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Synthesis and Antibacterial Activity of Novel Levofloxacin Analogues

TONG-XIN ZHANG[1], WEI-XI ZHANG[1], HUA-JUN ZHU[2], LONG LIANG[2], ZHI-PENG CHENG[2] and MEI-MING LUO[1,*]

[1]Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P.R. China
[2]Sichuan Kelun Pharmaceutical Co., Ltd, 18, 19/F, 2/Building, Jinjiang Times Garden, 107 Jinli West Road, Chengdu 610067, P.R. China

*Corresponding author: Tel: +86 28 85462021; E-mail: luomm@scu.edu.cn

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To search for new fluoroquinolones with better biological activities, twenty-six levofloxacin analogues were designed, synthesized and evaluated for antimicrobial activity against Gram-positive and Gram-negative bacterias. The results indicated that most compounds tested in this study exhibited comparable or better antimicrobial activity than levofloxacin as reference drug. Among these compounds, **ZY6a** was the most active compound against *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, its activity was found to be 2 to 16 times better than levofloxacin.

Keywords: Fluoroquinolones, Levofloxacin, 2-Methylpiperazine, Antibacterial activity, Synthesis.

INTRODUCTION

Fluoroquinolones (FQs) constitute an important class of antibacterial agents which play a major role in the treatment of ocular infections, soft tissue infections, respiratory infections, typhoid fever, bone-joint infections, community acquired pneumonia, *etc*[1]. The fluoroquinolones express antibacterial action by interfering with the function of two bacterial type-II topoisomerase enzymes[2], DNA gyrase and topoisomerase IV. In general, the portions of a fluoroquinolone molecule (Fig. 1), C-3 carboxyl, C-4 keto, C-6 fluorine, are considered as essential, major improvements focus on C-7 position[3]. The substituents at C-7 position are associated with some properties of fluoroquinolones such as their antibacterial spectrum, bioavailability, solubility and pharmacokinetics[4]. The most common substituents at C-7 are cyclic nitrogen-containing groups such as piperazine derivatives which are extensively investigated. Moreover, the basic N-4 position of piperazine is a suitable site for introducing new functionality[5]. Levofloxacin (Fig. 1), a chiral version of the earlier fluoroquinolone ofloxacin, has a fused ring connecting the N-1 to C-8 position, which is different from the typical quinolones bicyclic ring substructure. It has already been widely used in human and veterinary medicine and expresses broad-spectrum antibacterial activity[6]. Although many advances in the fluoroquinolone field, the growing of multidrug-resistant pathogens has become a great cause for concern. It is therefore important to search for new fluoroquinolones capable of dealing with the resistant strains.

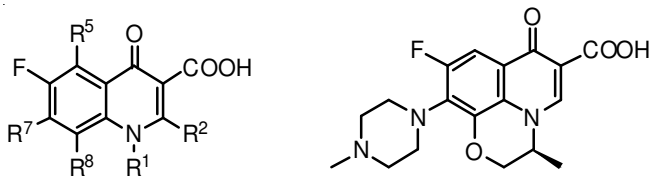


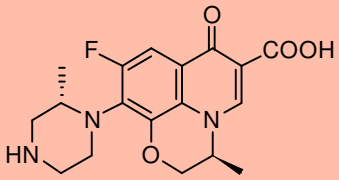
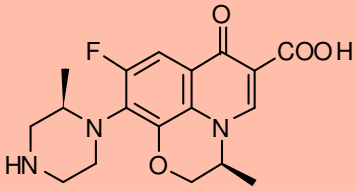
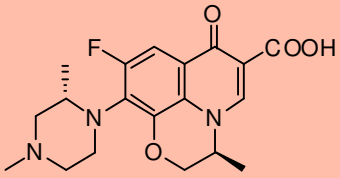
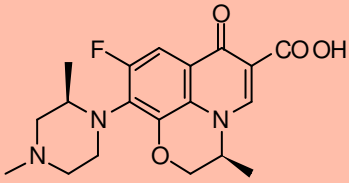
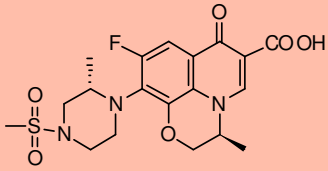
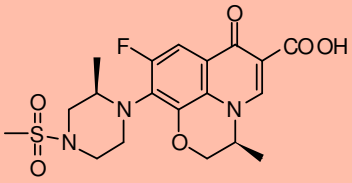
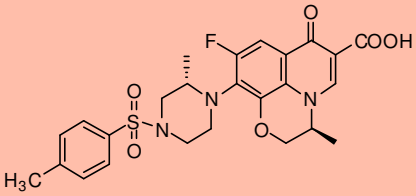
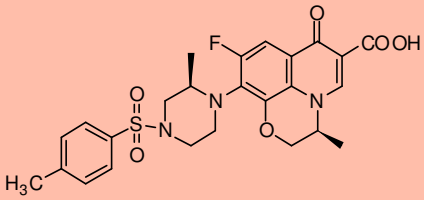
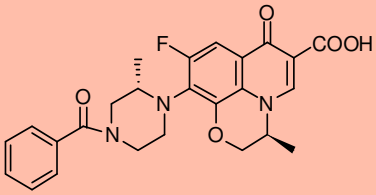
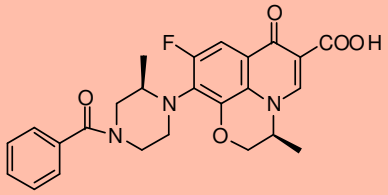
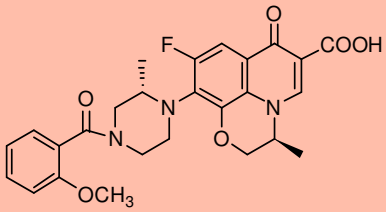
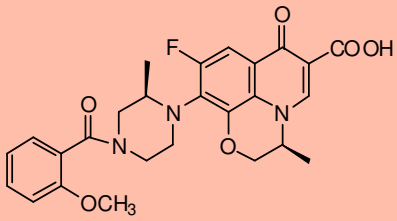
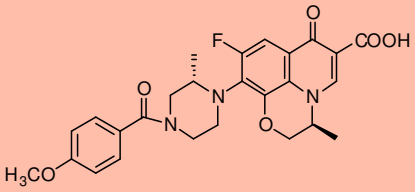
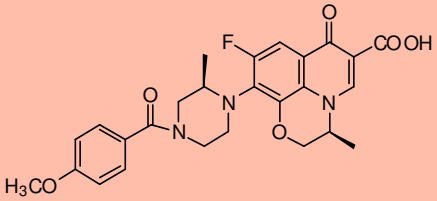
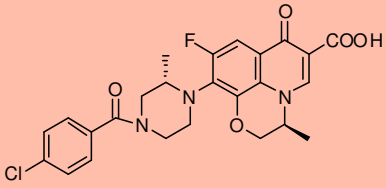
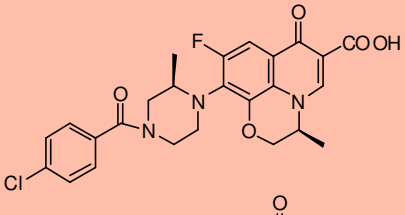
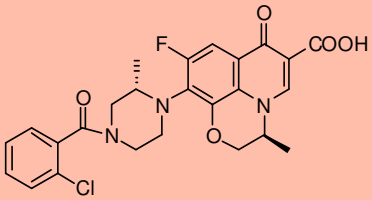
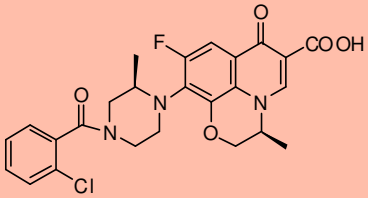
Fig. 1. Structural features of fluoroquinolones and levofloxacin

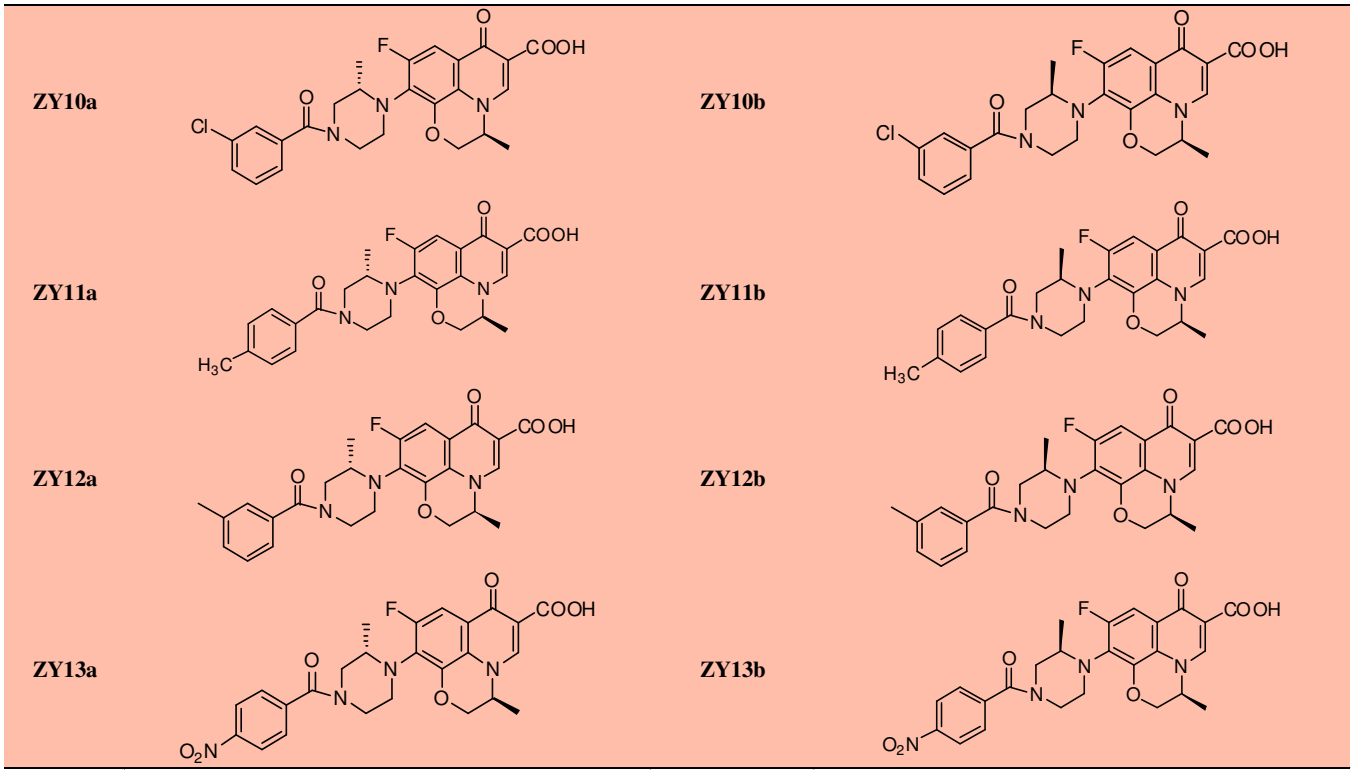
The knowledge that planar feature of piperazinyl ring at C-7 and naphthyridine ring in a fluoroquinolone molecule is associated with antibacterial activity attracted our attention[7]. In this paper, we designed and synthesized novel lead fluoroquinolones by introducing 2-methylpiperazin-1-yl ring to tricyclic ring structure of levofloxacin at C-7 position, which could change the former dihedral angle between piperazinyl ring and naphthyridine ring. In addition, a new series of derivatives with different kinds of Pharmacophores[8] (alkyl, acyl and sulfonyl) were also synthesized (Table-1).

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and were used without further purification. Melting points were determined with XRC-1 melting point apparatus without corrected. Thin layer chromatography was carried out using Merck silica gel GF254 plates and spots were visualized with ultraviolet (UV) light. Mass spectra was recorded with Agilent 6210 spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionization (ESI) method. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded

TABLE-1
STRUCTURES OF THE NEW FLUOROQUINOLONES

Entry	Compound	Entry	Compound
ZY1a		**ZY1b**	
ZY2a		**ZY2b**	
ZY3a		**ZY3b**	
ZY4a		**ZY4b**	
ZY5a		**ZY5b**	
ZY6a		**ZY6b**	
ZY7a		**ZY7b**	
ZY8a		**ZY8b**	
ZY9a		**ZY9b**	

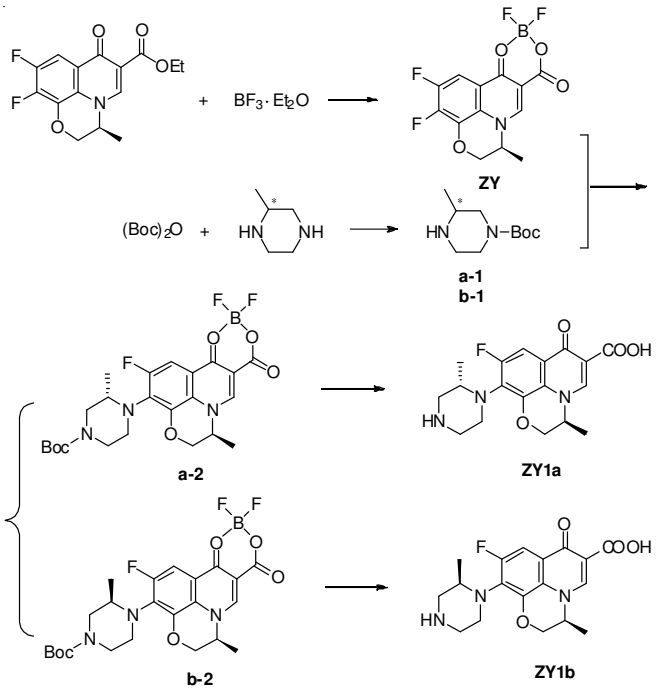


in $CDCl_3$, D_2O or DMSO-d_6. Chemical shifts are reported in ppm using TMS as internal standard.

General procedure for the synthesis of compounds ZY1a and ZY1b (Scheme-I): Compounds **ZY**, **a-1** and **b-1** were synthesized according to the literature[9]. A solution of **a-1**(**b-1**) (2 g, 10 mmol) in DMSO (20 mL) was slowly added to dimethyl sulfoxide (40 mL) solution containing **ZY** (1.65 g, 5 mmol) under an argon atmosphere. The mixture was stirred at 40 °C until the reactants were completely converted by TLC monitoring. Then the reaction mixture was poured into water (100 mL) in an ice-bath. The resulting mixture was filtered and the residue was the crude product **a-2**(**b-2**). A solution of **a-2**(**b-2**) in methanol (60 mL) was stirred for 12 h under reflux. The concentrated aqueous HCl (12 mL) was carefully added and the mixture was stirred for another 12 h under reflux. The solvent was evaporated, the residue was then dissolved in water and neutralized with aqueous NaOH (20 %). The resulting mixture was filtered and the residue was recrystallized from EtOH to afford the pure products **ZY1a**, **ZY1b**.

ZY1a: White solid. Yield: 75 %. m.p.: 203-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1H), 7.79 (d, $^3J_{F\text{-}H}$ = 10.8 Hz, 1H), 4.50 (d, J = 9.2 Hz, 2H), 4.36-4.39 (m, 1H), 3.67 (s, 1H), 3.07-3.24 (m, 5H), 2.70-2.75 (m, 1H), 2.17 (s, 1H), 1.62 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, D_2O): δ = 174.6, 168.4, 159.3, 145.8, 144.1, 128.9 , 124.5, 121.7, 105.7, 103.0, 102.8, 68.1, 56.3, 50.7, 48.4, 46.1, 43.3, 17.0, 15.1. HRMS (ESI): *m/z* calcd. for $C_{18}H_{21}N_3O_4F$ $[M + H]^+$: 362.1516, found: 362.1514.

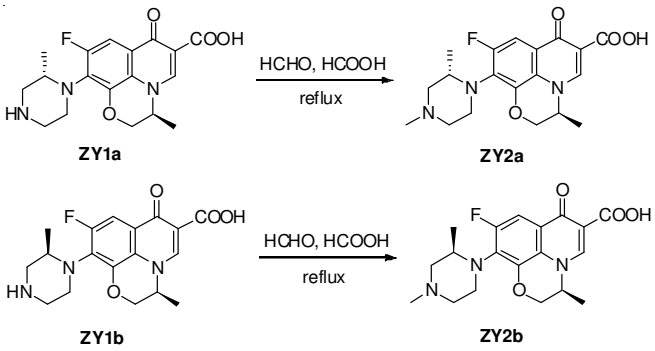
ZY1b: White solid. Yield: 68 %. m.p.: 193-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s,1H) , 7.77 (d, $^3J_{F\text{-}H}$ = 11.2 Hz, 1H), 4.46-4.50 (m, 2H), 4.34-4.37 (m,1H), 3.56 (d, J = 6.8 Hz, 1H), 2.98-3.19 (m, 5H), 2.66-2.71 (m, 1H), 2.17 (s, 1H), 1.63 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H). ^{13}C



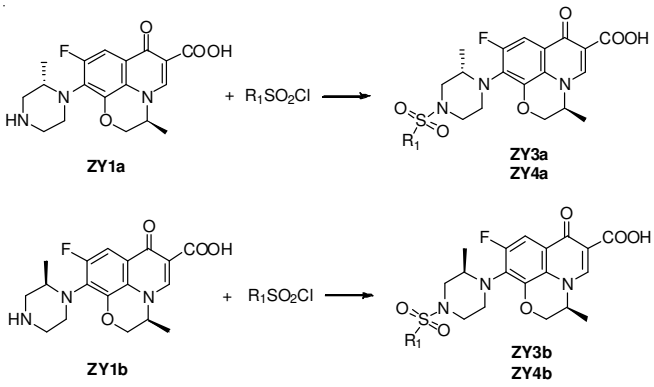
Scheme-I: Synthetic routes to compounds **ZY1a** and **ZY1b**

NMR (100 MHz, DMSO): δ = 176.4, 165.9, 158.9, 156.4, 146.1, 144.5, 128.9, 128.8, 124.5, 122.9, 122.9, 106.9, 102.8, 102.5, 68.2, 54.8, 49.9, 48.4,.46.2, 43.3, 17.9, 15.9. HRMS (ESI): *m/z* calcd. for $C_{18}H_{21}N_3O_4F$ $[M + H]^+$: 362.1516, found: 362.1513.

General procedure for the synthesis of compounds ZY2a, **ZY2b (Scheme-II):** The mixture of **ZY1a** (**ZY1b**) (1 g, 3 mmol), formaldehyde solution (1 g, 12 mmol) and formic acid (20 mL) was refluxed for 12 h under argon with stirring. After cooling to room temperature, the solvent was removed



Scheme-II: Synthetic routes to compounds **ZY2a** and **ZY2b**



ZY3a, 3b: R_1 = CH_3 **ZY4a, 4b: R_1 = 4-methylphenyl**

Scheme-III: Synthetic routes to compounds **ZY3a**, **ZY4a**, **ZY3b** and **ZY4b**

under reduced pressure. The residue was recrystallized from ethyl acetate to afford the pure products **ZY2a**, **ZY2b**.

ZY2a: White solid. Yield: 85 %. m.p.: 184-188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.43 (s, 1H), 7.76 (d, $^3J_{F\text{-}H}$ = 10.0 Hz, 1H), 4.52-4.57 (m, 2H), 4.39-4.42 (m, 1H), 3.99 (s, 1H), 3.61-3.67 (m, 1H), 3.18-3.26 (m, 3H), 2.89-2.94 (m, 1H), 2.68 (s, 3H), 2.51-2.56 (m, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 167.3, 166.9, 145.0, 144.3, 130.2, 124.2, 123.9, 108.2, 104.9, 104.7, 68.5, 60.7, 55.6, 54.3, 51.4, 48.6, 44.5, 18.4, 17.0. HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}N_3O_4F$ [M + H]$^+$: 376.1673, found: 376.1670.

ZY2b: White solid. Yield: 82 %. m.p.: 194-196 °C. ^{1}H NMR (400 MHz, DMSO): δ = 9.01 (s, 1H), 8.16 (s, 1H), 7.58 (d, $^3J_{F\text{-}H}$ = 12.4 Hz, 1H), 4.92-4.97 (m, 1H), 4.59 (d, *J* = 10.4 Hz, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 3.60 (s, 1H), 3.14-3.19 (m, 2H), 2.70-2.72 (m, 1H), 2.60-2.62 (m, 1H), 2.40-2.45 (m, 1H), 2.28 (s, 3H), 2.11-2.16 (m, 1H), 1.43 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 176.9, 166.4, 163.9, 159.5, 157.0, 146.7, 144.4, 131.0, 130.9, 125.1, 122.7, 107.4, 103.3, 103.1, 68.5, 61.9, 55.5, 55.2, 52.4, 49.1, 46.0, 18.4, 17.1. HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}N_3O_4F$ [M + H]$^+$: 376.1673, found: 376.1671.

General procedure for the synthesis of compounds ZY3a, ZY4a, ZY3b, ZY4b (Scheme-III): To a mixture of **ZY1a** (**ZY1b**) (1 g, 3 mmol), triethylamine (1 mL, 6 mmol) and CH_2Cl_2 (40 mL), a solution of sulfonyl chloride (6 mmol) in CH_2Cl_2 (5 mL) was slowly added. The mixture was stirred for another 2 h at room temperature, then washed with aqueous HCl and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to afford the pure products **ZY3a**, **ZY4a**, **ZY3b**, **ZY4b**.

ZY3a: Light yellow solid. Yield: 89 %. m.p.: 218-222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.80 (s, 1H), 8.69 (s, 1H), 7.74 (d, $^3J_{F\text{-}H}$ = 10.8 Hz, 1H), 4.39-4.59 (m, 3H), 3.75 (s, 1H), 3.27-3.57 (m, 6H), 2.85-2.96 (m, 1H), 2.85 (s, 3H), 1.62 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 167.2, 159.2, 156.7, 145.4, 143.3, 130.8, 130.7, 124.5, 122.8, 107.8, 105.0, 104.8, 68.6, 55.8, 53.1, 51.9, 48.9, 46.4, 34.7, 18.5, 16.0. HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}N_3O_6SF$ [M + H]$^+$: 440.1292, found: 440.1293.

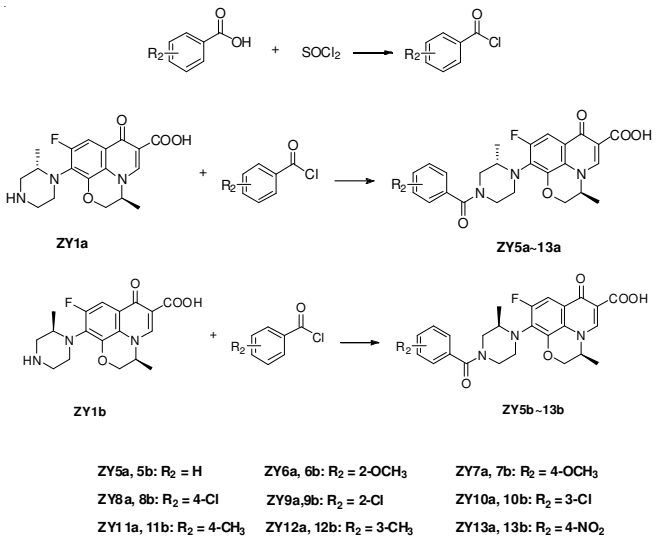
ZY4a: Light yellow solid. Yield: 90 %. m.p.: 146-150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.78 (s, 1H), 8.65 (s, 1H), 7.66-7.72 (m, 3H), 7.36-7.52 (m, 2H), 4.34-4.55 (m, 3H), 3.75 (s, 1H), 3.26-3.41 (m, 4H), 2.95-2.99 (m, 1H), 2.58-2.63 (m, 1H), 2.58 (s, 3H), 1.44 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 166.9, 158.8, 157.2, 145.0, 143.9, 132.7, 130.9, 130.8, 129.8, 127.8, 124.3, 123.2, 108.1, 104.9, 104.7, 68.4, 55.5, 52.6, 52.3, 48.8, 46.7, 21.6, 18.4, 16.2. HRMS (ESI): *m/z* calcd. for $C_{25}H_{27}N_3O_6SF$ [M + H]$^+$: 516.1605, found: 516.1603.

ZY3b: Light yellow solid. Yield: 90 %. m.p.: 202-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.78 (s, 1H), 8.68 (s, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 10.8 Hz, 1H), 4.38-4.56 (m, 3H), 3.71(d, *J* = 6.0 Hz, 1H), 3.27-3.56 (m, 6H), 2.92-2.97 (m, 1H), 2.85 (s, 3H), 1.62 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 166.9, 158.9, 157.2, 145.1, 143.3, 130.9, 130.8, 124.5, 123.2, 123.2, 108.1, 104.8, 104.7, 68.4, 55.5, 52.9, 52.1, 48.8, 46.5, 34.6, 18.4, 16.1. HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}N_3O_6SF$ [M + H]$^+$: 440.1292, found: 440.1295.

ZY4b: Light yellow solid. Yield: 87 %. m.p.: 142-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.76 (s, 1H), 8.64 (s, 1H), 7.66-7.74 (m, 3H), 7.36-7.38 (m, 2H), 4.44-4.51 (m, 2H), 4.33-4.35 (m, 1H), 3.72 (s, 1H), 3.32-3.40 (m, 4H), 2.95-2.98 (m, 1H), 2.59-2.64 (m, 1H), 2.47 (s, 3H), 1.61 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 166.9, 144.9, 143.9, 143.2, 132.8, 130.9, 130.8, 129.8, 127.8, 124.4, 123.4, 108.2, 105.0, 104.8, 68.3, 55.4, 52.7, 52.3, 48.8, 46.7, 21.6, 18.4, 16.2. HRMS (ESI): *m/z* calcd. for $C_{25}H_{27}N_3O_6SF$ [M + H]$^+$: 516.1605, found: 516.1600.

General procedure (Scheme-IV) for the synthesis of compounds ZY5a-13a, ZY5b-13b: The mixture of aryl carboxylic acid (6 mmol) and thionyl chloride (15 mL) was stirred for 3 h under reflux. Redundant thionyl chloride was distilled off under reduced pressure to obtain the corresponding acyl chloride. To a mixture of **ZY1a** (**ZY1b**) (1 g, 3 mmol), triethylamine (1 mL, 6 mmol) and CH_2Cl_2 (40 mL), a solution of the prepared acyl chloride in CH_2Cl_2 (5 mL) was slowly added. The mixture was stirred for another 2 h at room temperature, then washed with aqueous HCl and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to afford the pure products **ZY5a-13a**, **ZY5b-13b**.

ZY5a: Light yellow solid. Yield: 90 %. m.p.: 232-235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.82 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 11.2Hz, 1H), 7.44 (s, 5H), 4.49-4.57 (m, 2H), 4.37-4.41 (m, 1H), 4.06-4.21 (m, 1H), 3.12-3.71 (m, 6H), 1.62 (d, *J* = 6.4 Hz, 3H), 0.95-1.09 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 170.7, 166.9, 159.2, 156.7, 145.1, 143.1,



Scheme-IV: Synthetic routes to compounds **ZY5a-13a** and **ZY5b-13b**

135.7, 131.1, 130.9, 129.8, 128.6, 127.1, 124.4, 122.9, 107.9, 104.9, 104.7, 68.5, 55.6, 53.3, 48.4, 42.9, 18.4, 16.0. HRMS (ESI): *m/z* calcd. for $C_{22}H_{25}N_3O_5F$ $[M + H]^+$: 466.1778, found: 466.1775.

ZY6a: Light yellow solid. Yield: 83 %. m.p.: 226-230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.84 (s, 1H), 8.65 (s, 1H), 7.76 (d, $^3J_{F\text{-}H}$ = 11.6Hz, 1H), 7.28-7.39 (m, 2H), 6.93-7.01 (m, 2H), 4.46-4.55 (m, 2H), 4.37-4.39 (m, 1H), 4.03-4.09 (m, 1H), 3.72-3.74 (d, 3H), 3.07-3.68 (m, 6H), 1.62 (d, *J* = 6.4 Hz, 3H), 0.90-0.96 (m, 3H). ^{13}C NMR (100 MHz, CDCl3): δ = 177.0, 168.2, 168.2, 167.0, 155.2, 145.1, 131.3, 131.2, 130.6, 128.3, 128.1, 127.8, 125.5, 124. 6, 124.5, 122.4, 121.1, 111.1, 110.9, 107.9, 104.9, 104.8, 68.5, 55.6, 55.6, 53.4, 53.1, 52.7, 49.1, 48.5, 47.9, 47.7, 47.6, 42.4, 42.2, 18.4, 16.1, 15.8, 15.7, 15.4. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_6F$ $[M + H]^+$: 496.1884, found: 496.1886.

ZY7a: Light yellow solid. Yield: 88 %. m.p.: 136-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.83 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 10.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.48-4.55 (m, 2H), 4.40 (d, *J* = 10.0 Hz, 1H), 4.02 (s, 1H), 3.18-3.85 (m, 6H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 170.7, 167.0, 160.9, 159.3, 156.8, 145.1, 143.0, 131.1, 130.9, 129.2, 127.6, 124.4, 123.0, 122.9, 113.8, 108.0, 104.9, 104.8, 68.5, 55.6, 55.4, 53.4, 49.2, 18.4, 16.1. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_6F$ $[M + H]^+$: 496.1884, found: 496.1881.

ZY8a: Light yellow solid. Yield: 80 %. m.p.: 210-212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.80 (s, 1H), 8.67 (s, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 10.8 Hz, 1H), 7.39-7.44 (m, 4H), 4.49-4.57 (m, 2H), 4.38-4.41 (m, 1H), 4.06-4.18 (m, 1H), 3.13-3.73 (m, 6H), 1.62 (d, *J* = 6.8 Hz, 3H), 0.95-1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 169.7, 167.0, 159.2, 156.7, 145.2, 143.1, 135.9, 133.9, 130.9, 130.8, 128.7, 124.4, 122.9, 107.9, 104.9, 104.8, 68.5, 55.6, 53.4, 48.5, 18.4, 15.9. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_3O_5ClF$ $[M + H]^+$: 500.1389, found: 500.1386.

ZY9a: Light yellow solid. Yield: 75 %. m.p.: 230-232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.81 (s, 1H), 8.66 (d, *J* = 4 Hz, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 10.8 Hz, 1H), 7.33-7.44 (m, 4H), 4.46-4.53 (m, 2H), 4.37-4.39 (m, 1H), 3.96-4.05 (m, 1H), 3.05-3.68 (m, 6H), 1.62 (d, *J* = 6.8 Hz, 3H), 0.89-1.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 167.3, 167.0, 145.1, 135.7, 135. 6, 135.4, 131.2, 131.1, 130.4, 129.9, 129.7, 128.1, 127.9, 127.3, 127.2, 124.4, 122.6, 107.9, 105.0, 104.8, 68.5, 55.6, 53.2, 52.7, 49.4, 49.0, 48.6, 47.8, 47.6, 42.4, 42.2, 18.4, 16.4, 15.9, 15.5. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_3O_5ClF$ $[M + H]^+$: 500.1389, found: 500.1388.

ZY10a: Light yellow solid. Yield: 78 %. m.p.: 94-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.80 (s, 1H), 8.66 (s, 1H), 7.78 (d, $^3J_{F\text{-}H}$ = 12.8 Hz, 1H), 7.32-7.45 (m, 4H), 4.49-4.55 (m, 2H), 4.38-4.40 (d, 1H), 4.06-4.18 (d, 1H), 3.56-3.72 (m, 3H), 3.13-3.42 (m, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 0.96-1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 169.2, 166.9, 145.1, 137.4, 134.7, 130.9, 130.0, 127.3, 125.2, 124.4, 123.1, 108.1, 105.0, 104.9, 68.5, 55.6, 53.9, 53.3, 49.4, 48.4, 18.4, 16.1. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_3O_5ClF$ $[M + H]^+$: 500.1389, found: 500.1381.

ZY11a: Light yellow solid. Yield: 85 %. m.p.: 216-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.83 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 11.2Hz, 1H), 7.35-7.37 (m, 2H), 7.22-7.24 (m, 2H), 4.48-4.54 (m, 2H), 4.36-4.40 (m, 1H), 4.06-4.19 (m, 1H), 3.60-3.73 (m, 3H), 3.13-3.41 (m, 3H), 2.39 (s, 3H), 1.62 (d, *J* = 6.8 Hz, 3H), 0.95-1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 166.9, 144.9, 140.0, 132.7, 131.2, 129.2, 127.3, 124.4, 108.1, 105.1, 104.9, 68.4, 55.6, 21.4, 18.4, 15.9. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_5F$ $[M + H]^+$: 480.1935, found: 480.1933.

ZY12a: Light yellow solid. Yield: 78 %. m.p.: 138-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.83 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F\text{-}H}$ = 11.2 Hz, 1H), 7.21-7.33 (m, 4H), 4.49-4.58 (m, 2H), 4.37-4.40 (m, 1H), 4.04-4.21 (m, 1H), 3.58-3.71 (d, 3H), 3.11-3.43 (m, 3H), 2.39 (s, 3H), 1.62 (d, *J* = 6.8 Hz, 3H), 0.95-1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 166.9, 144. 9, 138.5, 135.6, 130.5, 128.4, 127.8, 124.4, 124.0, 108.1, 105.1, 104.9, 68.4, 55.6, 53.1, 48.5, 21.4, 18.4. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_5F$ $[M + H]^+$: 480.1935, found: 480.1938.

ZY13a: Light yellow solid. Yield: 75 %. m.p.: 242-245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.77 (s, 1H), 8.66 (s, 1H), 8.33 (d, *J* = 8.4 Hz, 2H), 7.78 (d, $^3J_{F\text{-}H}$ = 11.2 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 4.50-4.56 (m, 2H), 4.41-4.42 (m, 1H), 4.10-4.39 (m, 1H), 3.44-3.80 (m, 4H), 3.16-3.27 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.10-1.11 (m, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 176.5, 167.4, 165.9, 158.4, 155.9, 147. 8, 146.3, 143.7, 142.1, 130.0, 129.8, 128.3, 124.6, 123.8, 122.2, 122.1, 106.9, 103.0, 102.8, 68.3, 54.9, 52.6, 48.3, 47.9, 47.6, 17.8, 15.6, 15.3. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_4O_7F$ $[M + H]^+$: 511.1629, found: 511.1623.

ZY5b: Light yellow solid. Yield: 91 %. m.p.: 264-269 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.81 (s, 1H), 8.66 (s,1H), 7.77 (d, $^3J_{F\text{-}H}$ = 11.2 Hz, 1H), 7.45-7.52 (m, 5H), 4.48-4.51 (m, 2H), 4.37-4.39 (m, 1H), 4.19-4.20 (m, 1H), 3.15-3.58 (m, 6H), 1.63 (d, *J* = 6.4 Hz, 3H), 0.95-1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 170.8, 166.9, 156.8, 144.9, 142.9, 135.6, 131.2, 129.9, 128.6, 124.5, 123.0, 108.0, 104.9, 104.7, 68.3, 55.4, 53.3, 50.8, 48.5, 18.4, 16.0. HRMS (ESI): *m/z* calcd. for $C_{22}H_{25}N_3O_5F$ $[M + H]^+$: 466.1778, found: 466.1771.

ZY6b: Light yellow solid. Yield: 75 %. m.p.: 216-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.84 (s, 1H), 8.65 (s, 1H),

7.76 (d, $^3J_{F-H}$ = 11.2 Hz, 1H), 7.35-7.40 (m, 1H), 7.31-7.36 (m, 1H), 7.01-7.03 (m, 1H), 6.93-7.00 (m, 2H), 4.47-4.54 (m, 2H), 4.36-4.39 (m, 2H), 3.85-3.88 (m, 3H), 3.07-3.70 (m, 6H), 1.63 (d, *J* = 6.4 Hz, 3H), 0.89-1.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 166.9, 155.2, 144.7, 130.6, 128.1, 121.1, 110.9, 108.2, 104.9, 68.2, 55.5, 55.4, 53.3, 53.2, 47.7, 47.6, 18.4, 16.1. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_6F$ [M + H]$^+$: 496.1884, found: 496.1882.

ZY7b: Light yellow solid. Yield: 85 %. m.p.: 110-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.81 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F-H}$ = 11.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.36-4.51 (m, 3H), 4.02 (s, 1H), 3.85-3.87 (m, 3H), 3.66-3.70 (m, 3H), 3.20-3.32 (m, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 170.7, 166.9, 160.9, 159.4, 156.9, 144.9, 142.9, 131.2, 131.1, 129.2, 127.7, 124.5, 122.9, 113.8, 108.0, 104.9. 104.7, 68.3, 55.5, 55.4, 53.3, 48.0, 18.4, 16.1. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_6F$ [M + H]$^+$: 496.1884, found: 496.1885.

ZY8b: Light yellow solid. Yield: 80 %. m.p.: 238-240 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.79 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F-H}$ = 10.8 Hz, 1H), 7.39-7.44 (m, 4H), 4.48-4.55 (m, 2H), 4.36-4.40 (m, 1H), 4.08-4.18 (m, 1H), 3.23-3.67 (m, 6H), 1.63 (d, *J* = 6.8 Hz, 3H), 0.95-1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 169.7, 167.0, 159.3, 156.8, 145.1, 142.9, 135.9, 133.9, 131.0, 130.9, 124.6, 122.8, 107.9, 104.9, 104.7, 68.4, 55.5, 53.4, 49.4, 48.5, 18.5, 15.9. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_3O_5ClF$ [M + H]$^+$: 500.1389, found: 500.1382.

ZY9b: Light yellow solid. Yield: 75 %. m.p.: 232-236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.80 (s,1H), 8.65-8.66 (d, 1H), 7.77 (d, $^3J_{F-H}$ = 11.2 Hz, 1H), 7.33-7.45 (m, 4H), 4.46-4.52 (m, 2H), 4.36-4.39 (m, 1H), 3.96-3.99 (m, 1H), 3.05-3.66 (m, 6H), 1.63 (d, *J* = 6.4 Hz, 3H), 1.09-1.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 167.3, 167.0, 158.9, 156.6, 145.1, 142.8, 142.4, 135.7, 135.5, 135.4, 131.1, 130.5, 130.4, 130.3, 129.9, 129.7, 128.1, 127.9, 127.9, 127.4, 127.2, 124.6, 122.9, 122.5, 107.9, 104.9, 104.7, 68.4, 55.5, 53.3, 53.1, 52.7, 49.4, 49.0, 48.6, 47.7, 47.6, 47.5, 42.4, 42.2, 18.5, 16.39, 16.0, 15.9, 15.5. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_3O_5ClF$ [M + H]$^+$: 500.1389, found: 500.1387.

ZY10b: Light yellow solid. Yield: 81 %. m.p.: 114-118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.80 (s, 1H), 8.67 (s, 1H), 7.77 (d, $^3J_{F-H}$ = 10.8 Hz, 1H), 7.32-7.45 (m, 4H), 4.49-4.58 (m, 2H), 4.37-4.40 (m, 1H), 4.06-4.21 (m, 1H), 3.56-3.78 (m, 3H), 3.15-3.40 (m, 3H), 1.64 (d, *J* = 6.8 Hz, 3H), 0.96-1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 169.2, 166.9, 144.9, 137.4, 134.7, 130.0, 127.3, 125.2, 124.5, 123.2, 108.2, 105.1, 104.9, 68.3, 55.4, 53.9, 48.4, 18.4, 15.9. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_3O_5ClF$ [M + H]$^+$: 500.1389, found: 500.1385.

ZY11b: Light yellow solid. Yield: 83 %. m.p.: 228-230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.82 (s, 1H), 8.66 (s, 1H), 7.77 (d, $^3J_{F-H}$ = 11.2 Hz, 1H), 7.74-7.77 (m, 2H), 7.23-7.24 (m, 2H), 4.47-4.56 (m, 2H), 4.35-4.39 (m, 1H), 4.19-4.21 (m, 1H), 3.61-3.69 (m, 3H), 3.39-3.50 (m, 3H), 2.39 (s, 3H), 1.63 (d, *J* = 6.4 Hz, 3H), 0.95-1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 166.9, 144.8, 140.0, 132.7, 131.2, 129.2, 127.3, 124.5, 123.1, 108.2, 105.0, 104.9, 68.3, 55.4, 53.1, 48.6, 21.4, 18.4, 15.9. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_5F$ [M + H]$^+$: 480.1935, found: 480.1937.

ZY12b: Light yellow solid. Yield: 80 %. m.p.: 130-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.80 (s, 1H), 8.65 (s, 1H), 7.78 (d, $^3J_{F-H}$ = 11.2 Hz, 1H), 7.21-7.33 (m, 4H), 4.48-4.53 (m, 2H), 4.36-4.38 (m, 1H), 4.06-4.19 (m, 1H), 3.58-3.77 (m, 3H), 3.13-3.40 (m, 3H), 2.39 (s, 3H), 1.63 (d, *J* = 6.4 Hz, 3H), 0.95-1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 166.9, 145.1, 138.5, 135.6, 131.1, 130.6, 128.4, 127.7, 124.5, 124.0, 108.0, 104.9, 104.7, 68.4, 55.5, 53.5, 48.4, 21.4, 18.5, 16.1. HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}N_3O_5F$ [M + H]$^+$: 480.1935, found: 480.1932.

ZY13b: Light yellow solid. Yield: 78 %. m.p.: 242-244 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.76 (s, 1H), 8.66 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 2H), 7.78 (d, $^3J_{F-H}$ = 8.8 Hz, 1H), 7.63-7.65 (m, 2H), 4.49-4.56 (m, 2H), 4.38-4.41 (m, 1H), 4.11-4.25 (m, 1H), 3.42-3.79 (m, 4H), 3.17-3.26 (m, 2H), 1.64 (d, *J* = 6.8 Hz, 3H), 0.97-1.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 166.8, 148.5, 144.9, 141.8, 128.2, 124.5, 124.0, 108.2, 105.0, 104.9, 68.4, 55.4, 53.8, 53.2, 49.4, 48.5, 43.9, 18.4, 16.1, 15.9. HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}N_4O_7F$ [M + H]$^+$: 511.1629, found: 511.1626.

RESULTS AND DISCUSSION

The newly synthesized compounds were evaluated for antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus epidermidis*) and Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) using conventional agar-dilution method. The minimum inhibitory concentration (MIC) values were determined by comparison with levofloxacin as reference drug (Table-2).

In general, most compounds exhibited potent antibacterial activity against Gram-positive and Gram-negative bacteria. The MIC values of newly synthesized compounds against *Staphylococcus* strains indicated that most compounds (**ZY5a**, **ZY6a**, **ZY7a**, **ZY8a**, **ZY6b**) possessed a comparable or better antibacterial activity with respect to reference drug. Compound **ZY6a** (MIC = 0.03 μg/mL) was the most active compound against *Staphylococcus aureus*, its activity was found to be 16 times better than levofloxacin (MIC = 0.5 μg/mL). Derivatives **ZY5a** and **ZY6a** were the most active compounds against *Staphylococcus epidermidis*, being two fold more active than levofloxacin. Only several compounds showed moderate activity against *Escherichia coli*. It is noticeable that most compounds were potent against *Pseudomonas aeruginosa* and were significantly better than levofloxacin. As is evident from the data, compound **ZY6a** (MIC = 0.25 μg/mL) is the superior in inhibiting the growth of *Pseudomonas aeruginosa* and its activity was found to be 16 times better than levofloxacin (MIC = 4 μg/mL).

In terms of structure-activity relationship studies, compounds **ZY1a**-**13a** showed better antibacterial activity than compounds **ZY1b**-**13b** against both Gram-positive and Gram-negative bacteria. The results of MIC tests revealed that acyl derivatives were usually more active than alkyl and sulfonyl derivatives. Comparison between MIC values of acyl derivatives with electron-donating group and electron-withdrawing group revealed that acyl derivatives with electron-donating

TABLE-2
ANTIBACTERIAL ACTIVITIES OF NEW FLUOROQUINOLONES AGAINST SELECTED STAINS[a] (MICs in μg/mL)

Compound	S.a.	S.e.	E.c.	P.a.
ZY1a	4	8	0.125	1
ZY2a	1	1	0.125	1
ZY3a	4	4	8	8
ZY4a	4	4	64	8
ZY5a	2	0.25	32	8
ZY6a	0.03	0.25	256	0.25
ZY7a	0.5	2	0.5	1
ZY8a	0.5	4	128	32
ZY9a	2	2	64	32
ZY10a	2	4	64	4
ZY11a	4	16	128	256
ZY12a	8	4	64	16
ZY13a	8	8	16	16
ZY1b	4	16	0.5	2
ZY2b	2	2	0.5	2
ZY3b	4	8	16	2
ZY4b	1	2	64	8
ZY5b	8	4	256	4
ZY6b	0.5	2	64	1
ZY7b	1	2	64	8
ZY8b	4	16	64	32
ZY9b	2	4	128	4
ZY10b	2	2	64	16
ZY11b	1	4	64	32
ZY12b	2	4	256	64
ZY13b	2	8	8	16
Levofloxacin	0.5	0.5	0.03	4

[a]S.a.: *Staphylococcus aureus*, S.e.: *Staphylococcus epidermidis*, E.c.: *Escherichia coli*, P.a.: *Pseudomonas aeruginosa*

group seemed to have more powerful influence on the antibacterial activity against various bacteria strains. For example, compound **ZY6a** was the most active compound against *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, its activity was found to be 2 to 16 times better than levofloxacin.

Conclusion

In conclusion, we have described the synthesis and antibacterial evaluation of a series of novel fluoroquinolones. Biological data indicated that among the newly synthesized twenty-six compounds, most compounds demonstrated comparable or better activity against Gram-positive and Gram-negative bacteria than levofloxacin as reference drug. Notably, **ZY6a** was the most active compound against *Staphylococcus aureus, Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, its activity was found to be 2 to 16 times better than levofloxacin. These data encourage us to develop several compounds tested in this study as potential drug candidate.

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