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 25.43, 27.69. 36.81, 49.69, 54.32, 109.12, 113.56, 115.78, 126.72, 129.54, 138.22, 138.61, 149.08, 150.44, 153.42, 165.62, 177.13; LC–MS (ESI, *m/z*): 412.1 (M+H).

*1-Cyclopropyl-6-fluoro-7-(4-morphol in-4-ylmethyl-[1,2,3]triazol-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6f**)*

Compound **6f** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2958 (ArH), 2541 (acid –OH), 1720 (acid –C=O),

1610 (–C=C), 1489 (acid –C–O), 1007 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.26–1.32 (4H, m, cyclopropyl), 2.49–2.51 (4H, m, morpholine-NCH_2), 3.31 (4H, bs, morpholine–OCH_2), 3.72 (2H, s, –CH_2–), 3.94 (1H, m, cyclopropyl), 8.37 (1H, d, J = 10.2 Hz, ArH), 8.72–8.77 (2H, m, ArH and triazole H), 8.83 (1H, s, ArH), 14.59 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.21, 36.91, 53.62, 55.81, 72.23, 108.27, 113.55, 115.85, 126.71, 129.49, 138.23, 138.57, 149.82, 150.44, 153.51, 165.72, 177.00; LC–MS (ESI, *m/z*): 414.1 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-piperazin-1-ylmethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid (**6g**)*

Compound **6g** was obtained as yellow solid; IR (ATR, cm^{-1}) υ: 3059 (ArH), 2647 (acid –OH), 1710 (acid –C=O & quinolone –C=O), 1610 (–C=C), 1491 (acid –C–O), 1004 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.26–1.35 (4H, m, cyclopropyl), 3.46 (8H, m, piperazine), 3.94 (1H, bs, cyclopropyl), 4.67 (2H, s, –CH_2-), 8.42 (1H, d, J = 10.5 Hz, ArH), 8.80–8.84 (2H, m, ArH & triazole H), 9.09 (1H, s, ArH), 9.91 (2H, bs,–NH_2^+), 14.57 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.23, 36.83, 47.40, 49.60, 108.30, 113.61, 116.19, 126.85, 129.65, 137.64, 138.56, 149.92, 150.38, 153.28, 165.73, 177.00; LC–MS (ESI, *m/z*): 413.2 (M+H).

*1-Cyclopropyl-6-fluoro-7-[4-(isopropylamino-methyl)-[1,2,3]triazol-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6h**)*

Compound **6h** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2967 (ArH), 2509 (acid –OH), 1715 (acid –C=O & quinolone –C=O), 1610 (–C=C), 1452 (acid –C–O), 1007 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.26–1.34 (10H, m, isopropyl–CH_3 & cyclopropyl), 3.38 (1H, m, isopropyl –CH), 3.95 (1H, bs, cyclopropyl), 4.42 (2H, s, –CH_2–), 8.42 (1H, d, J = 10.5 Hz, ArH), 8.77 (1H, d, J = 5.4 Hz, ArH), 8.85 (1H, s, triazole H), 9.04 (1H, s, ArH), 9.48 (2H, bs, –NH_2^+), 14.49 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.19, 18.96, 36.78, 49.65, 60.54, 108.30, 113.50, 113.79, 115.90, 128.13, 138.60, 140.58, 149.85, 150.37, 153.21, 165.70, 176.98; LC–MS (ESI, *m/z*): 386.1 (M+H).

*1-Cyclopropyl-7-(4-cyclopropylaminomethyl-[1,2,3]triazol-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6i**)*

Compound **6i** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2974 (ArH), 2513 (acid –OH), 1722 (acid –C=O), 1692 (quinolone –C=O), 1617 (–C=C), 1484 (acid –C–O), 1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.79–0.93 (4H, m, cyclopropyl), 1.17–1.34 (4H, m, cyclopropyl), 3.05–3.08 (1H, m, cyclopropyl), 3.96 (1H, m, cyclopropyl), 4.50 (2H, s, –CH_2–), 8.41 (1H, d, J = 10.5 Hz, ArH), 8.76 (1H, d, J = 5.7 Hz, ArH), 8.85 (1H, s, triazole H), 9.01 (1H, s, ArH), 9.77 (2H, bs,–NH_2^+), 14.48 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 4.04, 8.10, 30.01, 35.60, 60.52, 110.48, 113.72, 114.01, 115.21, 128.39, 137.94, 141.24, 149.36, 149.89, 152.69, 164.50, 171.79; LC–MS (ESI, *m/z*): 384.2 (M+H).

*7-(4-Cyclopentylaminomethyl-[1,2,3]triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6j**)*

Compound **6j** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 3154 (–NH), 2956 (ArH), 2662 (acid –OH), 1713 (acid –C=O & quinolone –C=O), 1610 (—C=C), 1467 (acid –C–O), 1012 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.26–1.34 (4H, m, cyclopropyl), 1.54 (2H, bs, cyclopentyl), 1.74–1.76 (4H, m, cyclopentyl), 2.00–2.02 (2H, m, cyclopentyl), 3.55 (1H, bs, cyclopentyl), 3.96 (1H, bs, cyclopropyl), 4.41 (2H, s, –CH_2–), 8.41 (1H, d, J = 10.5 Hz, ArH), 8.77 (1H, d, J = 5.7 Hz, ArH), 8.84 (1H, s, triazole H), 9.06 (1H, s, ArH), 9.68 (2H, bs,–NH_2^+), 14.47 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.18, 24.07, 29.45, 31.15, 36.78, 58.38, 108.28, 113.51, 113.80, 115.88, 128.17, 138.60, 140.52, 149.84, 150.39, 153.20, 165.70, 177.00; LC–MS (ESI, *m/z*): 412.2 (M+H).

*7-(4-Cyclohexylaminomethyl-[1,2,3]triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6k**)*

Compound **6k** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 3155 (–NH), 2941 (ArH), 2691 (acid –OH), 1717 (acid –C=O & quinolone –C=O), 1613 (–C=C), 1466 (acid –C–O), 997 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.34–1.42 (10H, m, cyclopropyl & cyclohexyl), 1.77–1.81 (2H, m, cyclohexyl), 2.14–2.17 (2H, m, cyclohexyl), 3.08 (1H, bs, cyclohexyl), 3.95 (1H, bs, cyclopropyl), 4.44 (2H, s, –CH_2–), 8.42 (1H, d, J = 10.8 Hz, ArH), 8.77 (1H, d, J = 5.7 Hz, ArH), 8.85 (1H, m, triazole H), 9.04 (1H, s, ArH), 9.48 (2H, bs,–NH_2^+), 14.58 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.19, 24.40, 25.23, 28.80, 36.78, 38.29, 56.09, 108.30, 113.52, 113.80, 115.87, 128.18, 138.60, 140.59, 149.85, 150.40, 153.20, 165.70, 177.00; LC–MS (ESI, *m/z*): 426.2 (M+H).

*7-(4-Cycloheptylaminomethyl-[1,2,3]triazol-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6l**)*

Compound **6l** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 2926 (ArH), 2357 (acid –OH), 1727 (acid –C=O),

1682 (quinolone –C=O), 1624 (–C=C), 1478 (acid –C–O), 1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.26–1.70 (14H, m, cyclopropyl & cycloheptyl), 2.12–2.15 (2H, m, cycloheptyl), 3.39 (1H, bs, cycloheptyl), 3.96 (1H, bs, cyclopropyl), 4.43 (2H, s, –CH_{2-}), 8.41 (1H, d, $J = 10.5$ Hz, ArH), 8.77 (1H, d, $J = 5.7$ Hz, ArH), 8.85 (1H, s, triazole H), 9.05 (1H, s, ArH), 9.46 (2H, bs,–NH_2^+); 14.57 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.09, 24.08, 28.52, 34.19, 39.20, 41.79, 57.80, 110.39, 113.73, 114.97, 128.70, 137.91, 147.98, 149.35, 149.78, 152.68, 164.54, 171.77; LC–MS (ESI, *m/z*): 440.1 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-(4-phenylaminomethyl-[1,2,3]triazol-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid (**6m**)*

Compound **6m** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 3057 (ArH), 2357 (acid –NH), 1713 (acid –C=O & quinolone –C=O), 1611 (–C=C), 1490 (acid –C–O), 1024 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.24–1.31 (4H, m, cyclopropyl), 3.94 (1H, bs, cyclopropyl), 4.57 (2H, d, $J = 5.4$ Hz, –CH_{2-}), 6.84 (1H, bs, ArH), 6.98 (2H, d, $J = 6.6$ Hz, ArH), 7.21 (2H, t, $J = 6.9$ Hz, ArH), 8.37 (1H, d, $J = 10.5$ Hz, ArH), 8.73–8.82 (3H, m, ArH & triazole H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.19, 38.30, 58.22, 108.30, 113.52, 113.81, 115.78, 128.18, 129.31, 132.42, 132.55, 138.60, 140.59, 142.32 149.85, 150.40, 153.20, 165.70, 177.01; LC–MS (ESI, *m/z*): 420.4 (M+H).

*1-Cyclopropyl-6-fluoro-7-{4-[(4-fluoro-phenylamino)-methyl]-[1,2,3]triazol-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6n**)*

Compound **6n** was obtained as yellow solid; IR (ATR, cm^{-1}) υ: 3058 (ArH), 2553 (acid –OH), 1726 (acid –C=O & quinolone –C=O), 1612 (–C=C), 1492 (acid –C–O), 1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.25–1.33 (4H, m, cyclopropyl), 3.94 (1H, bs, cyclopropyl), 4.51 (2H, d, $J = 5.4$ Hz, –CH_{2-}), 6.88 (2H, bs, ArH), 7.02 (2H, t, $J = 8.4$ Hz, ArH), 8.37 (1H, d, $J = 10.5$ Hz, ArH), 8.73–8.75 (2H, m, ArH & triazole H), 8.82 (1H, s, ArH); LC–MS (ESI, *m/z*): 438.1 (M+H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.20, 38.89, 57.02, 108.31, 113.56, 113.81, 115.77, 117.82, 121.41, 128.20, 138.61, 140.59, 142.64, 149.85, 150.44, 153.21, 154.98, 165.71, 177.01; LC–MS (ESI, *m/z*): 438.1 (M+H).

*7-{4-[(4-Chloro-phenylamino)-methyl]-[1,2,3]triazol-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6o**)*

Compound **6o** was obtained as pale yellow solid; IR (ATR, cm^{-1}) υ: 3051 (ArH), 2354 (–NH), 1728 (acid –C=O & quinolone –C=O), 1618 (–C=C), 1491 (acid –C–O), 1046 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.24–1.32 (4H, m, cyclopropyl), 3.94 (1H, bs, cyclopropyl), 4.45 (2H, 2, –CH_{2-}), 6.73 (2H, d, $J = 8.4$ Hz, ArH), 7.12 (2H, d, $J = 8.4$ Hz, ArH), 8.36 (1H, d, $J = 10.5$ Hz, ArH), 8.73-8.74 (2H, m, ArH & triazole H), 8.82 (1H, s, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.18, 38.88, 57.04, 108.33, 113.54, 113.81, 115.72, 117.81, 121.42, 128.20, 138.66, 140.58, 141.66, 149.86, 150.45, 152.26, 154.99, 165.73, 177.33; LC–MS (ESI, *m/z*): 454.6 (M+H).

*1-Cyclopropyl-6-fluoro-7-{4-[(4-methoxy-phenylamino)-methyl]-[1,2,3]triazol-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6p**)*

Compound **6p** was obtained as off-white solid; IR (ATR, cm^{-1}) υ: 2998 (ArH), 2358 (–NH), 1729 (acid –C=O & quinolone –C=O), 1610 (–C=C), 1512 (acid –C–O), 1015 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.25–1.31 (4H, m, cyclopropyl), 3.72 (3H, s, –OMe), 3.94 (1H, bs, cyclopropyl), 4.64 (2H, 2, –CH_{2-}), 6.94 (2H, bs, ArH), 7.19 (2H, bs, ArH), 8.38 (1H, d, $J = 9.9$ Hz, ArH), 8.73–8.83 (3H, m, ArH & triazole H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.20, 38.30, 56.22, 57.23, 108.31, 113.54, 113.80, 115.75, 118.12, 121.29, 128.22, 138.66, 140.58, 141.66, 143.51, 149.86, 150.45, 153.21, 165.71, 177.01; LC–MS (ESI, *m/z*): 450.1 (M+H).

*1-Cyclopropyl-6-fluoro-4-oxo-7-[4-(p-tolylamino-methyl)-[1,2,3]triazol-1-yl]-1,4-dihydro-quinoline-3-carboxylic acid (**6q**)*

Compound **6q** was obtained as off-white solid; IR (ATR, cm^{-1}) υ: 2998 (ArH), 2359 (–NH), 1728 (acid –C=O & quinolone –C=O), 1617 (—C=C), 1511 (acid –C–O), 1023 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.25–1.33 (4H, m, cyclopropyl), 2.22 (3H, s, –ArMe), 3.94 (1H, bs, cyclopropyl), 4.59 (2H, 2, –CH_{2-}), 7.01 (2H, bs, ArH), 7.08–7.10 (2H, m, ArH), 8.37 (1H, d, $J = 10.8$ Hz, ArH), 8.73 (1H, d, $J = 5.7$ Hz, ArH), 8.82 (2H, m, ArH & triazole H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.20, 23.26, 38.31, 56.12, 108.31, 113.53, 113.82, 114.78, 115.82, 126.82, 127.96, 130.21, 138.61, 140.54, 140.96, 149.86, 150.41, 153.22, 165.69, 177.00; LC–MS (ESI, *m/z*): 434.5 (M+H).

*7-[4-(Benzylamino-methyl)-[1,2,3]triazol-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6r**)*

Compound **6r** was obtained as pale yellow solid; IR (ATR, cm-1) υ: 3058 (ArH), 2709 (acid –OH), 1717 (acid –C=O & quinolone –C=O), 1611 (–C=C), 1492 (acid –C–O),

1022 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.26–1.33 (4H, m, cyclopropyl), 3.96 (1H, bs, cyclopropyl), 4.27 (2H, s, $–CH_{2}–$), 4.42 (2H, s, $–CH_{2}–$), 7.43 (3H, bs, ArH), 7.60 (2H, bs, ArH), 8.41 (1H, d, $J = 10.5$ Hz, ArH), 8.78 (1H, d, $J = 5.1$ Hz, ArH), 8.84 (1H, s, triazole H), 9.05 (1H, s, ArH), 10.09 (2H, bs, $–NH_{2}^{+}$); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.20, 36.77, 56.32, 57.21, 108.27, 113.50, 113.81, 115.84, 128.14, 128.34, 129.46, 129.51, 138.25, 139.66, 140.52, 149.84, 150.39, 153.20, 165.70, 177.00; LC–MS (ESI, *m/z*): 434.0 (M+H).

*1-Cyclopropyl-6-fluoro-7-{4-[(4-fluoro-benzylamino)-methyl]-[1,2,3]triazol-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6s**)*

Compound **6s** was obtained as yellow solid; IR (ATR, cm^{-1}) υ: 3012 (ArH), 2357 (acid –NH), 1715 (acid –C=O & quinolone –C=O), 1611 (–C=C), 1492 (acid –C–O), 1001 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.26–1.32 (4H, m, cyclopropyl), 3.95 (1H, bs, cyclopropyl), 4.27 (2H, s, $–CH_{2}–$), 4.42 (2H, s, $–CH_{2}–$), 7.30 (2H, t, $J = 8.1$ Hz, ArH), 7.60 (2H, bs, ArH), 8.42 (1H, d, $J = 10.5$ Hz, ArH), 8.77 (1H, d, $J = 5.4$ Hz, ArH), 8.85 (1H, s, triazole H), 9.02 (1H, s, ArH), 9.97 (2H, bs,$–NH_{2}^{+}$); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.19, 36.78, 56.32, 58.11, 108.28, 113.54, 113.78, 115.86, 128.21, 128.69, 129.72, 138.57, 139.42, 140.48, 149.82, 150.41, 153.21, 154.53, 165.71, 176.87; LC–MS (ESI, *m/z*): 452.1 (M+H).

1-Cyclopropyl-6-fluoro-7-(4-imidazol-1-ylmethyl-[1,2,3]triazol-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (6t)

Compound **6t** was obtained as yellow solid; IR (ATR, cm^{-1}) υ: 3061 (ArH), 1714 (acid –C=O & quinolone –C=O), 1611 (–C=C), 1491 (acid –C–O), 1021 (–C–F); ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.25–1.31 (4H, m, cyclopropyl), 3.93 (1H, bs, cyclopropyl), 5.75 (2H, s, $–CH_{2}–$), 7.74 (1H, s, Imidazole H), 7.88 (1H, s, Imidazole H), 8.40 (1H, d, $J = 10.8$ Hz, ArH), 8.77–8.84 (2H, m, ArH & triazole H), 9.04 (1H, s, ArH), 9.37 (1H, bs, Imidazole H), 14.75 (1H, bs, –COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.20, 36.79, 54.64, 108.25, 113.54, 115.87, 124.52, 126.77, 128.51, 129.54, 138.14, 138.57, 140.23, 149.82, 150.34, 153.49, 165.78, 177.00; LC–MS (ESI, *m/z*): 395.4 (M+H).

Antibacterial activity

All compounds were screened for their in vitro antibacterial activity against representative Gram-positive and Gram-negative strains, by means of standard twofold serial dilution method using agar media. Minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to give complete inhibition of bacterial growth after incubation at 35 °C for 24 h.

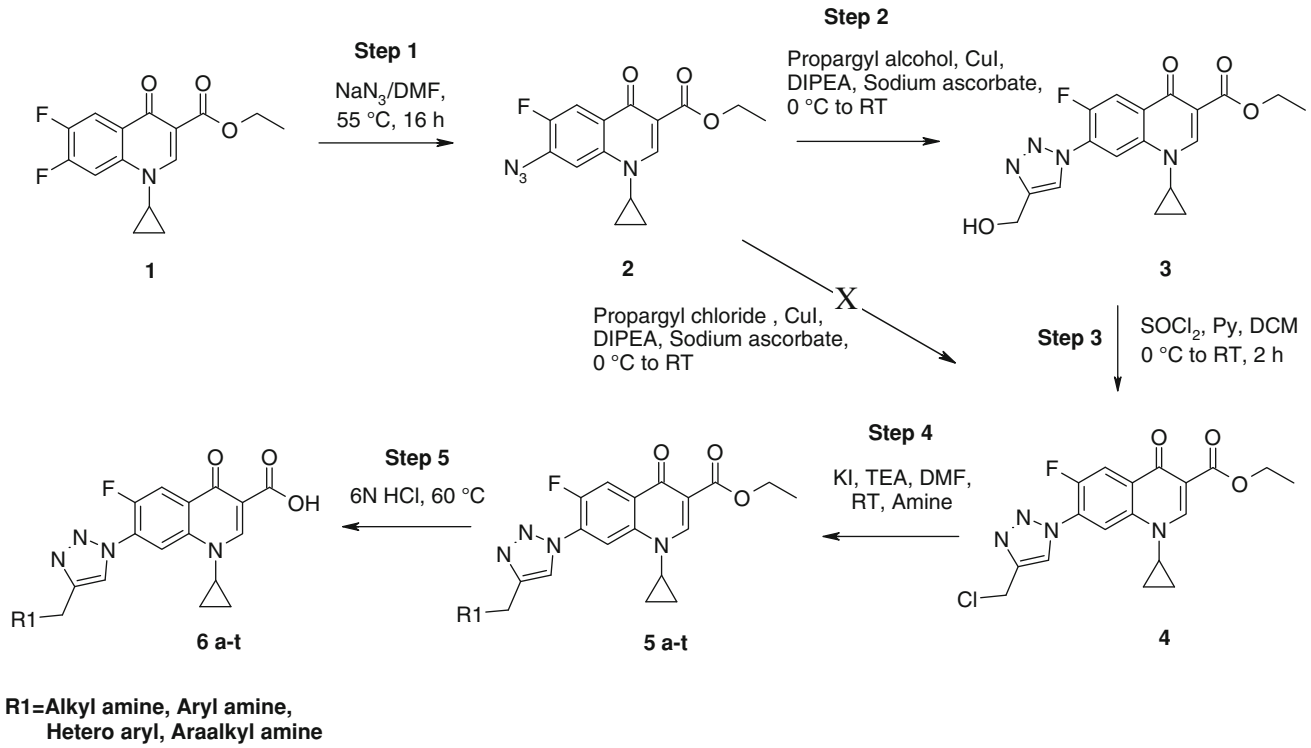
Result and discussion

Chemistry

The new fluoroquinolone derivatives described herein were synthesized as shown in Schemes 1. The quinolone ester **1** was conveniently synthesized from the commercially available 2,4,5-trifluoro-benzoic acid in four steps as per the reported procedure (Ledoussal et al, 1992) and the spectral data of the compound was in agreement with the reported data (Dubar et al, 2009). After having synthesized known compound **1,** reaction of compound **1** with sodium azide at 50 °C yielded selectively 7-azido derivate **2** in good yield. After having synthesized compound **2**, our initial efforts to convert compound **2**–**4** by reacting the compound **2** with propargyl chloride as per our earlier click chemistry protocol (Selvakumar Natesan et al, 2011) did not result the desired compound **4**. Unfortunately, similar reaction conditions with propargyl bromide also did not result the corresponding bromo analog of compound **4**.

At this juncture, we have planned to synthesize compound **4** in two steps from compound **2**. Then reaction of compound **2** with propargyl alcohol as per standard click chemistry conditions (Selvakumar Natesan et al, 2011) smoothly resulted in the compound **3** in good yield. Then the key intermediate **4** readily obtained in excellent yield (96 %) by reacting the compound **3** with thionyl chloride at room temperature. The amino alky derivatives **5a–t** smoothly obtained by reacting compound **4** with corresponding amines at room temperate. Finally, the target compounds **6a–t** were synthesized in good yields from their precursors **5a–t** by refluxing them with 6N hydrochloric acid at 60 °C.

The structures of all the newly synthesized compounds were confirmed by IR, ^{1}H and ^{13}C NMR, and LC mass spectral studies. The structure of compound **2** was confirmed by their IR and LCMS analyses. The IR spectrum of **2** revealed the presence of $–N_3$ group due to the appearance of strong band at 2119 cm^{-1}, while that of –C=O of ester was observed at 1718 cm^{-1}. Further, the LCMS showed its molecular ion peak at 317.2 (M+H), which is in accordance with its molecular formula $C_{15}H_{15}FN_4O_3$. The formation of alcohol **3** from azide **2** was evidenced by its IR, ^{1}HNMR, and LC–MS spectra. Its IR spectrum showed absorbance bands at 3474 and 1668 cm^{-1} indicating the presence of –OH and –C=O groups, respectively, while its



Scheme 1 Synthetic route to synthesize compounds **6a–t**

^{1}H NMR spectrum showed sharp singlet at δ 8.56 clearly confirming the conversion of $-N_3$ to [1,2,3] triazole. The LCMS spectrum of **3** showed a molecular ion peak at 373.1 (M+H), which matches with its molecular formula $C_{18}H_{17}FN_4O_4$.

The formation of chloro derivative **4** from alcohol **3** was confirmed by its ^{1}HNMR and LC–MS spectra. Its ^{1}H NMR spectrum showed sharp singlet at δ 4.99 confirming the formation of the chloro derivative **4**. The LCMS spectrum of **4** showed a molecular ion peak at 391.0 (M+H), which matches with its molecular formula $C_{18}H_{16}ClFN_4O_3$. The structures of compounds **5–t** were interpreted by their IR, ^{1}HNMR, and LCMS analyses. The IR spectrum of **5a** revealed the presence of ester –C=O group due to the appearance of strong band at 1725 cm^{-1}, while that of –C=O of quinoline was observed at 1698 cm^{-1}. In its ^{1}H NMR spectrum the appearance of a singlet at δ 2.22 confirmed the presence of newly introduced $-N(CH_3)_2$ group. Further, the LCMS showed its molecular ion peaks at 383.1 (M+H) and 400.0 (M+2+H), which is in accordance with its molecular formula $C_{20}H_{22}FN_5O_3$.

The structures of compounds **6a–t** were elucidated by their IR, ^{1}H and ^{13}C NMR, and LCMS analyses. The IR spectrum of **6a** revealed the presence of acid –OH group due to the appearance of absorbance bands at 2537 cm^{-1}, while that of –C=O of acid was observed at 1712 cm^{-1}. The ^{1}H NMR spectrum of **6a** showed singlet at δ 2.80, for six protons which correspond to $-N(CH_3)_2$ and appearance of broad singlet δ 11.16 (which disappeared on D_2O exchange) that corresponds to –OH proton of acid. The C13 NMR signals at 165.7 and 177.29 correspond to the presence of two different carbonyl fictional groups in the molecule and also signal at 42.81 confirms the presence of $N(CH_3)_2$. The structure of **6a** was further confirmed by LCMS. It showed the molecular ion peak at *m/z* 372.1 (M+H), which conforms to its molecular formula $C_{18}H_{18}FN_5O_3$.

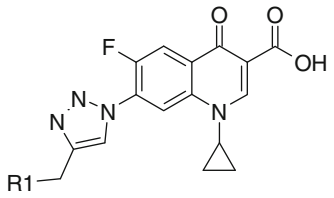
The physicochemical characteristics of the newly synthesized compounds are presented in Table 1.

Antibacterial evaluation

All the newly synthesized 20 compounds (**6a–t**) were evaluated for their in vitro antibacterial activities against human pathogens by means of standard twofold serial dilution method using agar media. The in vitro antibacterial activity were performed against three Gram-positive bacterial strains including Methicillin-resistant *Staphylococcus aureus*, Vancomycin-Resistant *Enterococcus faecalis*, and three Gram-negative strains including *Klebsiella pneumoniae* (clinical). Ciprofloxacin and Linezolid were used as reference drugs.

The data generated from this study (Table 2) showed that some of the target compounds exhibit good potency in inhibiting the growth of Gram-positive bacteria such as

Table 1 Physicochemical characteristics of N-substituted amino methyl-[1,2,3] triazolyl derivatives at C7 position of fluoroquinolones (**6a–o**)



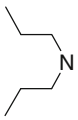
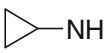
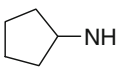
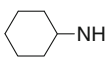
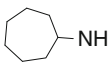
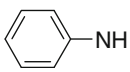
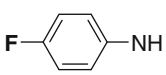
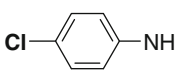
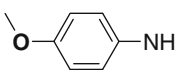
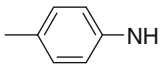
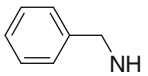
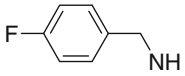
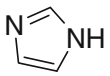
Compound	R1	MF/M.Wt.	Yield (%)	Mp[a] (°C)
6a		$C_{18}H_{18}FN_5O_{3./}$ 371.37	92	179.1–180.2 °C
6b		$C_{20}H_{22}FN_5O_3$/ 399.43	93	209.3–209.8 °C
6c		$C_{22}H_{26}FN_5O_3$/ 427.48	92	180.0–180.9 °C
6d		$C_{20}H_{20}FN_5O_3$/ 397.41	87	252.4–253.9 °C
6e		$C_{21}H_{22}FN_5O_3$/ 411.44	87	188.1–189.1 °C
6f		$C_{20}H_{20}FN_5O_4$/ 413.41	79	250.5–251.5 °C
6g		$C_{20}H_{21}FN_6O_3$/ 412.43	87	212.7–213.1 °C
6 h		$C_{19}H_{20}FN_5O_3$/ 385.40	82	285.2–286.7 °C
6i		$C_{19}H_{18}FN_5O_3$/ 383.39	84	221.4–222.9 °C
6j		$C_{21}H_{22}FN_5O_3$/ 411.44	86	280.4–282.3 °C
6 k		$C_{22}H_{24}FN_5O_3$/ 425.47	82	202.1–203.4 °C
6l		$C_{23}H_{26}FN_5O_3$/ 439.49	84	161.7-162.2 °C
6m		$C_{22}H_{18}FN_5O_3$/ 419.42	83	200.6–201.4 °C
6n		$C_{22}H_{17}F_2N_5O_3$/ 437.41	85	213.9–215.2 °C
6o		$C_{22}H_{17}ClFN_5O_3$/ 453.86	83	193.2–194.6 °C
6p		$C_{23}H_{20}FN_5O_4$/ 449.45	91	225.4–226.1 °C

Table 1 continued

Compound	R1	MF/M.Wt.	Yield (%)	Mp[a] (°C)
6q		$C_{23}H_{20}FN_5O_3$/ 433.45	89	213.2–214.0 °C
6r		$C_{23}H_{20}FN_5O_3$/ 433.45	81	259.0–259.6 °C
6s		$C_{23}H_{19}F_2N_5O_3$/ 451.44	82	249.7–250.2 °C
6t		$C_{19}H_{15}FN_6O_3$/ 394.37	86	129.2–131.0 °C

[a] Melting point of compounds at their decomposition

Table 2 Antibacterial activity of new fluoroquinolones **6a–t**

Compound	Gram positive panel MIC (μg/mL)			Gram negative panel MIC (μg/mL)		
	ATCC 29213 *Staphylococcus aureus* (MSSA)	ATCC 33591 *Staphylococcus aureus* (MRSA)	ATCC 700802 *Enterococcus faecalis* (VR)	AB 356 *Klebsiella pneumoniae* (Clinical)	BAA 747 *Acinetobacter baumannii*	ATCC 25238 *Moraxella catarrhalis*
6a	4	8	16	2	8	1
6b	8	32	32	16	16	16
6c	8	32	32	8	16	2
6d	2	8	16	2	8	1
6e	4	16	16	2	8	1
6f	8	16	16	16	16	4
6g	16	16	32	8	32	8
6h	16	16	16	4	16	1
6i	16	16	16	32	32	32
6j	16	16	16	4	16	1
6k	16	32	32	2	8	1
6l	32	32	32	16	16	8
6m	0.25	0.5	2	1	1	0.125
6n	0.25	1	4	2	2	0.25
6o	0.25	0.25	1	1	0.5	0.125
6p	0.5	0.5	2	4	8	0.5
6q	0.5	0.5	2	4	8	0.125
6r	2	2	4	1	8	1
6s	2	2	4	2	8	1
6t	32	32	32	32	32	8
Linezolid	4	2	2	>32	>32	4
Ciprofloxacin	0.5	0.5	0.5	0.125	0.5	0.25

Staphylococci aureus including MRSA and VRE *faecalis* (0.25–8.00 μg/mL). The in vitro activity of compound **6o** against Gram-positive bacteria such as Methicillin-resistant *Staphylococcus aureus* and Vancomycin-Resistant *E. faecalis* are superior to the marketed drugs Linezolid and Ciprofloxacin.

The in vitro activity of compound **6o** against Gram-negative bacteria such as *Klebsiella pneumonia, Acinetobacter baumannii, and Moraxella catarrhalis* are superior to the marketed drug Linezolid and comparable to Ciprofloxacin.

The antibacterial activity of compounds **6m** to **6q** suggested that introduction of *N*-aryl amino methyl-[1,2,3]

triazolyl derivatives at C-7 position of the fluoroquinolone significantly improved the antibacterial activity against Gram-positive strains with retention of activity against Gram-negative strains. However, *N*-alkyl amino methyl-[1,2,3] triazolyl derivatives are less potent than the reference compounds such as Linezolid and Ciprofloxacin.

Conclusion

The twenty new fluoroquinolone compounds (**6a–t**) were synthesized through multistep synthesis. The synthe sized compounds were characterized by ^{1}H NMR, ^{13}C NMR, ESI–MS, and IR. The in vitro antibacterial activity was examined using representative Gram-positive and Gram-negative strains. Out of the twenty derivatives, aryl substituted amino derivatives (**6m** to **6q**) exhibited very good potency in inhibiting the growth of MSSA, MRSA, and VRE *faecalis*. The in vitro activity of compounds 6**m** and **6o** against MSSA, MRSA, and VRE *faecalis* are superior to the marketed drugs Linezolid and Ciprofloxacin.

The antibacterial activity of compounds **6m** to **6q** suggested that introduction of N-aryl amino methyl-[1,2,3] triazolyl derivatives at C-7 position of the fluoroquinolone significantly improved the antibacterial activity against Gram-positive strains with retention of activity against Gram-negative strains.

Acknowledgments We are thankful to Anthem biosciences management, Anthem biosciences, Bangalore, India, for their invaluable support and allocation of resources for this work. We would like thank Analytical chemistry team, Department of analytical chemistry, Anthem biosciences, Bangalore, India, for having carried out all the analytical work.

References

Bryskier A, Chantot JF (1995) Classification and structure-activity relationships of fluoroquinolones. Drugs 49(suppl 2):16–28

De Souza MVN (2005) New fluoroquinolones: a class of potent antibiotics. Mini-Rev Med Chem 5:1009–1017

Domagala JM (1994) Structure-activity and structure-side-effect relationships for the quinolone antibacterials. J Antimicrob Chemother 33:685–706

Dubar F, Anquetin G, Pradines B, Dive D, Khalife J, Biot C (2009) Enhancement of the antimalarial activity of ciprofloxacin using a double prodrug/bioorganometallic approach. J Med Chem 52:7954–7957

Hooper David C (2001) Mechanisms of action of antimicrobials: focus on fluoroquinolones. Clin Infect Dis 32:S9–S15

Koga H, Itoh A, Murayama S, Suzue S (1980) Structure-activity relationships of antibacterial 6,7- and 7,8-disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids. J Med Chem 23(12):1358–1363

Ledoussal B, Bouzard D, Coroneos E (1992) Potent non-6-fluoro-substituted quinolone antibacterials: synthesis and biological activity. J Med Chem 35(1):198–200

Mitscher LA (2005) Bacterial topoisomerase inhibitors: quinolone and pyridone antibacterial agents. Chem Rev 105:559–592

Patpi SR, Pulipati L, Yogeeswari P, Sriram D, Jain N, Sridhar B, Murthy R, Anjana Devi T, Kalivendi SV, Kantevari S (2012) Design, synthesis, and structure-activity correlations of novel dibenzo[b,d]furan, dibenzo[b,d]thiophene, and *N*-methylcarbazole clubbed [1,2,3] triazoles as potent inhibitors of Mycobacterium tuberculosis. J Med Chem 55(8):3911–3922

Piddock LJV, Marshall AJ, Jin YF (1994) Activity of Bay y3118 against quinolone-susceptible and -resistant gram-negative and gram-positive bacteria. Antimicrob Agents Chemother 38:422–427

Selvakumar Natesan, Rajulu Gavara Govinda, Pazhanimuthu annamalia, ganesh sambasivam (2011) Histone deacetylase inhibitors, WO2011/021209 A1

Shanmugavelan P, Nagarajan S, Sathishkumar M, Ponnuswamy A, Yogeeswari P, Sriram D (2011) Efficient synthesis and in vitro antitubercular activity of [1,2,3] triazoles as inhibitors of *Mycobacterium tuberculosis*. Bioorg Med Chem Lett 21(24):7273–7276

Sumangala V, Poojary B, Chidananda N, Fernandes J, Kumari NS (2010) Synthesis and antimicrobial activity of [1,2,3] triazoles containing quinoline moiety. Arch Pharm Res 33(12):1911–1918