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Fluorinated 1,3-benzothiazin-4-ones containing fluoroquinolone fragment

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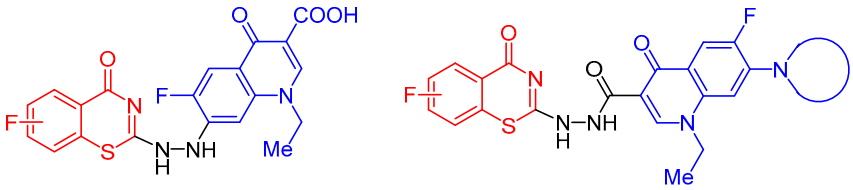


We have developed an efficient synthetic approach to potential antibacterial agents with double mechanism of action through the combination of antibacterial fluoroquinolones with 1,3-benzothiazin-4-ones.

Keywords: fluorobenzothiazin-4-ones, *o*-fluorobenzoyl isothiocyanates, 7-hydrazinoquinolone-3-carboxylic acid, quinolone-3-carboxylic acid hydrazides, cyclocondensation.

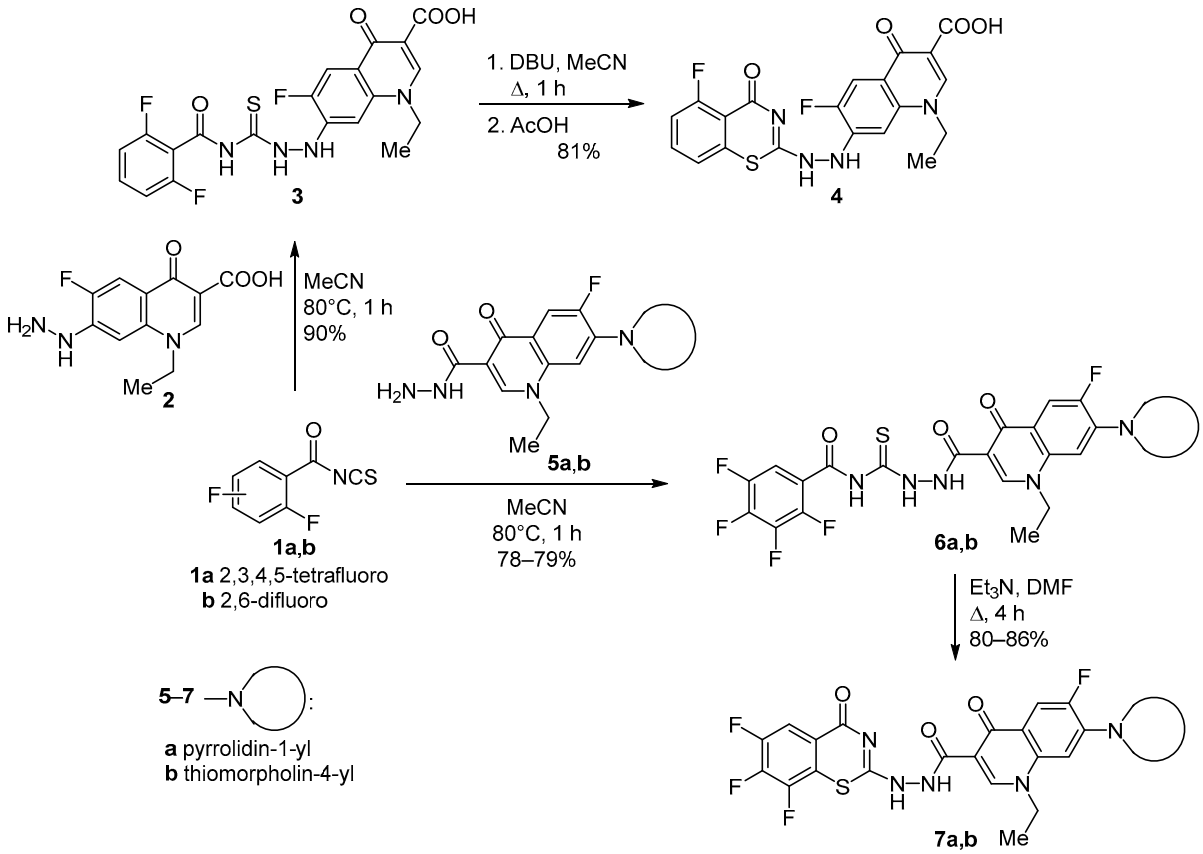
Design of dual action antibiotics is an important approach in the search for new promising drugs.[1] Fluoroquinolones demonstrate high activity toward tuberculosis (TB) mycobacteria and are of considerable interest as agents for the combined chemotherapy of multidrug-resistant tuberculosis.[2] Notably, that nowadays the creation of 4-quinolone hybrids is considered as one of the most promising ways for the design of antibacterial agents.[3] A large number of fluoroquinolone hybrid compounds, in which the fluoroquinolone fragment is covalently connected with such antibacterial agents as oxazolidinones, macrolides, rifamycin, tetracycline, benzylpyrimidines, anilinouracils, cephalosporines, aminoglycosides, is described in literature.[1] Recently, new 2-oxo-2*H*-chromen-3-yl-substituted bi- and tricyclic fluoroquinolones, which are of interest due to inhibition of GyrA and GyrB subunits of DNA girase and the potential expansion of the spectrum of action on pathogens, were obtained.[4]

Benzothiazinone derivatives are of particular interest due to their recently discovered ability to be active against TB mycobacteria by blocking decaprenylphosphoryl-β-D-ribose-2'-epimerase (DprE1), the enzyme catalyzing transformation of decaprenylphosphoryl-substituted ribose into its epimere, the corresponding arabinose, and this conversion proved to be the key step in biosynthesis of arabinan, as a building block for TB mycobacteria cell wall.[5] Obviously, other mechanisms of action can exist for benzothiazinones not containing nitro group at position 8.

Earlier we demonstrated that interaction of tetrafluorobenzoyl isothiocyanates with aminoazines and aminoazoles as N-nucleophiles represents an effective approach to 2-heterylamino-6,7,8-trifluoro-1,3-benzothiazin-4-ones.[6] Some of the synthesized 6,7,8-trifluoro-1,3-benzothiazin-4-ones derivatives possess high antitubercular activity.[7] This year we reported fluorinated 2-cycloalkylamino-1,3-benzothiazin-4-ones exhibiting antitubercular activity.[8]

In present work, we studied the reaction of *o*-fluorobenzoyl isothiocyanates with hydrazino and hydrazido derivatives of fluoroquinolones and found convenient conditions leading to the formation of molecules containing covalently bound fluoroquinolone and fluorobenzothiazinone fragments. It worth noting that hydrazide spacer was previously used for fluoroquinolone modifications, for example, in the design of *N*'-(aldehydoglycosylquinolon-

Scheme 1



3-yl)carbohydrazides.[9] Condensation of 3-formylrifamycin SV and 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrazide led to the compound active toward Gram-positive microorganisms and TB micobacteria.[10]

We demonstrated that 2,3,4,5-tetra- and 2,6-difluorobenzoyl isothiocyanates **1a**,**b**, obtained by interaction of the corresponding benzoyl chlorides with ammonium isothiocyanate, smoothly react with hydrazine **2** and hydrazides **5a**,**b** in MeCN at 80°C for 1 h, and addition products **3**, **6a**,**b** were obtained with 78–90% yields (Scheme 1). Compound **3** was found to undergo intramolecular cyclization into 1,3-benzothiazin-4-one **4** under reflux in MeCN in the presence of DBU for 1 h, treatment with AcOH allowed to transform salt **4**·DBU into the target product **4**. Intermediates **6a**,**b** underwent intramolecular cyclization into 1,3-benzothiazin-4-ones **7a**,**b** under reflux in DMF in the presence of Et_3N for 4 h.

Structure of compounds **3**–**7** was confirmed by the data of ^1H, ^{13}C, ^{19}F NMR spectra and mass spectra. ^{19}F NMR spectrum of compound **3** proved to exhibit two signals, from two fluorine atoms of $C_6H_3F_2$ fragment at –113.54 ppm and from atom F-6' of fluoroquinolone fragment at –131.78 ppm. In ^1H NMR spectrum of compound **3**, signals of three NH groups were observed. As for cyclization product **4**, signals from two fluorine atoms were observed in ^{19}F NMR spectrum: atom F-5 of benzothiazinone fragment at –110.87 ppm and atom F-6' of fluoroquinolone fragment at –130.89 ppm. ^1H NMR spectrum of compound **4** contains one two-proton broadened signal of NHNH fragment.

One-proton multiplet at 7.62–7.68 ppm in the ^1H NMR spectra of addition products **6a**,**b** is typical for the tetrafluorobenzoyl moiety. In ^1H NMR spectra of benzothiazinone derivatives **7a**,**b**, the multiplicity of H-5 signal has changed to a double doublet of doublets (7.94–7.95 ppm), while one NH signal has expectedly disappeared.

The molecular ion peak in mass spectrum of benzothiazinone **4** has 100% intensity. The molecular ion peaks in mass spectra of compounds **7a**,**b** have relative intensities of 15–21%. The ions with *m*/*z* 287 and *m*/*z* 259 with 100% intensity were observed for pyrrolidine-containing derivative **7a** and thiomorpholine-containing one **7b**, respectively.

Earlier[11] we have demonstrated that *p*-nitrophenylhydrazine smoothly reacts with tetrafluorobenzoyl isothiocyanate upon boiling in MeCN (reaction time 30 min) to give thiosemicarbazide, which was subjected to cyclization by boiling in DMSO for 15 min; as a result, 1,3-benzothiazinone was isolated. By boiling tetrafluorobenzoyl isothiocyanate **1a** with (4,6-dimethylpyrimidin-2-yl)hydrazine in MeCN for 1 h we directly obtained fluorine-containing 2-(4,6-dimethylpyrimidin-2-yl)-4*H*-1,3-benzothiazin-4-one. 4,6-Diphenylpyrimidin-2-ylhydrazine reacted with isothiocyanate **1a** in boiling MeCN in a different way, and the product was substituted [1,2,4]triazolo[4,3-*a*]pyrimidine. As for benzoylthiosemicarbazides obtained from aryl-

hydrazides and isothiocyanate **1a**, they failed to cyclize into 2-substituted benzothiazinones in the presence of base, their thermal cyclization in Dowtherm A led to thiadiazoloquinazolines.[12]

The hybrid fluorinated benzothiazinones **4**, **7a**,**b** were screened to estimate the level of their activity against *Mycobacterium tuberculosis* $H_{37}R_v$ strain. Derivatives **4**, **7a**,**b** demonstrated low activity (MIC 12.5 mg/ml).

To sum up, we have developed an effective approach for the design of molecules combining antibacterial fluoroquinolones and benzothiazine derivatives in one core structure.

Experimental

^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on a Bruker Avance II DMX400 spectrometer (400, 100, and 376 MHz, respectively) in DMSO-d_6. TMS was used as internal standard for ^{1}H and ^{13}C NMR spectra, $CFCl_3$ (C_6F_6 as a secondary reference, δ_F –162.9 ppm) for ^{19}F NMR spectra. Assignments in ^{13}C NMR spectra were made based on a literature data.[4,8] Mass spectra were recorded on a Shimadzu GCMS-QP2010 Ultra instrument (EI). Elemental analyses were performed on a PerkinElmer 2400 elemental analyzer. Melting points were determined on a Stuart SMP3 instrument.

7-Hydrazinylquinoline-3-carboxylic acid **2**[13] and quinoline-3-carboxylic acid hydrazides **5a**,**b**[14] were synthesized by reported procedures.

7-(2-{[(2,6-Difluorophenyl)carbonyl]carbamothioyl}-hydrazinyl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3). A solution of ammonium isothiocyanate (0.09 g, 1.17 mmol) in MeCN (7 ml) was added to 2,6-difluorobenzoyl chloride (0.205 g, 1.17 mmol). The reaction mixture was stirred at 40°C for 5 min, the precipitate of NH_4Cl was filtered off, and hydrazine **2** (0.3 g, 1.13 mmol) was added to resulting solution of 2,6-difluorobenzoyl isothiocyanate **1b**. The mixture was stirred at 80°C for 1 h and then cooled. The precipitate was filtered off, washed with hexane, and recrystallized from DMSO. Yield 0.47 g (90%), colorless crystals, mp 328–330°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, t, J = 7.2, CH_3); 4.46 (2H, q, J = 7.2, CH_2); 7.02 (1H, d, $^4J_{HF}$ = 7.0, H-8'); 7.15−7.17 (2H, m, H-3,5); 7.55−7.59 (1H, m, H-4); 7.92 (1H, d, $^3J_{HF}$ = 11.6, H-5'); 8.91 (1H, s, H-2'); 9.3 (1H, br. s, NH); 10.8 (1H, br. s, NH); 15.3 (2H, br. s, COOH, C(O)NHC(S)). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.6 (CH_3); 49.4 (NCH_2); 110.8 (d, $^2J_{CF}$ = 23.8, C-5'); 112.0 (dd, $^2J_{CF}$ = 23.8, $^4J_{CF}$ = 4.6, C-3,5); 114.0 (t, $^2J_{CF}$ = 21.8, C-1); 122.3 (d, $^3J_{CF}$ = 2.7, C-8'); 127.3 (d, $^3J_{CF}$ = 7.8, C-4a'); 127.7 (C-3'); 129.3 (d, $^2J_{CF}$ = 18.1, C-7'); 132.6 (t, $^3J_{CF}$ = 10.6, C-4); 135.5 (d, $^4J_{CF}$ = 1.3, C-8a'); 149.5 (C-2'); 157.2 (d, $^1J_{CF}$ = 250.7, C-6'); 158.8 (dd, $^1J_{CF}$ = 253.4, $^3J_{CF}$ = 8.7, C-2,6); 164.9 (d, $^3J_{CF}$ = 5.9, C=O); 165.7 (COO); 168.6 (C(O)Ar); 178.2 (C=S). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –113.50 ÷ –113.55 (2F, m, F-2,6); –131.78 (dd, $^3J_{FH}$ = 11.5, $^4J_{FH}$ = 7.0, F-6'). Found, %: C 51.53; H 3.33; N 12.12. $C_{20}H_{15}F_3N_4O_4S$. Calculated, %: C 51.72; H 3.26; N 12.06.

Tetrafluorobenzamides 6a,b were synthesized by the method used for compound **3** synthesis. Tetrafluorobenzoyl chloride, ammonium isothiocyanate, and hydrazides **5a**,**b** were taken in ratio 1.03:1.03:1, solvent – MeCN. After addition of hydrazine **5a**,**b**, mixture was stirred at 80°C for 1 h.

***N*-{2-[1-Ethyl-6-fluoro-4-oxo-7-(pyrrolidin-1-yl)-1,4-dihydroquinoline-3-carbonyl]hydrazine-1-carbonothioyl}-2,3,4,5-tetrafluorobenzamide (6a)**. Yield 0.49 g (79%), colorless crystals, mp 320–322°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48 (3H, t, J = 7.4, CH_3); 2.03−2.06 (4H, m, $(CH_2)_2$); 3.60−3.62 (4H, m, $N(CH_2)_2$); 4.47 (2H, q, J = 7.4, CH_2); 6.58 (1H, d, $^4J_{HF}$ = 7.4, H-8'); 7.63−7.68 (1H, m, C_6HF_4); 7.84 (1H, d, $^3J_{HF}$ = 11.5, H-5'); 8.74 (1H, s, H-2'); 12.02 (1H, br. s, NH); 13.33 (1H, br. s, NH); 13.51 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.5 ($(CH_2)_2$); 14.6 (CH_3); 45.5 ($N(CH_2)_2$); 49.4 (NCH_2); 110.8 (d, $^2J_{CF}$ = 24.0, C-5'); 112.1 (d, $^2J_{CF}$ = 19.9, C-6); 122.3 (d, $^3J_{CF}$ = 3.5, C-8'); 127.1 (d, $^3J_{CF}$ = 7.8, C-4a'); 128.2 (C-3'); 129.8 (d, $^2J_{CF}$ = 18.1, C-7'); 129.7–130.0 (m, C-1); 135.6 (d, $^4J_{CF}$ = 1.5, C-8a'); 139.8 (dt, $^1J_{CF}$ = 249.8, $^2J_{CF}$ = 15.0, C -3); 141.4 (dt, $^1J_{CF}$ = 253.6, $^2J_{CF}$ = 13.4, C-4); 145.1 (dd, $^1J_{CF}$ = 246.6, $^2J_{CF}$ = 13.4, C-2); 146.0 (dd, $^1J_{CF}$ = 246.6, $^2J_{CF}$ = 11.8, C-5); 149.4 (C-2'); 157.2 (d, $^1J_{CF}$ = 250.4, C-6'); 159.2 (C=O); 161.7 (CONH); 176.6 (d, $^4J_{CF}$ = 2.4, C-4'); 178.5 (CS). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –128.16 (1F, dd, $^3J_{FH}$ = 11.5, $^3J_{FH}$ = 7.4, F-6'); –136.80 ÷ –136.85 (1F, m); –138.35 ÷ –138.40 (1F, m); –150.65 ÷ –150.70 (1F, m); –155.10 ÷ –155.15 (1F, m). Found, %: C 52.19; H 3.61; N 12.72. $C_{24}H_{20}F_5N_5O_3S$. Calculated, %: C 52.08; H 3.64; N 12.65.

***N*-{2-[1-Ethyl-6-fluoro-4-oxo-7-(thiomorpholin-4-yl)-1,4-dihydroquinoline-3-carbonyl]hydrazine-1-carbonothioyl}-2,3,4,5-tetrafluorobenzamide (6b)**. Yield 0.51 g (78%), colorless crystals, mp 279–281°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (3H, t, J = 7.3, CH_3); 2.81−2.83 (4H, m, $S(CH_2)_2$); 3.57−3.59 (4H, m, $N(CH_2)_2$); 4.55 (2H, q, J = 7.3, CH_2); 7.14 (1H, d, $^4J_{HF}$ = 7.1, H-8'); 7.62−7.66 (1H, m, C_6HF_4); 7.96 (1H, d, $^3J_{HF}$ = 13.0, H-5'); 8.87 (1H, s, H-2'); 12.0 (1H, br. s, NH); 13.4 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.5 (CH_3); 26.4 ($S(CH_2)_2$); 45.5 ($N(CH_2)_2$); 49.3 (NCH_2); 110.6 (d, $^2J_{CF}$ = 23.8, C-5'); 112.1 (d, $^2J_{CF}$ = 19.9, C-6); 122.2 (d, $^3J_{CF}$ = 3.5, C-8'); 127.1 (d, $^3J_{CF}$ = 7.8, C-4a'); 128.2 (C-3'); 129.8 (d, $^2J_{CF}$ = 18.1, C-7', C-1); 135.6 (d, $^4J_{CF}$ = 1.5, C-8a'); 139.8 (dt, $^1J_{CF}$ = 247.9, $^2J_{CF}$ = 14.8, C-3); 141.4 (dt, $^1J_{CF}$ = 253.6, $^2J_{CF}$ = 12.9, C-4); 145.1 (dd, $^1J_{CF}$ = 246.3, $^2J_{CF}$ = 12.9, C-2); 146.0 (dd, $^1J_{CF}$ = 246.3, $^2J_{CF}$ = 11.6, C-5); 149.4 (C-2'); 156.9 (d, $^1J_{CF}$ = 250.4, C-6'); 159.2 (C=O); 161.6 (CONH); 176.6 (d, $^4J_{CF}$ = 2.4, C-4'); 178.4 (CS). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –123.16 (1F, dd, $^3J_{FH}$ = 12.5, $^3J_{FH}$ = 7.4, F-6'); –136.60 ÷ –136.65 (1F, m); –138.30 (1F, dd, $^3J_{FF}$ = 21.1, $^3J_{FH}$ = 13.2, $^4J_{FF}$ = 8.0, F-2); –150.55 (1F, td, $^3J_{FF}$ = 20.8, $^3J_{FH}$ = 14.9, $^4J_{FF}$ = 6.2, F-5); –155.06 (1F, t, $^3J_{FF}$ = 21.1, F-4). Found, %: C 49.31; H 3.45; N 11.99. $C_{24}H_{20}F_5N_5O_3S_2$. Calculated, %: C 49.23; H 3.44; N 11.96.

1-Ethyl-6-fluoro-7-[2-(5-fluoro-4-oxo-4*H*-1,3-benzothiazin-2-yl)hydrazinyl]-4-oxo-1,4-dihydroquinoline-

3-carboxylic acid (4). DBU (0.24 ml, 1.448 mmol) was added to a suspension of compound **3** (0.336 g, 0.724 mmol) in MeCN (12 ml) . Reaction mixture was refluxed for 1 h, and then cooled. The precipitate was filtered off, suspended in H_2O, and pH was adjusted to 5 by addition of diluted AcOH. The precipitate was filtered off and recrystallized from EtOH. Yield 0.26 g (81%), light-yellow crystals, mp 276–278°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.1, CH_3); 4.41 (2H, q, *J* = 7.1, CH_2); 6.77 (1H, d, $^4J_{HF}$ = 6.8, H-8'); 7.08 (1H, dd, $^3J_{HF}$ = 10.1, $^3J_{HH}$ = 8.7, H-6); 7.30 (1H, d, $^3J_{HH}$ = 8.5, H-8); 7.68 (1H, td, $^3J_{HH}$ = 8.4, $^4J_{HF}$ = 5.4, H-7); 8.03 (1H, dd, $^3J_{HF}$ = 11.5, J_{HH} = 1.5, H-5'); 8.83 (1H, s, H-2'); 10.9 (2H, br. s, 2NH); 13.2 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.6 (CH_3); 49.4 (NCH_2); 110.8 (d, $^2J_{CF}$ = 23.8, C-5'); 112.4 (d, $^2J_{CF}$ = 13.0, C-4a); 116.3 (d, $^2J_{CF}$ = 24.2, C-6); 122.3 (two d, $^4J_{CF}$ = 5.4, C-8 and $^3J_{CF}$ = 2.7, C-8'); 127.3 (d, $^3J_{CF}$ = 7.8, C-4a'); 127.7 (C-3'); 129.3 (d, $^2J_{CF}$ = 18.1, C-7'); 133.6 (d, $^3J_{CF}$ = 7.8, C-7); 134.4 (C-8a); 135.5 (d, $^4J_{CF}$ = 1.3, C-8a'); 149.5 (C-2'); 154.5 (C-2); 157.1 (d, $^1J_{CF}$ = 250.7, C-6'); 161.8 (d, $^1J_{CF}$ = 262.3, C-5); 165.0 (d, $^3J_{CF}$ = 5.9, C=O); 165.7 (COO); 176.6 (d, $^4J_{CF}$ = 2.4, C-4). ^{19}F NMR spectrum, δ, ppm: –110.87 (1F, s); –130.89 (1F, s). Mass spectrum, *m*/*z* (I_{rel}, %): 444 $[M]^+$ (7), 374 (66), 401 (10), 400 (45), 250 (19), 207 (13), 206 (99), 205 (12), 196 (91), 191 (42), 178 (17), 163 (35), 150 (14), 149 (14), 138 (100), 137 (75), 122 (23), 110 (76), 109 (26), 108 (33), 94 (13), 83 (11), 82 (26), 81 (16). Found, %: C 54.28; H 3.41; N 12.25. $C_{20}H_{18}F_2N_4O_4S$. Calculated, %: C 54.05; H 3.18; N 12.61.

Synthesis of 6,7,8-trifluorobenzothiazin-4-ones 7a,b (General method). Et_3N (0.1 ml, 0.546 mmol) was added to a suspension of compound **6a**,**b** (0.273 mmol) in DMF (2 ml). The reaction mixture was refluxed for 4 h and then cooled. The precipitate was filtered off, washed with H_2O (15 ml) and EtOH (3 ml).

1-Ethyl-6-fluoro-4-oxo-7-(pyrrolidin-1-yl)-*N*'-(6,7,8-trifluoro-4-oxo-4*H*-benzo[*e*][1,3]thiazin-2-yl)-1,4-dihydroquinoline-3-carbohydrazide (7a). Yield 0.072 g (80%), light-yellow crystals, mp 330–332°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (3H, t, *J* = 7.3, CH_3); 2.05−2.07 (4H, m, $(CH_2)_2$); 3.61−3.63 (4H, m, $N(CH_2)_2$); 4.47 (2H, q, *J* = 7.3, CH_2); 6.57 (1H, d, $^4J_{HF}$ = 7.3, H-8'); 7.94 (1H, ddd, $^3J_{HF}$ = 10.5, $^4J_{HF}$ = 7.5, $^5J_{HF}$ = 2.2, H-5); 7.98−8.00 (1H, m, H-5'); 8.77 (1H, s, H-2'); 12.28 (1H, br. s, NH); 12.98 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.5 ($(CH_2)_2$); 14.6 (CH_3); 45.5 ($N(CH_2)_2$); 49.4 (CH_2); 111.4 (d, $^2J_{CF}$ = 22.3, C-5); 110.8 (d, $^2J_{CF}$ = 24.0, C-5'); 113.1 (d, $^3J_{CF}$ = 25.1, C-4a); 118.2 (m, C-8a); 122.3 (d, $^3J_{CF}$ = 3.5, C-8'); 127.1 (d, $^3J_{CF}$ = 7.8, C-4a'); 128.2 (C-3'); 129.8 (d, $^2J_{CF}$ = 18.1, C-7'); 135.6 (d, $^4J_{CF}$ = 1.5, C-8a'); 141.4 (dt, $^1J_{CF}$ = 252.6, $^2J_{CF}$ = 12.6, C-7); 145.4 (dd, $^1J_{CF}$ = 244.2, $^2J_{CF}$ = 13.9, C-8); 149.4 (C-2'); 149.5 (dd, $^1J_{CF}$ = 248.4, $^2J_{CF}$ = 12.6, C-6); 157.2 (d, $^1J_{CF}$ = 250.4, C-6'); 154.5 (C-2); 161.7 (CONH); 164.5 (C=O); 176.6 (d, $^4J_{CF}$ = 2.4, C-4'). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): –128.30 (1F, dd, $^3J_{FH}$ = 11.8, $^3J_{FH}$ = 7.4, F-6'); –132.75 ÷ –132.80 (1F, m, F-8); –135.17 (1F, dd, $^3J_{FF}$ = 21.5, $^4J_{FF}$ = 4.6, F-6); –151.62 ÷ –151.67 (1F, m, F-7). Mass spectrum, *m/z* (I_{rel} %): 533 $[M]^+$ (21), 288 (18), 287 (100), 260 (11), 259 (12). Found, %: C 54.13; H 3.52; N 13.21. $C_{24}H_{19}F_4N_5O_3S$. Calculated, %: C 54.03; H 3.59; N 13.13.

1-Ethyl-6-fluoro-4-oxo-7-(thiomorpholin-4-yl)-*N*'-(6,7,8-trifluoro-4-oxo-4*H*-benzo[*e*][1,3]thiazin-2-yl)-1,4-dihydroquinoline-3-carbohydrazide (7b). Yield 0.29 g (86%), light-yellow crystals, mp 309–311°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.2, CH_3); 2.94−2.97 (4H, m, $S(CH_2)_2$); 3.57−3.60 (4H, m, $N(CH_2)_2$); 4.55 (2H, q, *J* = 7.2, CH_2); 7.13−7.15 (1H, m, H-8'); 7.95 (1H, ddd, $^3J_{HF}$ = 9.9, $^4J_{HF}$ = 7.5, $^5J_{HF}$ = 2.1, H-5); 7.97−8.01 (1H, m, H-5'); 8.87 (1H, s, H-2'); 12.32 (1H, br. s, NH); 12.86 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.5 (CH_3); 26.4 ($S(CH_2)_2$); 45.5 ($N(CH_2)_2$); 49.3 (NCH_2); 110.6 (d, $^2J_{CF}$ = 23.8, C-5'); 111.3 (d, $^2J_{CF}$ = 22.6, C-5); 113.1 (d, $^3J_{CF}$ = 24.9, C-4a); 118.1–118.3 (m, C-8a); 122.2 (d, $^3J_{CF}$ = 3.5, C-8'); 127.1 (d, $^3J_{CF}$ = 7.8, C-4a'); 128.2 (C-3'); 129.8 (d, $^2J_{CF}$ = 18.1, C-7'); 135.6 (d, $^4J_{CF}$ = 1.5, C-8a'); 141.5 (dt, $^1J_{CF}$ = 252.6, $^2J_{CF}$ = 12.4, C-7); 145.3 (dd, $^1J_{CF}$ = 242.9, $^2J_{CF}$ = 12.7, C-8); 149.4 (C-2' and dd, $^1J_{CF}$ = 247.8, $^2J_{CF}$ = 12.3, C-6); 154.4 (C-2); 156.9 (d, $^1J_{CF}$ = 250.4, C-6'); 161.6 (CONH); 164.4 (C=O); 176.6 (d, $^4J_{CF}$ = 2.4, C-4'). ^{19}F NMR spectrum, δ, ppm: –123.36 (1F, s); –132.75 ÷ –132.80 (1F, m); –135.03 (1F, dd, $^3J_{FF}$ = 21.6, $^4J_{FF}$ = 4.6); –151.54 ÷ –151.59 (1F, m). Mass spectrum, *m/z* (I_{rel}, %): 565 $[M]^+$ (15), 507 (11), 336 (21), 334 (14), 333 (64), 320 (14), 319 (86), 293 (14), 292 (85), 287 (26), 286 (11), 262 (11), 261 (71), 260 (27), 259 (100), 258 (13), 245 (19), 244 (39), 243 (21), 233 (19), 232 (12), 231 (13), 219 (10), 218 (52), 217 (15), 216 (21), 203 (32), 190 (47), 188 (11), 175 (15), 174 (11), 162 (40), 161 (19), 160 (12), 148 (12), 147 (12), 146 (13), 134 (15), 133 (14), 132 (11), 130 (11), 120 (11), 107 (15), 93 (18), 87 (17), 75 (14), 74 (10), 46 (34), 44 (92), 38 (12), 36 (29). Found, %: C 50.89; H 3.40; N 12.43. $C_{24}H_{19}F_4N_5O_3S_2$. Calculated, %: C 50.97; H 3.39; N 12.38.

Antibacterial activity tests of compounds 4, **7a**,**b** were performed as previously reported.[4,8]

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