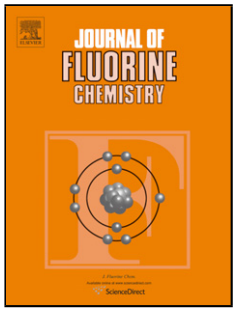

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PII: S0022-1139(17)30402-5
DOI: https://doi.org/10.1016/j.jfluchem.2018.01.007
Reference: FLUOR 9106

To appear in: *FLUOR*

Received date: 20-9-2017
Revised date: 13-1-2018
Accepted date: 15-1-2018

Please cite this article as: Valery N.Charushin, Nataliya N.Mochulskaya, Fedor V.Antipin, Svetlana K.Kotovskaya, Emiliya V.Nosova, Marina A.Ezhikova, Mikhail I.Kodess, Marionella A.Kravchenko, SYNTHESIS AND ANTIMYCOBACTERIAL EVALUATION OF NEW (2-OXO-2H-CHROMEN-3-YL) SUBSTITUTED FLUOROQUINOLONES, Journal of Fluorine Chemistry https://doi.org/10.1016/j.jfluchem.2018.01.007

SYNTHESIS AND ANTIMYCOBACTERIAL EVALUATION OF NEW (2-OXO-2*H*-CHROMEN-3-YL) SUBSTITUTED FLUOROQUINOLONES

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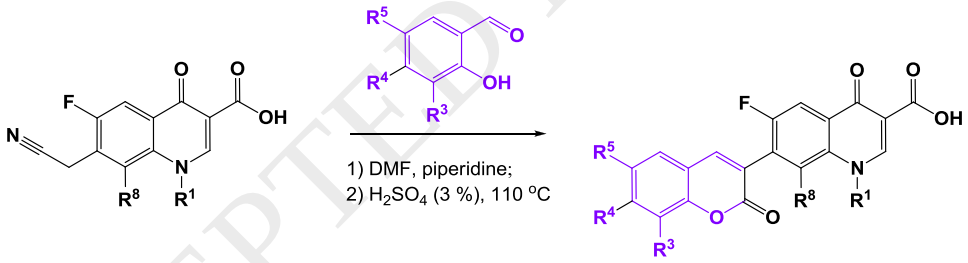
Graphical Abstract



Highlights

- The cyanomethyl fragment was incorporated into the benzene ring of fluoroquinolones
- Cyanomethyl fluoroquinolones was converted to (2-oxo-2*H*-chromen-3-yl) fluoroquinolones
- Substitution of another fluorine atom provides 1,4-dihydro[1]-benzoxepino[2,3-*g*]quinolones
- Some of new fluoroquinolones exhibit antimicobacterial activity

Abstract

An efficient method for incorporation of the cyanomethyl fragment into the benzene ring of bi- and tricyclic fluoroquinolones through the nucleophilic substitution of a fluorine atom with carbanions derived

from CH-active cyanoacetates, followed by an acidic hydrolysis of the reaction intermediates was developed. The reaction of cyanomethyl derivatives of bi- and tricyclic fluoroquinolones with *ortho*-hydroxy substituted benzaldehydes proved to give the corresponding condensation products, which can be regarded as the key intermediates in the synthesis of previously unknown (2-oxo-2*H*-chromen-3-yl) substituted bi- and tricyclic fluoroquinolones. It has been shown that an increase in the reaction temperature and exposition time promotes the competitive process, leading to substitution of one more fluorine atom to give 1,4-dihydro[1]-benzoxepino[2,3-*g*]quinolones. New fluoroquinolones proved to exhibit anti-mycobacterial activity, thus indicating that a search of biologically active compounds in this family of heterocycles appears to be a reasonable approach.

Keywords: fluoroquinolones; (2-oxo-2*H*-chromen-3-yl)-substituted fluoroquinolones; 1,4-dihydro[1]-benzoxepino[2,3-*g*]quinolones; tuberculosis; multidrug-resistant tuberculosis; *in vitro* activity.

1. Introduction

Bacterial infections represent one of the main social concerns, and tuberculosis takes the second place in the list of mortality from infectious diseases; new multi-drug resistant (MDR) and extensive-drug resistant (XDR) forms of tuberculosis are spreading rapidly all over the world, especially in India, China, Russia, and some other African and Asian countries, therefore urgent measures are needed to be taken by the global health care community. In 2016 the World Health Organization (WHO) reported that 10.4 million people were diagnosed with tuberculosis (TB) infection, and a global mortality due to this disease reached up to 1.7 million people during the same year [1].

Main complications with medical therapy of tuberculosis are associated with a limited arsenal of anti-TB drugs, as well as with a wide spread of multi-drug resistant strains of *M. tuberculosis* (MDR-TB), which are resistant to Isoniazid and Rifampicin, the main two front-line anti-tuberculosis agents. In 2016, there were 600 000 new cases with resistance to rifampicin, the most effective first-line drug, of which 490 000 had MDR-TB [1].

Fluoroquinolone drugs are known to show a high bactericidal activity towards tuberculosis mycobacteria in both *in vitro* and *in vivo* experiments. Fluoroquinolones are of considerable interest as remedies for the combined MDR-TB chemotherapy due to their optimal pharmacokinetics, high intracellular concentrations, and good adult's tolerance for a prolonged use (Figure 1) [2]. Indeed, according to the WHO recommendations, Levofloxacin can be used for the treatment of MDR-TB, and Moxifloxacin is known to be a suitable drug for application in cases of the proved extensive drug resistance.

The mechanism of action of fluoroquinolones in mycobacterial cells differs significantly from that of other known anti-tuberculosis drugs, thus providing a bactericidal effect and activity

of fluoroquinolones towards both sensitive and resistant strains [3-5]. Fluoroquinolones proved to inhibit microbial cells during both dormant and growth periods; the mechanism of their action is based on inhibition of the DNA gyrase.

Bacterial DNA gyrase represents the proteinaceous tetramer, weighing 400 kDa and consisting of two subunits A (GyrA) and two subunits B (GyrB). Binding and splitting of DNA is dependent on GyrA. GyrB consists of the amine-terminus domain, which possesses ATP-ase activity, and the COOH-terminus domain, which interacts with GyrA and DNA. Most antibiotics, which are capable of inhibiting bacterial DNA gyrase, proved to be selective towards this enzyme; at the same time they are inactive to eukaryote topoisomerase type II. Fluoroquinolones are known to inhibit bacterial DNA gyrase. They bind with GyrA subunit and stabilize the splitting complex, thus inhibiting the gyrase function in general, that leads to cell death.

Inhibitors which bind GyrB subunit are less known. Several examples include coumarins, novobiocin and coumermycin A, cyclothialidine, cynodine and clerocidine. In particular, it has been shown that derivatives of the coumarin family bind GyrB rather strongly [6, 7]. Therefore, the synthesis of new compounds bearing in one molecule combination of fragments, inhibiting both DNA gyrase subunits, might be of interest for broadening the range of their action on pathogens. Notably, that nowadays the creation of 4-quinolone hybrids is considered as one of the most promising ways for the design of antibacterial agents [8, 9].

The overwhelming majority of publications, concerning structural modification of fluoro-quinolones, deal with incorporation of nitrogen-containing fragments at C-7 (or C-10) through nucleophilic substitution reactions, and 3-amino- or 3-aminomethylpyrrolidin-1-yl derivatives have been used predominantly as N-centered nucleophiles in such cases. On the other hand, not only 7-amino-6-fluoroquinolones obtained through the amino-defluorination process, but also carbon-centered nucleophiles and methods to form C–C^7 (or C–C^{10}) bonds are gaining a growing interest in the chemistry of fluoroquinolones, since a number of C-7 C-substituted quinolones, such as Rosoxacin and Garenoxacin have been shown to be highly active antibacterial drugs [10, 11].

The aim of this communication is to describe the synthesis of a new series of coumarin-3-yl (2-oxo-2*H*-chromen-3-yl) substituted fluoroquinolone derivatives, possessing antimicrobial activity, including that relative to multi-drug resistant strains of *M. tuberculosis*, to expand synthetic opportunities for the development of anti-tuberculosis agents.

2. Results and discussion

The synthesis of bi- and tricyclic fluoroquinolones **4a,b,** bearing the cyanomethyl fragment at C-7 (or C-10), was realized through nucleophilic substitution of the fluorine atom at C-7 (or C-10) by action of

carbon-centered nucleophiles, derived from ethyl cyanoacetate or *tert*-butyl cyanoacetate, followed by acidic hydrolysis of the intermediates **3a,b** (Scheme 1).

It has been found, that nucleophilic substitution of a fluorine atom with carbon-centered nucleophiles proceeds in both bicyclic and tricyclic fluoroquinolones **1a,b** under the same reaction conditions (heating at 70-80 °C for 4 hours), and the process can be scaled. We have failed to convert compounds **3a,b** into **4a,b** according to such methods, as refluxing in toluene in the presence of *p*-toluenesulfonic acid [12] or in acetic anhydride [13, 14]. The target fluoroquinolones **4a,b,** bearing the cyanomethyl group at C-7 (or C-10), were synthesized by heating of compounds **3a,b** in a mixture of sulfuric and acetic acids [15]. The reaction is accompanied by protonation of COOR groups, elimination of ethylene (butylene) and subsequent decarboxylation. It has also been shown that, when refluxing **3a,b** in a mixture of H_2SO_4/AcOH, the hydrolysis of the ethoxycarbonyl group at C-3 (or C-6) of fluoroquinolones proved to occur.

Condensation of cyanomethyl derivatives of bi- and tricyclic fluoroquinolones **4a,b** with *ortho*-hydroxybenzaldehydes was studied. Fluoroquinolone **4a** was shown to react smoothly with salicylic aldehydes **5a-e** in DMF solution in the presence of catalytic amounts of piperidine at room temperature. The reaction was carried out for 1−12 hours according to the known procedure [16]. The synthesis was accomplished without isolation of the intermediate condensation products **6a-e,** which were subjected to the hydrolysis in 3 % aqueous H_2SO_4 solution (heating for 5−9 hours at 110 °C) to form (2-oxo-2*H*-chromen-3-yl) substituted fluoroquinolones **7a-e** in 46−77 % yields (Scheme 2).

The structure of fluoroquinolones **7a-e** was confirmed by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, including 2D ^{1}H–^{13}C HSQC and HMBC experiments, as well as the mass-spectrometry data. In ^{1}H NMR spectra the signals, which are typical for 6-fluoro-7-substituted quinolones, have been observed, namely, singlets of H-2 and two doublets of H-5 and H-8 with coupling constants ^3J(H-5,F-7) = 9.7–9.8 Hz and ^4J (H-8,F-7) = 5.8–5.9 Hz. The ^{1}H NMR spectra of **7a-e** reveal a characteristic downfield singlet of H-4′ (at 8.39–8.45 ppm), that indicates at the presence of the coumarin-3-yl fragment. In the low-field area of the ^{13}C NMR spectra of compounds **7**, along with C-4 and COOH signals from quinolone fragment, coumarinyl carbonyl signal is appeared at δ_C ~158 ppm. The C-4′ carbon is split into doublet ($^4J_{C,F}$ = 1.6 Hz) due to the long-range spin-spin coupling with F-6. The diagnostic cross-peaks for pairs (H-4′, C-7) and (H-8, C-3′) were observed in 2D ^{1}H–^{13}C HMBC spectra.

Elucidation of the condensation reaction between cyanomethyl fluoroquinolone **4a** and salicylic aldehydes **5** has shown that both heating of reactants and increase in reaction time promotes the competitive intramolecular substitution of the fluorine atom at C-6, thus resulting in the formation of polycyclic structures **8a-c,e,f** (Scheme 2). Indeed, heating of 7-cyano-methylfluoroquinolone **4a** with aromatic hydroxyaldehydes **5** at 100 °C for 3 hours afforded polycyclic compounds as the only products.

The structure of polycyclic derivatives **8** was established on the basis of the data of mass spectrometry, as well as ^{1}H and ^{13}C NMR spectroscopy. Assignment of ^{1}H and ^{13}C signals for compounds **8** was achieved by using 2D ^{1}H–^{1}H NOESY and ^{1}H–^{13}C HSQC, HMBC experiments. The key signals of nodal carbons of the benzoxepinoquinoline core were assigned by using cross-peaks with protons of the neighboring rings in the HMBC spectra, for example, C-5a with H-13, C-6a with H-10 and H-11, C-12a with H-5 and H-11, C-13a with H-2 and H-5.

It has been shown that the reaction of cyanomethyl substituted tricyclic fluoroquinolone **4b** with salicylic aldehydes **5a-c** proceeds in DMF solution in the presence of catalytic amounts of piperidine at room temperature, and it takes 12 hours to be completed. Hydrolysis of the condensation products takes place in aqueous 3−5 % H_2SO_4 for 7-15 hours at 110 °C [14], thus allowing one to isolate (2-oxo-2*H*-chromen-3-yl) substituted tricyclic fluoroquinolones **9a-c** in 50−67 % yields (Scheme 3).

In compounds **9a-c** there are two elements of chirality: the asymmetric C-3 carbon atom and the chiral axis due to the hindered rotation around the C^{10}–$C^{3'}$ bond. As a sequence, compounds **9a-c** can exist as mixtures of comparable amounts of stable atropisomers, thus giving rise a double set of signals in the ^{1}H, ^{19}F and ^{13}C NMR spectra at room temperature. Heating of compounds **9a,c** in a sealed NMR tube up to 393 K resulted in coalescence of NMR signals of these isomers. The coalescence point for the methyl group protons of **9a** was observed approximately at 80 °C (Figure 2); the same story for F-6 signals, with the difference it is observed at 100−110 °C. The rotational energy barrier $\Delta G^{\#}$ at coalescence was calculated to be 18 kcal/mol.

of the methyl group protons of compound **9a**.

(2-Oxo-2*H*-chromen-3-yl) substituted bi- and tricyclic fluoroquinolones **7, 9** and 1,4-dihydro[1]benzoxepino[2,3-*g*]quinolines **8** were tested *in vitro* against *M. tuberculosis* $H_{37}Rv$, *avium, terrae* and MDR strains, and the data on the minimum inhibitory concentrations (MICs) of these compounds are presented in Table 1. All new compounds were compared with the commercially available drugs Isoniazid and Levofloxacin, tested under the same experimental conditions.

The results obtained show that tricyclic fluoroquinolones **9**, bearing the coumarinyl fragment, as well as 1,4-dihydro[1]benzoxepino[2,3-*g*]-quinolines **8** have a poor tuberculostatic activity, whereas their bicyclic analogues, 6-fluoro-7-(2-oxo-*2H*-chromen-3-yl) substituted fluoroquinolones **7** can be considered as promising anti-*M. tuberculosis* agents (Table 1). In particular, the compound **7e** exhibits the highest activity (MIC 0.7-1.5 μg/mL) not only against *M. tuberculosis* $H_{37}R_v$, but also against *M. avium, M. terrae* and MDR strains. It should be noted that, unlike the known anti-tuberculosis drug Isoniazide,

fluoroquinolone **7e** is active against MDR strains. Acute *in vivo* toxicity in mice LD_{50} for the most active compound **7e** was found to be 600 mg/kg.

3. Conclusion

In summary, an efficient synthetic approach to analogues of DNA gyrase inhibitors, Levofloxacin and Pefloxacin, based on nucleophilic substitution of a fluorine atom in bicyclic and tricyclic fluoroquinolones with carbon-centered nucleophiles, such as cyanoacetates, and subsequent cyclization of intermediates with *ortho*-hydroxy substituted benzaldehydes, has been advanced. As a result, novel (2-oxo-2*H*-chromen-3-yl) substituted fluoroquinolones and 1,4-dihydro[1]benzoxepino-[2,3-*g*]quinolones have first been obtained.

In the series of novel fluoroquinolones obtained a number of compounds proved to exhibit an antimycobacterial activity, which can possibly be improved to reach a better potency than the reference drugs. The results obtained show that novel fluoroquinolones can be regarded as promising anti-*M. tuberculosis* agents. Further research studies to get a more detailed information, concerning structure–activity relationships (QSAR) for this series of compounds are in progress in our laboratory.

4. Experimental

4.1. General

Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification.

^{1}H (500.1 MHz), ^{19}F (470.5 MHz) and ^{13}C (125.7 MHz) NMR spectra were recorded on the AVANCE-500 spectrometer in DMSO-d_6 solution. ^{1}H chemical shifts are given in parts per million downfield from tetramethylsilane, ^{19}F chemical shifts have been measured from internal C_6F_6 and are reported from external $CFCl_3$. Carbon chemical shifts were referenced to the carbon resonances of the solvent (DMSO-d_6: δ = 39.5 ppm). Peaks are labeled as singlet (s), broad singlet (br), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of quartets (dq) and multiplet (m). Full assignment of ^{1}H and ^{13}C signals of all compounds was achieved by using 2D ^{1}H–^{1}H NOESY and ^{1}H–^{13}C HSQC, HMBC experiments.

Mass spectra were recorded on the SHIMADZU GCMS-QP2010 Ultra instrument with electron ionization (EI) of the sample. Analytical HPLC of compounds **4a** was performed on a Knauer Smartline-1000 instrument using a Chiralcel OD-H column (250×4.6 mm, 5 µm), detection at 230 nm, 1 mL/min flow

rate. Melting points were measured on the instrument Boetius. Microanalyses (C, H, N) were performed using the Perkin–Elmer 2400 elemental analyzer.

4.2. Procedure for the Synthesis of Starting Substrate 4a

*Ethyl 7-(1-cyano-2-ethoxy-2-oxoethyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**3a**)*

Ethyl cyanoacetate (4.80 g, 42.66 mmol) and calcined potassium carbonate (11.79 g) were added to a solution of ethyl 6,7-difluoro-1-ethyl-4-oxo-1,4-dihydroquinolin-3-carboxylate (**1**) (10.00 g, 35.55 mmol) in dimethyl sulfoxide (65 mL). The mixture was refluxed with a calcium chloride tube at 80 °C for 4 h. After cooling the mixture was poured into ice water (~ 250 mL) and then HCl solution (18 %) was added at stirring to pH = 2−3. The product obtained was extracted with methylene chloride (~ 600 mL). Water layer was separated, and organic layer was washed twice with distilled water (200 mL) and once with saturated sodium chloride solution (2×200 mL), then dried over anhydrous sodium sulfate. Methylene chloride solution was concentrated at rotational vacuum evaporator, and diethyl ester (75 mL) was added to a residue. Colorless crystals of compound **3a** were filtered off, dried at air and recrystallized from ethanol. Yield 11.6 g (87 %), mp. 192−194 °C. ^{1}H NMR: δ = 1.22 (t, *J* = 7.1 Hz, 3H, H-4'), 1.30 (t, *J* = 7.1 Hz, 3H, H-3''), 1.41 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 4.24 (q, *J* = 7.1 Hz, 2H, H-2''), 4.27 (q, *J* = 7.1 Hz, 2H, H-3'), 4.41 (dq, *J* = 14.1, 7.1 Hz, 1H, NCH^B), 4.45 (dq, *J* = 14.1, 7.1 Hz, 1H, NCH^A), 6.13 (s, 1H, H-1'); 8.00 (d, *J* = 10.2 Hz, 1H, H-5), 8.09 (d, *J* = 5.9 Hz, 1H, H-8), 8.77 (s, 1H, H-2). ^{19}F NMR: δ = -119.93 (dd, *J* = 10.2, 5.9 Hz, F-6). ^{13}C NMR: δ = 13.8 (C-4'), 14.25 and 14.28 (2·CH_3), 37.9 (C-1'), 48.5 (NCH_2), 59.9 (C-2''), 63.2 (C-3'), 109.9 (C-3), 111.9 (d, $^{2}J_{CF}$ = 22.3 Hz, C-5), 115.2 (CN), 121.4 (d, $^{3}J_{CF}$ = 2.7 Hz, C-8), 124.2 (d, $^{2}J_{CF}$ = 17.7 Hz, C-7), 130.5 (d, $^{3}J_{CF}$ = 6.6 Hz, C-4a), 135.3 (d, $^{4}J_{CF}$ = 1.5 Hz, C-8a), 149.5 (C-2), 156.9 (d, $^{1}J_{CF}$ = 248.5 Hz, C-6), 163.9 (C-2'), 164.4 (C-1''), 171.5 (d, $^{4}J_{CF}$ = 2.1 Hz, C-4). MS (*m/z*, I_{rel} %): 375 $[M + 1]^+$ (1), 374 $[M]^+$ (6), 329 (7), 303 (18), 302 (100), 230 (7), 229 (7), 228 (7), 145 (5). Anal. Calc. for $C_{19}H_{19}FN_2O_5$, C 60.96, H 5.12, N 7.48. Found: C 60.92, H 5.12, N 7.43.

*7-(Cyanomethyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4a**)*

A mixture sulfuric acid/acetic acid/distilled water (1:20:20) was added to compound **3a** (10.00 g,

26.71 mmol), and the suspension was heated at 125 °C for 6 h. After cooling the precipitate was filtered off, washed with distilled water and dried at air. The colorless crystals of the product **4a** were recrystallized from the mixture ethanol/*N,N*-dimethylformamide. Yield 6.7 g, (91 %), mp. 235−237 °C. ^{1}H NMR: δ = 1.46 (t, *J* = 7.1 Hz, 3H, CH_3), 4.34 (s, 2H, CH_2CN), 4.60 (q, *J* = 7.1 Hz, 2H, NCH_2), 8.10 (d, *J* = 9.5 Hz, 1H, H-5), 8.22 (d, *J* = 6.0 Hz, 1H, H-8), 9.10 (s, 1H, H-2), 14.89 (s, 1H, COOH). ^{19}F NMR: δ = -118.06 (dd, *J* = 9.5, 6.0 Hz, F-6). ^{13}C NMR: δ = 14.5 (CH_3), 17.8 (*C*H_2CN), 49.4 (NCH_2), 107.7 (C-3), 110.9 (d, $^{2}J_{CF}$ = 22.8 Hz, C-5), 117.3 (CN), 121.2 (d, $^{3}J_{CF}$ = 3.6 Hz, C-8), 126.7 (d, $^{2}J_{CF}$ = 18.8 Hz, C-7), 126.9 (d, $^{3}J_{CF}$ = 7.7 Hz, C-4a), 135.8 (d, $^{4}J_{CF}$ = 1.4 Hz, C-8a), 149.4 (C-2), 157.7 (d, $^{1}J_{CF}$ = 249.9 Hz, C-6), 165.7 (COO), 176.6 (d, $^{4}J_{CF}$ = 2.6 Hz, C-4). MS (*m/z*, I_{rel} %): 275 $[M + 1]^+$ (1), 274 $[M]^+$ (7), 231 (14), 230 (100), 215 (53), 147 (10). Anal. Calc. for $C_{14}H_{11}FN_2O_3$, C 61.31, H 4.04, N 10.22. Found: C 61.24; H 3.86; N 10.15.

4.3. Procedure for the Synthesis of Starting Substrate 4b

*Ethyl (3S)-10-(2-tert-butoxy-1-cyano-2-oxoethyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylate (**3b**)*

tert-Butylcyanoacetate (0.55 g, 3.88 mmol) and calcined potassium carbonate (1.46 g) were added to a solution of ethyl (*3S*)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-*ij*]-quinoline-6-carboxylate (**1b**) (1.00 g, 3.23 mmol) in dimethyl sulfoxide (13 mL). The mixture was refluxed with a calcium chloride tube at 70 °C for 4 h. After cooling the mixture was poured into the mixture ethyl acetate/ice (150:100 mL) and then HCl solution (18 %) was added at stirring to pH= 2. Water layer was separated, and organic layer was washed twice with distilled water (2 × 100 mL) and once with saturated solution of sodium chloride (100 mL), than dried over anhydrous sodium sulfate. Ethyl acetate solution was concentrated at rotational vacuum evaporator, and diethyl ester (30 mL) was added to a residue. Colorless crystals of compound **3b** were filtered off, dried at air (yield 1.3 g, 93 %) and recrystallized from aqueous ethanol. The sample was isolated as a mixture of two diastereomers (ratio ≈ 1:1), mp. 164−165 °C. HPLC (Chiralcel OD-H, hexane:iPrOH:MeOH = 2:0.8:0.2, 1 mL/min): τ_1 = 9.7 min (47.5 %); τ_2 = 11.7 min (52.2 %). ^{1}H NMR: δ = 1.31 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.41−1.44 (m, 12H, ^{t}Bu and CH_3-C^{3}), 4.20−4.30 (m, 2H, OCH_2CH_3), 4.47 and 4.54 (both dd, *J* = 11.4, 2.3 Hz, 1H, H-2B), 4.65 and 4.68 (both dd, *J* = 11.4, 1.6 Hz, 1H, H-2A), 4.83 (m, 1H, H-3), 6.03 (s, 1H, H-1'), 7.51 and 7.52 (both d, *J* = 9.9 Hz, 1H, H-8), 8.71 and 8.72 (both s, 1H, H-5). ^{19}F NMR: δ = -118.34 and -118.21 (both d, *J* = 9.9 Hz, F-9). ^{13}C NMR: δ = 14.20 (OCH_2CH_3), 17.4 and 17.5 (CH_3-C^{3}), 27.18 and 27.19 ($(CH_3)_3C$), 33.03 and 33.08 (both d, $^{3}J_{CF}$ = 2.9 Hz, C-1'), 53.6 and 53.8 (C-3), 59.8 (OCH_2CH_3), 68.9 and 69.1 (C-2), 83.87 and 83.91 ($(CH_3)_3C$), 102.78 and 102.85 (both d, $^{2}J_{CF}$ =

23.5 Hz, C-8), 109.9 (C-6), 110.7 and 110.9 (both d, $^{2}J_{CF}$ = 17.2 Hz, C-10), 115.0 and 115.1 (CN), 123.16 and 123.18 (both d, $^{4}J_{CF}$ = 1.5 Hz, C-10b), 129.4 (d, $^{3}J_{CF}$ = 8.2 Hz, C-7a), 145.04 and 145.07 (both d, $^{3}J_{CF}$ = 6.3 Hz, C-10a), 146.2 and 146.3 (C-5), 156.5 and 156.6 (both d, $^{1}J_{CF}$ = 247.0 Hz, C-9), 162.8 and 162.9 (C-2'), 164.18 and 164.19 (COO), 171.11 and 171.13 (C-7). MS (*m/z*, I_{rel} %): 431 $[M + 1]^+$ (2), 430 $[M]^+$ (6), 358 (13), 302 (29), 284 (112), 258 (41), 243 (7), 216 (9), 57 (100), 41 (46), 39 (13). Anal. Calc. for $C_{22}H_{23}FN_2O_6$, C 61.39, H 5.39, N 6.51. Found: C 61.27, H 5.25, N 6.51.

*(3S)-10-(Cyanomethyl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**4b**)*

The mixture sulfuric acid/acetic acid/distilled water (1:20:20) was added to compound **3b** (0.31 g, 0.72 mmol), and the mixture was heated at 110 °C for 5 h. After cooling the precipitate was filtered off, washed with distilled water and dried at air. The colorless crystals of product **4b** were recrystallized from aqueous ethanol. Yield 0.12 g (55 %), mp. 237−238 °C. ^{1}H NMR: δ = 1.47 (d, *J* = 6.8 Hz, 3H, CH_3), 4.14 (AB system, J_{AB} = 17.7 Hz, 2H, H-1'), 4.51 (dd, *J* = 11.5, 2.4 Hz, 1H, H-2A); 4.71 (dd, *J* = 11.5, 1.9 Hz, 1H, H-2B), 5.01 (qt, *J* = 6.8, 2.3 Hz, 1H, H-3), 7.72 (d, *J* = 9.6 Hz, 1H, H-8), 9.09 (s, 1H, H-5), 14.89 (s, 1H, COOH). ^{19}F NMR: δ = -115.39 (d, *J* = 9.6 Hz, F-9). ^{13}C NMR: δ = 11.4 (d, $^{3}J_{CF}$ = 3.7 Hz, C-1'), 17.7 (CH_3), 54.8 (C-3), 68.9 (C-2), 102.3 (d, $^{2}J_{CF}$ = 24.0 Hz, C-8), 107.7 (C-6), 111.5 (d, $^{2}J_{CF}$ = 21.6 Hz, C-10), 116.8 (CN), 123.9 (d, $^{4}J_{CF}$ = 1.5 Hz, C-10b), 126.2 (d, $^{3}J_{CF}$ = 9.5 Hz, C-7a), 145.6 (d, $^{3}J_{CF}$ = 7.5 Hz, C-10a), 146.5 (C-5), 157.7 (d, $^{1}J_{CF}$ = 248.1 Hz, C-9), 165.6 (COO), 176.5 (d, $^{4}J_{CF}$ = 3.1 Hz, C-7). MS (*m/z*, I_{rel} %): 302 $[M]^+$ (15), 259 (18), 258 $[M\text{-}CO_2]^+$ (100), 243 (19), 216 (63), 53 (15), 41 (17). Anal. Calc. for $C_{15}H_{11}FN_2O_4$, C 59.60, H 3.67, N 9.27. Found: C 59.48, H 3.62, N 9.23.

4.4. General synthetic procedure for 7-(2-oxo-2H-chromen-3-yl)-substituted bicyclic fluoroquinolones (7a-e)

The corresponding salicylaldehyde **5** (1.82 mmol) was added to a suspension of 7-(cyanomethyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4a**) (0.500 g, 1.82 mmol) in DMF (5 mL), and then 5 drops of piperidine was added. The mixture was heated for 1−2 min, and after that it was stirred at room temperature for 12 h. The precipitate was filtered off, added to 3 % H_2SO_4 solution (20 mL), and the mixture was heated at 110 °C for 6 h. After cooling the precipitate was filtered off and washed with distilled water, then with hexane or heptane. Compounds **7a,b,d** were recrystallized from the mixture ethanol/DMF.

*1-Ethyl-6-fluoro-4-oxo-7-(2-oxo-2H-chromen-3-yl)-1,4-dihydroquinoline-3-carboxylic acid (**7a**)*

Compound was obtained from salicylaldehyde (**5a**). Yield 0.48 g (69 %), mp. 323−324 °C. ^{1}H NMR: δ = 1.46 (t, *J* = 7.2 Hz, 3H, CH_3), 4.64 (q, *J* = 7.2 Hz, 2H, NCH_2), 7.46 (td, *J* = 7.5, 1.0 Hz, 1H, H-6'), 7.54 (br.d, *J* = 8.3 Hz, 1H, H-8'), 7.74 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H, H-7'), 7.86 (dd, *J* = 7.7, 1.6, 1H, H-5'), 8.16 (d, *J* = 9.7 Hz, 1H, H-5), 8.36 (d, *J* = 5.8, 1H, H-8), 8.45 (s, 1H, H-4'), 9.13 (s, 1H, H-2), 14.97 (s, 1H, COOH). ^{19}F NMR: δ = -115.06 (dd, *J* = 9.7, 5.8 Hz, F-6). ^{13}C NMR: δ = 14.6 (CH_3), 49.4 (NCH_2), 107.7 (C-3), 110.7 (d, $^{2}J_{CF}$ = 24.0 Hz, C-5), 116.2 (C-8'), 118.6 (C-4'a), 121.3 (C-3'), 122.2 (d, $^{3}J_{CF}$ = 3.3 Hz, C-8), 125.0 (C-6'), 127.1 (d, $^{3}J_{CF}$ = 8.1, C-4a), 129.1 (C-5'), 129.8 (d, $^{2}J_{CF}$ = 18.2 Hz, C-7), 132.9 (C-7'), 135.6 (C-8a), 144.7 (C-4'), 149.4 (C-2), 153.4 (C-8'a), 157.2 (d, $^{1}J_{CF}$ = 250.1 Hz, C-6), 158.6 (C-2'), 165.7 (COO), 176.6 (d, $^{4}J_{CF}$ = 2.3 Hz, C-4). MS (*m/z*, I_{rel} %): 379 $[M]^+$ (8), 336 (21), 335 $[M\text{-}CO_2]^+$ (100), 321 (8), 320 (40), 292 (6), 251 (6), 222 (6), 167 (6). Anal. Calc. for $C_{21}H_{14}FN_1O_5$, C 66.49, H 3.72, N 3.69. Found: C 66.05; H 3.71; N 3.65.

*7-(6-Bromo-2-oxo-2H-chromen-3-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7b**)*

Compound was obtained from 5-bromosalicylaldehyde (**5b**). Yield 0.59 g (77 %), mp. 309−310 °C. ^{1}H NMR: δ = 1.46 (t, *J* = 7.1 Hz, 3H, CH_3), 4.63 (q, *J* = 7.1 Hz, 2H, NCH_2), 7.52 (d, *J* = 8.9 Hz, 1H, H-8'), 7.89 (dd, *J* = 8.9, 2.4 Hz, 1H, H-7'), 8.11 (d, *J* = 2.4 Hz, 1H, H-5'), 8.17 (d, *J* = 9.7 Hz, 1H, H-5), 8.34 (d, *J* = 5.8 Hz, 1H, H-8), 8.39 (s, 1H, H-4'), 9.13 (s, 1H, H-2), 14.95 (s, 1H, COOH). ^{19}F NMR: δ = -115.21 (dd, *J* = 9.7, 5.8 Hz, F-6). ^{13}C NMR: δ = 14.6 (CH_3), 49.4 (NCH_2), 107.7 (C-3), 110.8 (d, $^{2}J_{CF}$ = 23.8 Hz, C-5), 116.4 (C-4'a), 118.5 (C-8'), 120.4 (C-6'), 122.3 (d, $^{3}J_{CF}$ = 2.7 Hz, C-8), 122.4 (C-3'), 127.3 (d, $^{3}J_{CF}$ = 7.8 Hz, C-4a), 129.3 (d, $^{2}J_{CF}$ = 18.1 Hz, C-7), 131.0 (C-5'), 135.2 (C-7'), 135.5 (d, $^{4}J_{CF}$ = 1.3 Hz, C-8a), 143.4 (d, $^{4}J_{CF}$ = 1.6 Hz, C-4'), 149.5 (C-2), 152.5 (C-8'a), 157.1 (d, $^{1}J_{CF}$ = 250.7 Hz, C-6), 158.1 (C-2'), 165.7 (COO), 176.6 (d, $^{4}J_{CF}$ = 2.4 Hz, C-4). MS (*m/z*, I_{rel} %): 460 $[M+2]^+$ (2),458 $[M]^+$ (2), 416 (22), 415 (100), 414 $[M\text{-}CO_2]^+$ (24), 413 (100), 400 (33), 398 (32), 369 (14), 222 (11), 207 (12), 206 (10), 194 (11). Anal. Calc. for $C_{21}H_{13}BrFNO_5$, C 55.04, H 2.86, N 3.06. Found: C 55.12, H 2.67, N 3.18.

*7-(6,8-Di-tert-butyl-2-oxo-2H-chromen-3-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**7c**)*

3,5-di-*tert*-Butylsalicylaldehyde (**5c**) (0.436 g, 1.86 mmol) was added to a suspension of 7-(cyanomethyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acid (**4a**) (0.510 g, 1.86 mmol) in

DMF (5 mL), then 5 drops of piperidine were added. The mixture was stirred at room temperature for 12 h. The precipitate was filtered off and washed with small amount of ethanol, then with hexane. To solid obtained 3 % H_2SO_4 solution (20 mL) was added, and the mixture was heated at 110 °C for 6 h. After cooling the precipitate was filtered off and washed with distilled water, then with hexane or heptane and recrystallized from acetonitrile. Yield 0.41 g (46 %), mp. 304−305 °C. ^{1}H NMR: δ = 1.36 (s, 9H, ^{t}Bu-C$^{6'}$), 1.47 (t, *J* = 7.1 Hz, 3H, CH_3), 1.51 (s, 9H, ^{t}Bu-C$^{8'}$), 4.65 (q, *J* = 7.1 Hz, 2H, NCH_2), 7.65 (d, *J* = 2.3 Hz, 1H, H-7'), 7.72 (d, *J* = 2.3 Hz, 1H, H-5'), 8.15 (d, *J* = 9.7 Hz, 1H, H-5), 8.36 (d, *J* = 5.9 Hz, 1H, H-8), 8.43 (s, 1H, H-4'), 9.12 (s, 1H, H-2), 14.97 (s, 1H, COOH). ^{19}F NMR: δ = -115.13 (dd, *J* = 9.7, 5.9, F-6). ^{13}C NMR: δ = 14.6 (CH_3), 29.5 ((CH_3)$_3$C-C$^{6'}$), 31.0 ((CH_3)$_3$C-C$^{8'}$), 34.4 ((CH_3)$_3$C-C$^{6'}$), 34.6 ((CH_3)$_3$C-C$^{8'}$), 49.4 (NCH_2), 107.6 (C-3), 110.7 (d, $^2J_{CF}$ = 24.0 Hz, C-5), 118.6 (C-4'a), 120.1 (d, $^3J_{CF}$ = 0.8 Hz, C-3'), 122.2 (d, $^3J_{CF}$ = 3.5, C-8), 123.9 (C-5'), 127.1 (d, $^3J_{CF}$ = 7.8, C-4a), 127.3 (C-7'), 129.8 (d, $^2J_{CF}$ = 18.1, C-7), 135.6 (d, $^4J_{CF}$ = 1.5, C-8a), 136.1 (C-6'), 146.0 (d, $^4J_{CF}$ = 1.5, C-4'), 146.6 (C-8'), 149.4 (C-2), 150.3 (C-8'a), 157.2 (d, $^1J_{CF}$ = 250.4, C-6), 158.3 (C-2'), 165.7 (COO), 176.6 (d, $^4J_{CF}$ = 2.4, C-4). MS (*m/z*, I_{rel} %): 491 [M]$^+$ (5), 448 (31), 447 [M-CO_2]$^+$ (100), 432 (8), 216 (13), 202 (9), 57 (25), 41 (12). Anal. Calc. for $C_{29}H_{30}FNO_5$, C 70.86, H 6.15, N 2.85. Found: C 70.52, H 6.25, N 3.02.

*7-(6-Chloro-2-oxo-2H-chromen-3-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7d**)*

Compound was obtained from 5-chlorosalicylaldehyde (**5d**). Yield 0.47 g (62 %), mp. 325−326 °C. ^{1}H NMR: δ = 1.46 (t, 3H, *J* = 7.1 Hz, CH_3), 4.63 (q, *J* = 7.1 Hz, 2H, NCH_2), 7.59 (d, *J* = 8.9 Hz, 1H, H-8'), 7.77 (dd, *J* = 8.9, 2.5 Hz, 1H, H-7'), 7.98 (d, *J* = 2.5 Hz, 1H, H-5'); 8.17 (d, *J* = 9.8 Hz, 1H, H-5), 8.34 (d, *J* = 5.8 Hz, 1H, H-8), 8.39 (s, 1H, H-4'), 9.13 (s, 1H, H-2), 14.95 (s, 1H, COOH). ^{19}F NMR: δ = -115.24 (dd, *J* = 9.7, 5.8 Hz, F-6). ^{13}C NMR: δ = 14.6 (CH_3), 49.4 (NCH_2), 107.7 (C-3), 110.8 (d, $^2J_{CF}$ = 24.0 Hz, C-5), 118.3 (C-8'), 120.0 (C-4'a), 122.3 (d, $^3J_{CF}$ = 3.1 Hz, C-8), 122.4 (C-3'), 127.3 (d, $^3J_{CF}$ = 7.8 Hz, C-4a), 128.0 (C-5'), 128.6 (C-6'), 129.3 (d, $^2J_{CF}$ = 18.1 Hz, C-7), 132.4 (C-7'), 135.5 (d, $^4J_{CF}$ = 1.5 Hz, C-8a), 143.4 (d, $^4J_{CF}$ = 1.5 Hz, C-4'), 149.5 (C-2), 152.1 (C-8'a), 157.1 (d, $^1J_{CF}$ = 250.5 Hz, C-6), 158.2 (C-2'), 165.7 (COO), 176.6 (d, $^4J_{CF}$ = 2.3 Hz, C-4). MS (*m/z*, I_{rel} %): 415 [M+2]$^+$ (2), 413 [M]$^+$ (6), 372 (7), 371 (38), 370 (24), 369 [M-CO_2]$^+$ (100), 354 (41), 348 (8), 285 (7), 194 (7). Anal. Calc. for $C_{21}H_{13}ClFNO_5$, C 60.96, H 3.17, N 3.39. Found: C 60.68, H 3.02, N 3.59.

*7-(8-Ethoxy-2-oxo-2H-chromen-3-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7e**)*

3-Ethoxysalicylaldehyde (**5e**) (0.303 g, 1.82 mmol) was added to a suspension of 7-(cyanomethyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4a**) (0.500 g, 1.82 mmol) in DMF (5 mL),

then 5 drops of piperidine were added. The mixture was stirred at room temperature for 1 h. Then ethanol (10 mL) was added to a mixture, the precipitate was filtered off and washed with small amount of ethanol, then with heptane. To solid obtained 5 % H_2SO_4 solution (20 mL) was added, and the mixture was heated at 110 °C for 6 h. After cooling the precipitate was filtered off and washed with distilled water, then with hexane or heptane, and recrystallized from the mixture DMF/water. Yield 0.375 g (49 %), mp. 280–281 °C. ^{1}H NMR: δ = 1.43 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.47 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 4.23 (q, *J* = 7.0 Hz, 2H, OCH_2), 4.64 (q, *J* = 7.1 Hz, 2H, NCH_2), 7.34–7.41 (m, 3H, H-5', 6', 7'), 8.14 (d, *J* = 9.7 Hz, 1H, H-5), 8.35 (d, *J* = 5.9 Hz, 1H, H-8), 8.42 (s, 1H, H-4'), 9.12 (c, 1H, H-2), 14.97 (c, 1H, COOH). ^{19}F NMR: δ = -114.99 (dd, *J* = 9.7, 5.9, F-6). ^{13}C NMR: δ = 14.59 and 14.65 (2 CH_3), 49.5 (NCH_2), 64.5 (OCH_2), 107.7 (C-3), 110.8 (d, $^2J_{CF}$ = 24.0 Гц, C-5), 116.0 (C-7'), 119.3 (C-4'a), 121.5 (C-3'), 122.2 (d, $^3J_{CF}$ = 3.1, C-8), 125.0 (C-6'), 127.2 (d, $^3J_{CF}$ = 7.8, C-4a), 129.8 (d, $^2J_{CF}$ = 18.1, C-7), 135.6 (d, $^4J_{CF}$ = 1.2, C-8a), 142.9 (C-8'a), 145.0 (d, $^4J_{CF}$ = 1.5, C-4'), 145.7 (C-8'), 149.5 (C-2), 157.2 (d, $^1J_{CF}$ = 250.5, C-6), 158.4 (C-2'), 165.8 (COO), 176.7 (d, $^4J_{CF}$ = 2.7, C-4). MS (*m/z*, I_{rel} %): 424 $[M+1]^+$ (2), 423 $[M]^+$ (7), 380 (26), 379 (100), 336 (18), 176 (11). Anal. Calc. for $C_{23}H_{18}FNO_6$, C 65.25, H 4.29, N 3.31. Found: C 64.89, H 4.28, N 3.36.

4.5. General synthetic procedure for 12-cyano-8-R-1-ethyl-4-oxo-1,4-dihydro[1]benzoxepino-[2,3-g]quinoline-3-carboxylic acid (8a-c,e,f)

The corresponding salicylaldehyde **5** (2.19 mmol) was added to a suspension of 7-(cyanomethyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4a**) (0.400 g, 1.46 mmol) in DMF (4 mL), then piperidine (0.152 mL, 1.46 mmol) was added, and the mixture was heated at 100 °C for 3 h. After cooling ethanol (10 mL) was added to a reaction mass, the precipitate was filtered off and washed with small amount of ethanol, then with heptane. Compounds **8a,b,e,f** were recrystallized from the mixture ethanol/DMF, whereas compound **8c** was recrystallized from ethanol.

*12-Cyano-1-ethyl-4-oxo-1,4-dihydro[1]benzoxepino[2,3-g]quinoline-3-carboxylic acid (**8a**)*

Compound was obtained from salicylaldehyde (**5a**). Yield 0.24 g (45 %), mp. 318–319 °C. ^{1}H NMR: δ = 1.46 (t, *J* = 7.2 Hz, 3H, CH_3), 4.64 (q, *J* = 7.2 Hz, 2H, NCH_2), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H, H-9), 7.58–7.60 (m, 2H, H-7, H-10); 7.64 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H, H-8), 7.96 (s, 1H, H-13), 8.21 (s, 1H, H-11), 8.28 (s, 1H, H-5), 9.12 (s, 1H, H-2), 14.89 (s, 1H, COOH). ^{13}C NMR: δ = 14.2 (CH_3), 49.3 (NCH_2), 107.8 (C-3), 111.3 (C-12), 117.8 (C-13), 117.9 (CN), 118.0 (C-5), 121.8 (C-7), 126.2 (C-9), 127.2 (C-10a), 127.9 (C-4a), 131.5 (C-10), 131.9 (C-12a), 134.2 (C-8), 136.4 (C-13a), 146.4 (C-11), 149.9 (C-2), 154.5 (C-5a), 157.4 (C-6a), 165.6

(COO), 176.7 (C-4). MS (*m/z*, I_{rel} %): 358 $[M]^+$ (16), 315 (22), 314 $[M\text{-}CO_2]^+$ (100), 299 (25), 286 (8), 271 (8), 258 (8), 229 (8), 201 (8). Anal. Calc. for $C_{21}H_{14}N_2O_4$, C 70.39, H 3.94, N 7.82. Found: C 70.39, H 3.91, N 7.87.

*9-Bromo-12-cyano-1-ethyl-4-oxo-1,4-dihydro[1]-benzoxepino[2,3-g]quinoline-3-carboxylic acid (**8b**)*

Compound was obtained from 5-bromosalicylaldehyde (**5b**). Yield 0.53 g (83 %), mp. 342−343 °C. ^{1}H NMR: δ = 1.46 (t, *J* = 7.2 Hz, 3H, CH_3), 4.65 (q, *J* = 7.2 Hz, 2H, NCH_2), 7.85 (d, *J* = 8.5 Hz, 1H, H-7), 7.81 (dd, *J* = 8.5, 2.5 Hz, 1H, H-8), 7.83 (d, *J* = 2.5 Hz, 1H, H-10), 7.97 (s, 1H, H-13), 8.14 (s, 1H, H-11), 8.31 (s, 1H, H-5), 9.12 (s, 1H, H-2), 14.85 (s, 1H, COOH). ^{13}C NMR: δ = 14.2 (CH_3), 49.3 (NCH_2), 107.9 (C-3), 112.6 (C-12), 117.6 (CN), 118.06, 118.11 and 118.20 (C-5, C-10a and C-13), 124.0 (C-7), 128.1 (C-4a), 129.2 (C-9), 131.4 (C-12a), 133.5 (C-10), 136.4 (C-8), 136.5 (C-13a), 144.7 (C-11), 150.0 (C-2), 154.2 (C-5a), 156.5 (C-6a), 165.5 (COO), 176.7 (C-4). MS (*m/z*, I_{rel} %): 439 $[M+2]^+$ (3), 438 $[M+1]^+$ (14), 437 $[M]^+$ (4), 436 $[M-1]^+$ (15), 395 (23), 394 (45), 393 (25), 392 (100), 379 (26), 377 (22), 229 (13), 201 (21). Anal. Calc. for $C_{21}H_{13}BrN_2O_4$, C 57.69, H 3.00, N 6.41. Found: C 57.74, H 3.03, N 6.39.

*7,9-Di-tert-butyl-12-cyano-1-ethyl-4-oxo-1,4-dihydro[1]-benzoxepino[2,3-g]quinoline-3-carboxylic acid (**8c**)*

Compound was obtained from 3,5-di-*tert*-buthylsalicylaldehyde (**5c**). Yield 0.56 g (81 %); mp. 311−312 °C. ^{1}H NMR: δ = 1.27 (s, 9H, (^{t}Bu-C^9), 1.46 (t, *J* = 7.2 Hz, 3H, $NCH_2C\mathit{H}_3$), 1.54 (s, 9H, (^{t}Bu-C^7), 4.63 (q, *J* = 7.2 Hz, 2H, NCH_2), 7.46 (d, *J* = 2.5 Hz, 1H, H-10), 7.56 (d, *J* = 2.5 Hz, 1H, H-8), 7.89 (s, 1H, H-13), 8.04 (s, 1H, H-11), 8.23 (s, 1H, H-5), 9.10 (s, 1H, H-2), 14.77 (s, 1H, COOH). ^{13}C NMR: δ = 14.2 ($NCH_2\mathit{C}H_3$), 30.8 ($(\mathit{C}H_3)_3C\text{-}C^9$), 31.1 ($(\mathit{C}H_3)_3C\text{-}C^7$), 34.3 ($(CH_3)_3\mathit{C}\text{-}C^9$), 35.1 ($(CH_3)_3\mathit{C}\text{-}C^7$), 49.2 ($NCH_2$), 107.9 (C-3), 110.8 (C-12), 118.0 (C-5, C-13 and CN), 127.1 (C-4a), 127.8 (C-10a), 128.0 (C-10), 128.9 (C-8), 132.6 (C-12a), 136.2 (C-13a), 141.5 (C-7), 147.6 (C-9), 148.6 (C-11), 149.8 (C-2), 154.7 (C-6a), 155.1 (C-5a), 165.5 (COO), 176.5 (C-4). MS (*m/z*, I_{rel} %): 470 $[M]^+$ (25), 427 (31), 426 (100), 411 (26), 206 (20), 57 (21), 41 (16). Anal. Calc. for $C_{29}H_{30}N_2O_4$, C 74.02, H 6.43, N 5.95. Found: C 74.04, H 6.56, N 5.91.

*12-Cyano-8-ethoxy-1-ethyl-4-oxo-1,4-dihydro[1]-benzoxepino[2,3-g]quinoline-3-carboxylic acid (**8e**)*

Compound was obtained from 3-ethoxysalicylaldehide (**5e**). Yield 0.30 g (51 %), mp. 311−312 °C. ^{1}H NMR: δ = 1.46 (t, *J* = 7.2 Hz, 3H, $NCH_2C\mathit{H}_3$), 1.48 (t, *J* = 6.9 Hz, 3H, $OCH_2C\mathit{H}_3$), 4.18 (q, *J* = 6.9 Hz, 2H,

OCH_2), 4.65 (q, *J* = 7.2 Hz, 2H, NCH_2), 7.12 (dd, *J* = 7.9, 1.2 Hz, 1H, H-10), 7.27 (t, *J* = 7.9 Hz, 1H, H-9), 7.36 (dd, *J* = 8.3, 1.2 Hz, 1H, H-8), 7.98 (s, 1H, H-13), 8.18 (s, 1H, H-5), 8.22 (s, 1H, H-11), 9.12 (s, 1H, H-2), 14.83 (s, 1H, COOH). ^{13}C NMR: δ = 14.2 (NCH_2CH_3), 14.7 (OCH_2CH_3), 49.2 (NCH_2), 64.5 (OCH_2), 107.8 (C-3), 111.4 (C-12), 117.7 (C-5, C-8, C-13), 117.8 (CN), 122.0 (C-10), 126.4 (C-9), 127.8 (C-4a), 128.4 (C-10a), 132.1 (C-12a), 136.3 (C-13a), 145.1 (C-6a), 146.2 (C-11), 149.9 (C-2), 150.7 (C-7), 154.4 (C-5a), 165.6 (COO), 176.7 (C-4). MS (*m/z*, I_{rel} %): 402 $[M]^+$ (15), 359 (26), 358 $[M\text{-}CO_2]^+$ (100), 301 (9), 273 (19). Anal. Calc. for $C_{23}H_{18}N_2O_5$, C 68.65, H 4.51, N 6.96. Found: C 68.52, H 4.54, N 6.86.

*12-Cyano-8-diethylamino-1-ethyl-4-oxo-1,4-dihydro[1]-benzoxepino[2,3-g]quinoline-3-carboxylic acid (**8f**)*

Compound was obtained from 4-diethylaminosalicylaldehyde (**5f**). Yield: 0.50 g (81 %), mp. 250−251 °C. ^{1}H NMR: δ = 1.12 (t, *J* = 7.0 Hz, 6H, $N(CH_2CH_3)_2$), 1.46 (t, *J* = 7.2 Hz, 3H, $N^1CH_2CH_3$), 3.44 (q, 4H, *J* = 7.0 Hz, $N(CH_2CH_3)_2$), 4.61 (q, *J* = 7.2 Hz, 2H, N^1CH_2), 6.57 (dd, *J* = 9.0, 2.5 Hz, 1H, H-9), 6.83 (d, *J* = 2.5 Hz, 1H, H-7), 7.28 (d, *J* = 9.0 Hz, 1H, H-10), 7.77 (s, 1H, H-13), 7.82 (s, 1H, H-11), 8.24 (s, 1H, H-5), 9.08 (s, 1H, H-2), 15.02 (s, 1H, COOH). ^{13}C NMR: δ = 12.4 ($N(CH_2CH_3)_2$), 14.1 ($N^1CH_2CH_3$), 44.1 ($N(CH_2CH_3)_2$), 49.2 (N^1CH_2), 102.8 (C-12), 103.6 (C-7), 107.5 (C-3), 108.4 (C-9), 114.1 (C-10a), 116.1 (C-13), 118.4 (C-5), 119.3 (CN), 126.9 (C-4a), 133.6 (C-10), 133.8 (C-12a), 136.4 (C-13a), 146.4 (C-11), 149.6 (C-2), 152.9 (C-8), 153.2 (C-5a), 159.4 (C-6a), 165.8 (COO), 176.8 (C-4). MS (*m/z*, I_{rel} %): 430 $[M+1]^+$ (19), 429 $[M]^+$ (63), 414 (10), 385 (22), 371 (27), 370 (100), 342 (20), 314 (13). Anal. Calc. for $C_{25}H_{23}N_3O_4$, C 69.92, H 5.40, N 9.78. Found: C 69.57, H 5.45, N 9.69.

4.6. General synthetic procedure for 7-(2-oxo-2H-chromen-3-yl)-substituted tricyclic fluoroquinolones (9a-c)

The corresponding salicylaldehyde **5** (1.65 mmol) was added to a suspension of (-)-(*S*)-10-cyanomethyl-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-*d*,*e*]1,4-benzoxazin-6-carboxylic acid (**4b**) (0.500 g, 1.65 mmol) in DMF (5 mL), then 5 drops of piperidine were added. The mixture was stirred at room temperature for 12 h. The precipitate was filtered off, added to 3 % H_2SO_4 solution (15 mL), and the mixture was heated at 110 °C for 7-15 h. After cooling the precipitate was filtered off and washed with distilled water, then with hexane or heptane. Compounds **9a-c** were recrystallized from the mixture ethanol/DMF.

*(3S)-9-Fluoro-3-methyl-7-oxo-10-(2-oxo-2H-chromen-3-yl)-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxy-lic acid (**9a**)*

Compound was obtained from salicylaldehyde (**5a**), reaction mixture was heated at 110 °C in 3 % H_2SO_4 solution for 7 h. Yield: 0.38 g (56 %) (mixture of atropoisomers, ratio ≈ 1:1); mp. 322-323 °C with decomposition. ^{1}H NMR (t_{amb}): δ = 1.46 and 1.52 (both d, *J* = 6.7 Hz, 3H, CH_3), 4.42 and 4.50 (both dd, *J* = 11.6, 2.3 Hz, 1H, H-2^B), 4.59−4.62 (m, 1H, H-2^A), 5.01 (m, 1H, H-3), 7.45 (br.t, *J* = 7.5 Hz, 1H, H-6'), 7.53 (br d, *J* = 8.4 Hz, 1H, H-8'), 7.72-7.76 (m, 2H, H-7', H-8), 7.84 (dd, *J* = 7.7, 1.9 Hz, 1H, H-5'), 8.40 and 8.42 (both s, 1H, H-4'), 9.11 and 9.12 (both s, 1H, H-5), 14.95 and 14.96 (both s, 1H, COOH). ^{19}F NMR (t_{amb}): δ = -113.44 and -112.94 (both d, *J* = 9.4 Hz, F-9). ^{13}C NMR (t_{amb}): δ = 17.7 and 18.0 (CH_3), 54.9 and 55.0 (C-3), 68.6 and 68.8 (C-2), 102.1 and 102.3 (both d, $^2J_{CF}$ = 24.6 Hz, C-8), 107.6 and 107.7 (C-6), 115.5 and 115.8 (both d, $^2J_{CF}$ = 22.1 Hz, C-10), 116.4 (C-8'), 117.1 and 117.1 (C-3'), 118.37 and 118.40 (C-4'a), 123.9 and 124.1 (both d, $^4J_{CF}$ = 1.2 Hz, C-10b), 125.04 and 125.05 (C-6'), 126.6 (d, $^3J_{CF}$ = 9.7 Hz, C-7a), 128.97 and 128.99 (C-5'), 133.0 (C-7'), 145.7 and 146.0 (C-4'), 145.9 and 146.0 (both d, $^3J_{CF}$ = 7.1 Hz, C-10a), 146.5 and 146.7 (C-5), 153.40 and 153.41 (C-8'a), 157.4 (d, $^1J_{CF}$ = 247.0 Hz, C-9), 158.09 and 158.12 (C-2'), 165.73 and 165.75 (COO), 176.6 (C-7).

^{1}H NMR (t = 120 ºC): δ = 1.52 (d, *J* = 6.8 Hz, 3H, CH_3-C^3), 4.45 (br d, *J* = 11.6 Hz, 1H, H-2^B), 4.51 (dd, *J* = 11.6, 2.5 Hz, 1H, H-2^A), 4.93 (qt, *J* = 6.8, 2.6 Hz, 1H, H-3), 7.40 (td, *J* = 7.5, 1.0 Hz, 1H, H-6'), 7.45 (br d, *J* = 8.6 Hz, 1H, H-8'), 7.68 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H, H-7'), 7.71 (d, *J* = 9.6 Hz, 1H, H-8), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5'), 8.23 (s, 1H, H-4'), 8.93 (s, 1H, H-5), 14.52 (br. s, 1H, COOH). ^{19}F NMR (t = 120 ºC): δ = -113.18 (br. s, F-9). ^{13}C NMR (t = 120 ºC): δ = 16.8 (CH_3), 54.4 (C-3), 68.4 (C-2), 101.6 (d, $^2J_{CF}$ = 24.7 Hz, C-8), 107.6 (C-6), 115.3 (d, $^2J_{CF}$ = 22.1 Hz, C-10), 115.6 (C-8'), 116.9 (C-3'), 117.9 (C-4'a), 123.5 (d, $^4J_{CF}$ = 1.9 Hz, C-10b), 124.2 (C-6'), 126.3 (d, $^3J_{CF}$ = 9.6 Hz, C-7a), 128.2 (C-5'), 132.0 (C-7'), 144.7 (C-4'), 145.4 (d, $^3J_{CF}$ = 7.1 Hz, C-10a), 145.4 (C-5), 153.0 (C-8'a), 157.0 (d, $^1J_{CF}$ = 247.7 Hz, C-9), 157.3 (C-2'), 164.7 (COO), 176.0 (C-7). MS (*m/z*, I_{rel} %): 408 $[M+1]^+$ (5), 407 $[M]^+$ (19), 364 (22), 363 $[M-CO_2]^+$ (100), 349 (13), 182 (12). Anal. Calc. for $C_{22}H_{14}FN_1O_6$, C 64.87, H 3.46, N 3.44. Found: C 64.87, H 3.43, N 3.58.

*(3S)-10-(6-Bromo-2-oxo-2H-chromen-3-yl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**9b**)*

Compound was obtained from 5-bromosalicylaldehyde (**5b**), reaction mixture was heated at 110 °C in 3 % H_2SO_4 solution for 15 h. Yield 0.40 g (50 %) (mixture of atropisomers, ratio ≈ 1:1), mp. 326-327 °C. ^{1}H NMR (t_{amb}): δ = 1.46 and 1.51 (both d, *J* = 6.7 Hz, 3H, CH_3), 4.41 and 4.50 (both dd, *J* = 11.7, 2.2 Hz, 1H, H-2^B), 4.59−4.62 (m, 1H, H-2^A), 5.01 (m, 1H, H-3), 7.49 and 7.50 (both d, *J* = 8.8 Hz, 1H, H-8'), 7.74 (d, *J* = 9.4 Hz, 1H, H-8), 7.87 and 7.88 (both dd, *J* = 8.8, 2.3 Hz, 1H, H-7'), 8.09 (d, *J* = 2.3 Hz, 1H, H-5'), 8.34 and 8.36 (both s, 1H, H-4'), 9.11 and 9.12 (both s, 1H, H-5), 14.93 (br. s, 1H, COOH). ^{19}F NMR (t_{amb}): δ = -113.44

and -112.94 (both d, *J* = 9.4 Hz, F-9). ^{13}C NMR (t_{amb}): δ = 17.6 and 18.0 (CH_3), 54.8 and 55.0 (C-3), 68.7 and 68.8 (C-2), 102.2 and 102.3 (both d, $^2J_{CF}$ = 24.5 Hz, C-8), 107.67 and 107.73 (C-6), 115.0 and 115.3 (both d, $^2J_{CF}$ = 22.0 Hz, C-10), 116.49 and 116.51 (C-4'a), 118.23 and 118.27 (C-3'), 118.6 (C-8'), 120.1 and 120.2 (C-6')), 123.8 and 124.1 (both d, $^4J_{CF}$ = 1.2 Hz, C-10b), 126.7 (d, $^3J_{CF}$ = 9.6 Hz, C-7a), 130.90 and 130.92 (C-5'), 135.2 (C-7'), 144.4 and 144.7 (C-4'), 145.8 and 145.9 (both d, $^3J_{CF}$ = 7.0 Hz, C-10a), 146.5 and 146.7 (C-5), 152.4 (C-8'a), 157.54 and 157.57 (C-2'), 157.3 (d, $^1J_{CF}$ = 248.8 Hz, C-9), 165.64 (COO), 176.50 (C-7). MS (*m/z*, I_{rel} %): 488 $[M+2]^+$ (4), 487 $[M+1]^+$ (18), 486 $[M]^+$ (4), 485 $[M-1]^+$ (17), 444 (22), 443 (95), 442 (26), 441 (100), 428 (48), 426 (51), 221 (16), 53 (22), 41 (23). Anal. Calc. for $C_{22}H_{13}BrFN_1O_6$, C 54.34, H 2.69, N 2.88. Found: C 54.25, H 2.79, N 2.98.

*(3S)-10-(6,8-Di-tert-butyl-2-oxo-2H-chromen-3-yl)-9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (**9c**)*

Compound was obtained from 3,5-di-*tert*-butylsalicylaldehyde (**5c**), reaction mixture was heated at 110 °C in 3 % H_2SO_4 solution for 10 h. Yield: 0.58 g (67 %) (mixture of atropisomers, ratio ≈ 1:1), mp. 262−263 °C. ^{1}H NMR (t_{amb}): δ = 1.35 (s, 9H, ^{t}Bu), 1.46−1.52 (m, 12H, ^{t}Bu, CH_3-C^3), 4.42 and 4.49 (both dd, *J* = 11.6, 2.3 Hz, 1H, H-2^B), 4.60 and 4.61 (both dd, *J* = 11.6, 1.8 Hz, 1H, H-2^A), 5.01 (m, 1H, H-3), 7.65 (d, *J* = 2.4 Hz, 1H, H-7'), 7.69 and 7.70 (both d, *J* = 2.4 Hz, 1H, H-5'), 7.75 and 7.76 (d, *J* = 9.4 Hz, 1H, H-8), 8.36 and 8.38 (both s, 1H, H-4'), 9.11 and 9.12 (both s, 1H, H-5), 14.96 (br. s, 1H, COOH). ^{19}F NMR (t_{amb}): δ = -113.39 and -112.82 (both d, *J* = 9.4 Hz, F-9). ^{13}C NMR (t_{amb}): δ = 17.7 and 17.9 (CH_3-C^3), 29.5 ((CH_3)$_3$C-$C^{6'}$), 31.0 ((CH_3)$_3$C-$C^{8'}$), 34.4 ((CH_3)$_3$C-$C^{6'}$), 34.6 ((CH_3)$_3$C-$C^{8'}$), 54.9 and 55.0 (C-3), 68.6 and 68.8 (C-2), 102.1 and 102.2 (both d, $^2J_{CF}$ = 24.6 Hz, C-8), 107.6 and 107.7 (C-6), 115.6 and 115.8 (both d, $^2J_{CF}$ = 22.3 Hz, C-10), 116.00 and 116.02, 118.37 and 118.40 (C-4'a, C-3'), 123.71 and 123.73 (C-5'), 123.9 and 124.1 (both d, $^4J_{CF}$ = 1.2 Hz, C-10b), 126.6 (d, $^3J_{CF}$ = 9.6 Hz, C-7a), 127.4 (C-7'), 136.15 and 136.16 (C-6'), 145.8 and 145.9 (both d, $^3J_{CF}$ = 7.0 Hz, C-10a), 146.5 and 146.6 (C-5), 146.70 and 146.71 (C-8'), 146.9 and 147.2 (C-4'), 150.1 (C-8'a), 157.48 (d, $^1J_{CF}$ = 247.4 Hz, C-9), 157.79 and 157.84 (C-2'), 165.7 (COO), 176.54 (C-7).

^{1}H NMR (t = 110 ºC): δ = 1.36 (s, 9H, ^{t}Bu), 1.52 (d, *J* = 6.7 Hz, 3H, CH_3-C^3), 1.52 (s, 9H, ^{t}Bu), 4.45 (br. d, *J* = 11.6 Hz, 1H, H-2^B), 4.53 (dd, *J* = 11.6, 2.4 Hz, 1H, H-2^A), 4.94 (qt, *J* = 6.7, 2.5 Hz, 1H, H-3), 7.62 (d, *J* = 2.4 Hz, 1H, H-7'), 7.66 (d, *J* = 2.4 Hz, 1H, H-5'), 7.71 (d, *J* = 9.5 Hz, 1H, H-8), 8.22 (s, 1H, H-4'), 8.97 (s, 1H, H-5), 14.56 (br. s, 1H, COOH). ^{19}F NMR (t = 110 ºC): δ = -113.06 (br. s, F-9). ^{13}C NMR (t = 110 ºC): δ = 16.9 (CH_3-C^3), 29.2 ((CH_3)$_3$C-$C^{6'}$), 30.5 ((CH_3)$_3$C-$C^{8'}$), 33.8 ((CH_3)$_3$C-$C^{6'}$), 34.1 ((CH_3)$_3$C-$C^{8'}$), 54.4 (C-3), 68.4 (C-2), 101.7 (d, $^2J_{CF}$ = 24.7 Hz, C-8), 107.6 (C-6), 115.4 (d, $^2J_{CF}$ = 22.3 Hz, C-10), 115.8, 118.0 (C-4'a, C-3'), 123.0 (C-5'), 123.6 (unres. d, C-10b), 126.3 (d, $^3J_{CF}$ = 9.6 Hz, C-7a), 126.7 (C-7'), 136.0 (C-6'), 145.5 (d, $^3J_{CF}$ = 6.9 Hz, C-10a), 145.6 (C-5), 146.1 (C-8'), 146.4 (C-4'), 149.7 (C-8'a), 157.2 (C-2'), 157.2 (d, $^1J_{CF}$ = 247.4 Hz, C-9), 164.8

(COO), 176.1 (C-7). MS (*m/z*, I_{rel} %): 520 $[M+1]^+$ (5), 519 $[M]^+$ (16), 476 (33), 475 $[M\text{-}CO_2]^+$ (100), 460 (19), 376 (14), 230 (20), 216 (10), 57 (30), 41 (17). Anal. Calc. for $C_{30}H_{27}FNO_6$, C 69.35, H 5.82, N 2.70. Found: C 69.37, H 5.79, N 2.58.

4.7. Antimycobacterial assay

To evaluate the inhibitory efficiency of molecules on Mycobacterium tuberculosis (MTB), *M. tuberculosis* $H_{37}R_v$, which is susceptible to all classical anti-tuberculosis drugs, was used. The minimal inhibitory concentration (MIC) for *M. tuberculosis* $H_{37}R_v$ for each compound was determined by a micro broth dilution method. All molecules tested were dissolved in dimethyl sulfoxide and their 1/2 dilutions were prepared in 5 mL tubes using Löwenstein-Jensen medium. A few colonies from freshly grown *M. tuberculosis* $H_{37}R_v$ were suspended in Löwenstein-Jensen medium to obtain 1.0 McFarland turbidity and diluted ten times using the same medium and the tubes were incubated at 37 °C medium with a different concentration of the tested molecule and to a positive control tube containing only clear growth medium. After 24 hours the tubes were placed in a vertical position and the free edge of the buried 0.3 mL of the substance in the test compounds concentrations: 12.5, 6.25, 3.1, 1.5, 0.7, 0.37, 0.15 μg/mL. The tubes were then placed in thermostat at a temperature of 37 °C and incubated for 10 days. Growth estimate for the MTB were determined by standard methods, where the appearance of zones of growth retardation MTB (over 10 mm) indicated the presence of tuberculostatic properties in concentration of the compounds under study. Penetration size stunting MTB (in mm) is proportional to the degree of tuberculostatic activity. Growth delay of 100 mm or more is considered as a complete growth inhibition MTB. The multi-drug-resistant (MDR) tuberculosis strain was isolated from tuberculosis patients in Ural Research Institute for Phthisiopulmonology (Russia). The minimal inhibitory concentrations against *Mycobacterium tuberculosis avium*, *Mycobacterium tuberculosis terrae*, and MDR tuberculosis strains were evaluated similarly.

4.8. Evaluation of acute toxicity in vivo

All experimental protocols were carried out in accordance with the standard protocol approved by the Committee for the Ethical Use of Animals of the Ural Research Institute for Phthisiopulmonology (CEUA/URIP). The synthesized compounds were evaluated for their approximate LD_{50} in white healthy mice (17−20 g body weight) divided into 3 groups of 5 animals each for testing of one compound [18, 19]. Toxicity tests were carried out via a single per oral introduction of compound in a 1 % starch aqueous

solution. The volume introduced did not exceed 0.5 mL for mice. The observation period was 14 days. The median lethal doses LD_{50} were used as the criteria of toxicity.

Acknowledgment

The work was carried out with financial support from the Russian Scientific Foundation (grant 15-13-00077) and from the Ministry of Education of Russian Federation (State Contract 4.6351.2017/8.9, research of 1,4-dihydro[1]benzoxepino-[2,3-*g*]quinolones **8**).

The authors are thankful to PhD Andrey A. Tumashov (Postovsky Institute of Organic Synthesis, Ekaterinburg) for assistance with HPLC analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j. jfluchem.

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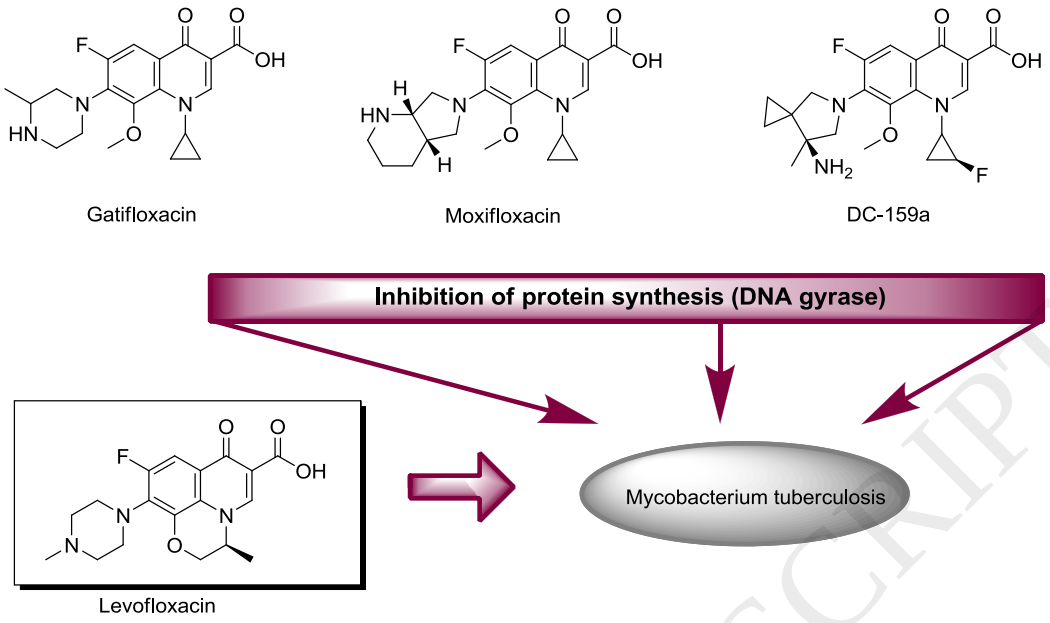


Figure 1. Fluoroquinolones recommended for the treatment of tuberculosis.

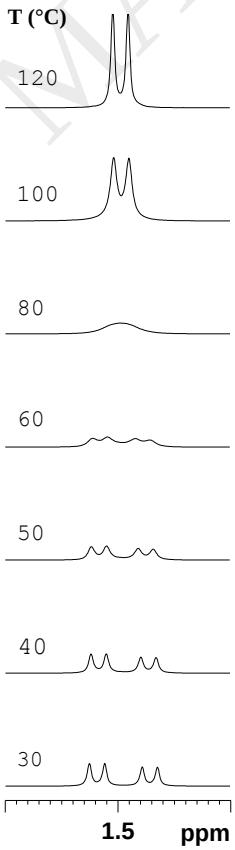
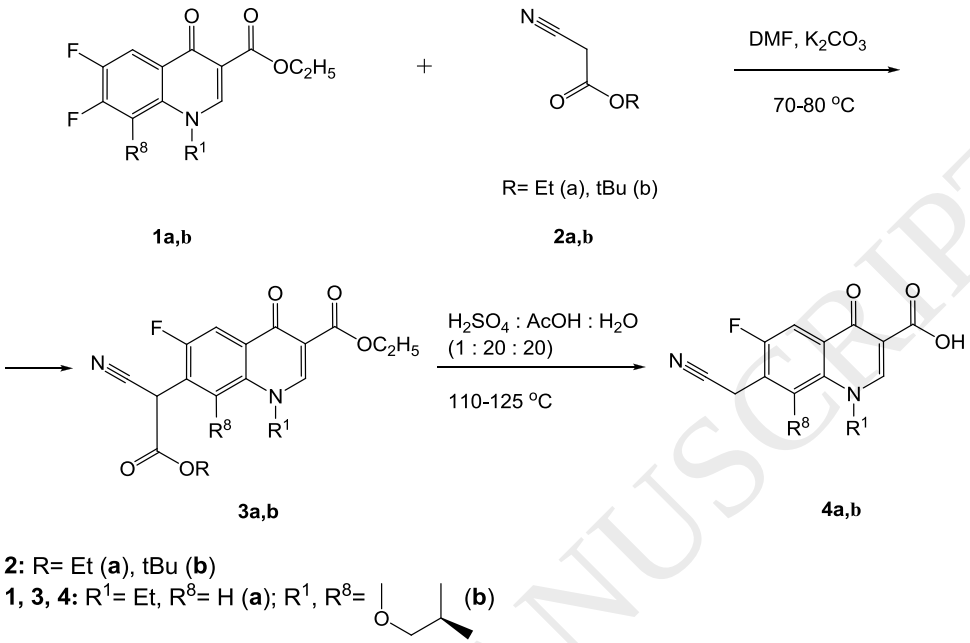
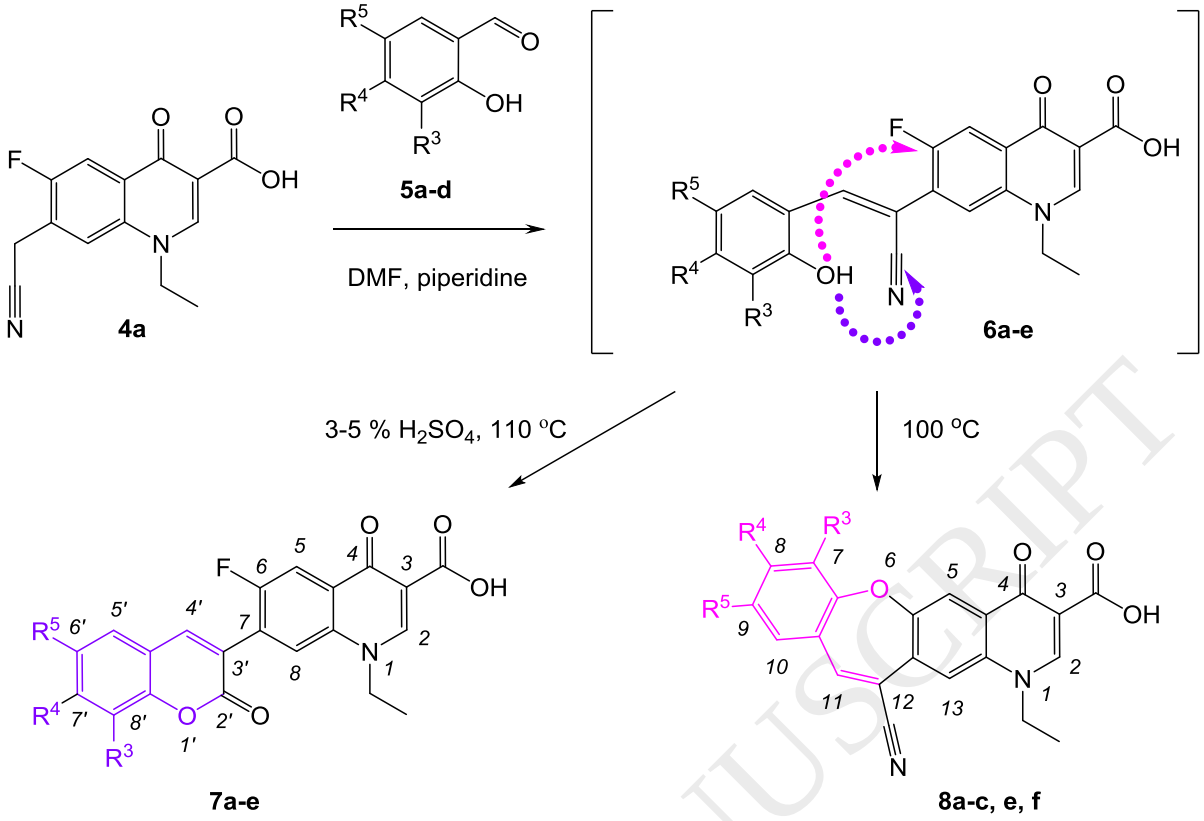


Figure 2. Variable-temperature ^{1}H NMR spectra (500 MHz, DMSO-d_6)



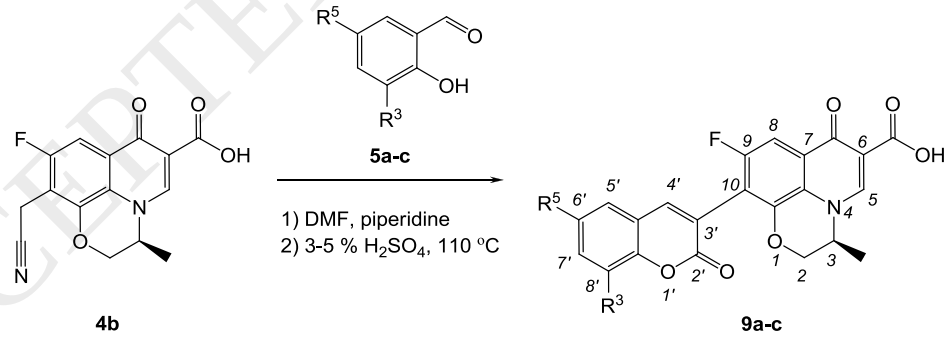
2: R= Et (**a**), tBu (**b**)
1, 3, 4: R^1= Et, R^8= H (**a**); R^1, R^8= (**b**)

Scheme 1. Synthesis of cyanomethyl fluoroquinolones **4**.



5-8: R^3= R^4= R^5= H (**a**); R^3= R^4= H, R^5= Br (**b**); R^3= R^5= tBu, R^4= H (**c**); R^3= R^4= H, R^5= Cl (**d**); R^3= OEt, R^4= R^5= H (**e**); R^3= R^5= H, R^4= NEt_2 (**f**)

Scheme 2. Synthesis of coumarinyl substituted bicyclic fluoroquinolones **7** and polycyclic quinolones **8**.



5, 9: R^3= R^5= H (**a**); R^3= H, R^5= Br (**b**); R^3= R^5= tBu = H (**c**)

Scheme 3. Synthesis of coumarinyl substituted tricyclic fluoroquinolones **9**.

Table 1

In vitro antimycobacterial activity of (2-oxo-*2H*-chromen-3-yl)-substituted bi- and tricyclic fluoroquinolones **7a-c,e** and **9a-c**.

Com-pound	Antimycobacterial activity against different strains of *M. tuberculosis* (MIC in μg/mL)				LD_{50} in mice (mg/kg)
	$H_{37}R_V$	*M. avium*	*M. terrae*	MDR-TB [a]	
7a	12.5	n.d.	n.d.	n.d.	n.d.
7b	6.2	6.2	6.2	6.2	n.d.
7c	3.1	3.1	1.5	3.1	n.d.
7e	1.5	1.5	0.7	1.5	600
9a	12.5	n.d.	n.d.	n.d.	n.d.
9b	12.5	n.d.	n.d.	n.d.	n.d.
9c	12.5	n.d.	n.d.	n.d.	n.d.
LEV	0.5 [b]	n.d.	n.d.	n.d.	1500-2000 [b]
INH	0.1	0.1	0.1	–	149[c] 151[d]

n.d. – not determined; INH – Izoniazid; LEV – Levofloxacin;

[a] MDR-TB – Rifampin and Izoniazid resistant *Mycobacterium tuberculosis* strain having Beijing genotype with a combination of mutations *Ser 531-Leu 315* and *Ser-Thr* in *rpoB* and *katC* genes, respectively.

[b] LD_{50} oral administration in mice and rats [17].

[c] LD_{50} i.v. administration in mice [17].

[d] LD_{50} i.p. administration in mice [17].