1,2,4-Triazino[5,6,1-*i*,*j*]quinolines: a new type of tricyclic analogs of fluoroquinolones

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The interaction of *C*-aryl-substituted amidrazones and *S*-methylisothiosemicarbazide with 3-ethoxy-2-polyfluorobenzoylacrylates results in corresponding *N*-(quinolin-1-yl)amidines that undergo conversion into derivatives of 1,2,4-triazino[5,6,1-*i*,*j*]quinoline by heating in acetic anhydride.

Key words: *C*-aryl-substituted amidrazones, *S*-methylisothiosemicarbazide, *N*-(quinolin-1-yl)amidines, 1,2,4-triazino[5,6,1-*i*,*j*]quinolines.

Recently, polycyclic derivatives of 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (the so-called "fluoroquinolones") have been the subject of increasing interest because they exhibit not only high antibacterial, but also antiviral, antitumor, and other types of activity.[1] Previously,[2,3] we have reported the synthesis of 1,3,4-thia(oxa)diazino[6,5,4-*i*,*j*]quinolones from derivatives of 2-polyfluorobenzoylacrylic acid and (thio)semicarbazides. This work concerns the annelation of the 1,2,4-triazine ring to the quinolone skeleton.

For this purpose, we studied the interaction of 3-ethoxy-2-polyfluorobenzoylacrylates (**1a**,**b**) with *C*-aryl-substituted amidrazones **2a—c** (Scheme 1). The reactions of benzamidrazone (**2a**) and *p*-nitrobenzamidrazone (**2c**) with acrylates **1a**,**b** in ethanol at room temperature resulted in the corresponding *N*-substituted benzamidrazones **3a**,**b**,**d**. The interaction of **1a** with *p*-methoxybenzamidrazone **2b** under the same conditions gave a mixture of acrylate **3c** with compound **4c** (a product of spontaneous cyclization of **3c**) in a 1 : 2 ratio (according to ^{1}H NMR data). To complete the cyclization of **3c** into **4c** and to convert acrylates **3a—d** into *N*-(quinolin-1-yl)carbamidines **4a—d** (in 82 to 89% yields), heating in toluene under reflux for 2 to 3 h is required.

Compound **4e** was synthesized by the reaction of *S*-methylisothiosemicarbazide (**2d**) with 3-ethoxy-2-tetrafluorobenzoylacrylate (**1a**) in toluene without isolation of intermediate acrylate **3e**. The structures of quinolones **4a—e** were confirmed by ^{1}H and ^{19}F NMR spectroscopy and by mass spectra (see Tables 1 and 2). In addition to the signal of the α-proton, H(2), of the pyridine ring (a singlet in the region δ 8.1—8.4) the ^{1}H NMR spectra of compounds **4a—e** exhibit a broadened singlet from two NH groups in the region δ 7.5—7.9. A characteristic signal of the H(5) proton (eight lines with a ddd pattern) in the interval δ 7.9—8.1 is also observed in the ^{1}H NMR spectra of derivatives **4a**,**c—e** (Table 1).

We failed to perform cyclization of compounds **4a—e** into their tricyclic analogs **5a—e** by refluxing in toluene (in the presence of potassium carbonate) or in acetonitrile (in the presence of KF or DBU), *i.e.*, under the conditions we used previously for the synthesis of polycyclic fluoroquinolones.[2—5] However, heating of compounds **4a**,**b**,**d**,**e** in acetic anhydride was found to be a useful procedure for the synthesis of tricyclic quinolones **5a**,**b**,**d**,**e**. Treatment of compound **4c** in the same manner leads to its transformation into *N*,*N*-diacetyl derivative of aminoquinolone **8** accompanied by destruction of the amidrazone fragment.

The structure of fused 1,2,4-triazino[5,6,1-*i*,*j*]quinolines **5a**,**b**,**d**,**e** was confirmed by ^{1}H and ^{19}F NMR spectroscopy data and by mass spectra (see Tables 3 and 4). The ^{1}H NMR spectra exhibit a signal of only one NH group in the region δ 10.4—11.0. The multiplicity of the signal of H(8) proton in the ^{1}H NMR spectra of derivatives **5a**,**d**,**e** (X = H) is reduced to a dd pattern observed in the region δ 7.2—7.3 (Table 3). The ^{19}F NMR spectra of compounds **5a**,**d**,**e** exhibit characteristic dd patterns for F(9) and F(10) in the regions δ 136.0—137.0 and 152.0—153.5, respectively (Table 4).

The possibility of the synthesis of close structural analogs of the known fluoroquinolone antibacterial agents[6—8] can be illustrated taking acid hydrolysis of the ester group of compound **5a** and replacement of the F(10) atom in carboxylic acid **6a** by the pyrrolidine residue (compound **7a**) as examples. The structures of derivatives **6a** and **7a** were confirmed by spectral data (see Tables 3 and 4).

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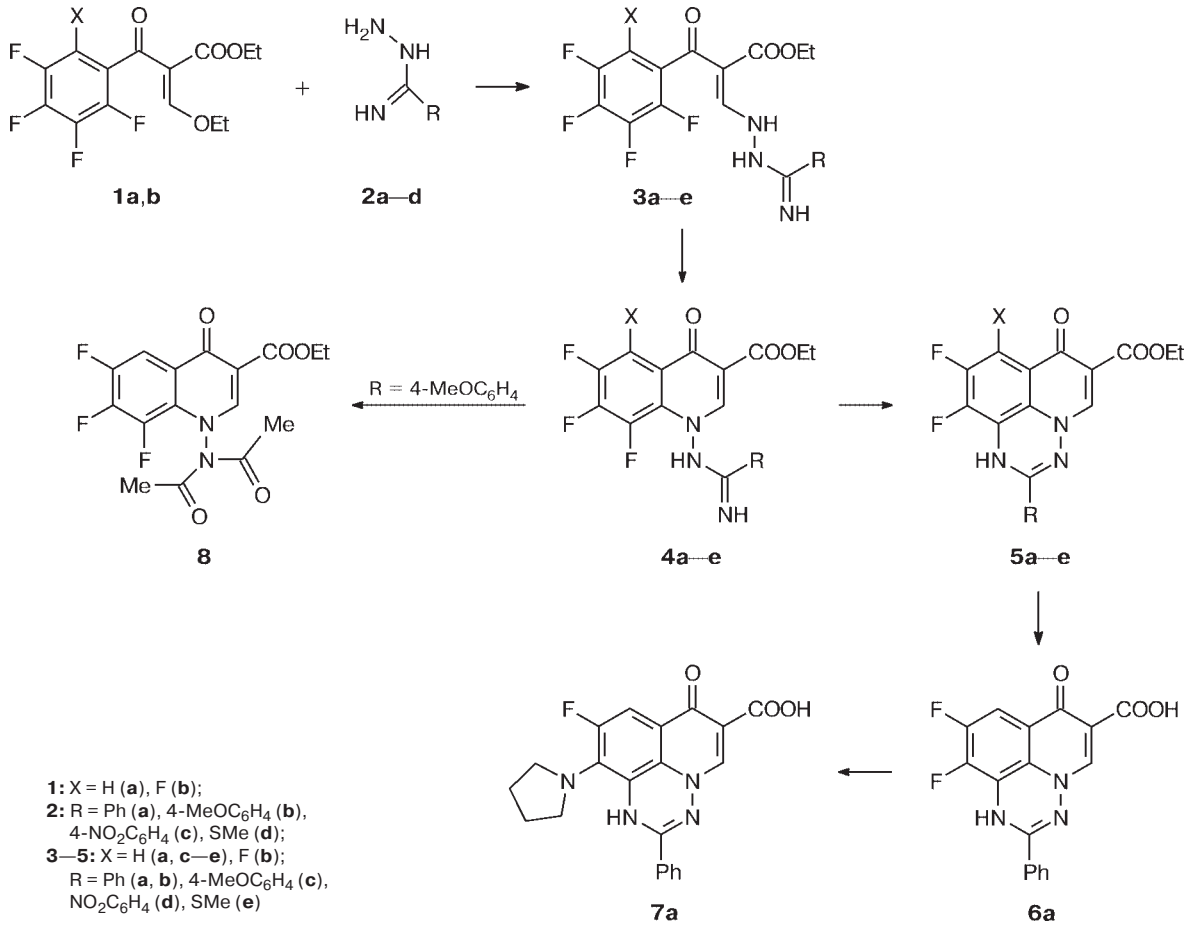
Scheme 1



Thus, we have first synthesized new fluorinated derivatives of 1,2,4-triazino[5,6,1-*i*,*j*]quinoline, that is, compounds **5**—**7**, which represent a novel class of fused fluoroquinolones.

Experimental

NMR Spectra were recorded on a Bruker WM-250 spectrometer (250 MHz for ^{1}H) and on a Bruker DRX-400 spec-

Table 1. ^{1}H NMR spectral parameters of compounds **4a**—**e** (DMSO-d_6)

Compound	δ, *J*/Hz					
	H(2) (s)	H(5) (ddd)	R	NH (br.s, 2 H)	Me (t)	OCH_2 (q)
4a	8.18	8.02 (^3J = 10.3, ^4J = 8.3, ^5J = 1.5)	7.51 (m, 3 H, H(3′), H(4′), H(5′)); 7.92 (m, 2 H, H(2′), H(6′))	7.5	1.32	4.23
4b	8.17	—	7.54 (m, 3 H, H(3′), H(4′), H(5′)); 7.89 (m, 2 H, H(2′), H(6′))	7.7	1.27	4.21
4c	8.23	8.01 (^3J = 10.8, ^4J = 8.1, ^5J = 1.5)	3.84 (s, 3 H, OMe); 7.06 (d, 2 H, H(3′), H(5′), ^3J = 8.9); 7.89 (d, 2 H, H(2′), H(6′), ^3J = 8.9)	7.5	1.27	4.22
4d	8.34	8.01 (^3J = 10.6, ^4J = 8.1, ^5J = 1.5)	8.16 (d, 2 H, H(2′), H(6′), ^3J = 8.8); 8.38 (d, 2 H, H(3′), H(5′), ^3J = 8.8)	7.9	1.28	4.23
4e	8.13	7.92 (^3J = 10.5, ^4J = 8.4, ^5J = 1.5)	2.47 (s, 3 H, SMe)	7.6	1.28	4.21

Table 2. ^{19}F NMR spectral parameters (DMSO-d_6) and mass spectra of compounds **4a**—**e**

Compound	δ_F, J/Hz				Mass spectrum, m/z (I_{rel} (%))
	F(5)	F(6) (ddd)	F(7)	F(8)	
4a	—	138.55 ($^3J_{F,F}$ = 22.8, $^3J_{F,H}$ = 10.3, $^4J_{F,F}$ = 3.8)	154.04 (ddd, $^3J_{F,F}$ = 18.5, $^3J_{F,F}$ = 22.8, $^4J_{F,H}$ = 8.3)	145.65 (dd, $^3J_{F,F}$ = 18.5, $^4J_{F,F}$ = 3.8)	389 $[M]^+$ (36), 369 (24), 341 (38), 317 (78), 297 (100), 199 (36), 119 (42), 104 (30), 77 (65)
4b	153.25 (dd, $^3J_{F,F}$ = 21.6, $^4J_{F,F}$ = 13.5)	151.22 ($^3J_{F,F}$ = 22.2, $^3J_{F,F}$ = 21.6, $^4J_{F,F}$ = 15.7)	163.05 (dd, $^3J_{F,F}$ = 22.2, $^3J_{F,F}$ = 21.6)	144.74 (ddd, $^3J_{F,F}$ = 21.0, $^4J_{F,F}$ = 13.5, $^5J_{F,F}$ = 6.9)	409 $[M]^+$ (47), 387 (9), 359 (14), 335 (79), 334 (44), 320 (69), 77 (100)
4c	—	138.22 ($^3J_{F,F}$ = 23.5, $^3J_{F,H}$ = 10.9, $^4J_{F,F}$ = 3.9)	153.74 (ddd, $^3J_{F,F}$ = 19.3, $^3J_{F,F}$ = 23.5, $^4J_{F,H}$ = 8.1)	145.82 (dd, $^3J_{F,F}$ = 19.3, $^4J_{F,F}$ = 3.9)	419 $[M]^+$ (49), 347(16), 226(14), 199(17), 150(16), 149(100), 134(34), 133(28), 92(18), 77(29)
4d	—	137.96 ($^3J_{F,F}$ = 23.3, $^3J_{F,H}$ = 10.6, $^4J_{F,F}$ = 3.5)	153.37 (ddd, $^3J_{F,F}$ = 23.2, $^3J_{F,F}$ = 19.1, $^4J_{F,H}$ = 8.1)	146.41 (dd, $^3J_{F,F}$ = 19.1, $^4J_{F,F}$ = 3.5)	
4e	—	138.05 ($^3J_{F,F}$ = 23.4, $^3J_{F,H}$ = 10.5, $^4J_{F,F}$ = 3.8)	153.47 (ddd, $^3J_{F,F}$ = 19.5, $^3J_{F,F}$ = 23.4, $^4J_{F,H}$ = 8.4)	146.14 (dd, $^3J_{F,F}$ = 19.5, $^4J_{F,F}$ = 3.8)	359 $[M]^+$ (49), 287(34), 271(14), 199(62), 169(16), 89(99), 88(36)

Table 3. ^{1}H NMR spectral parameters of compounds **5a**,**b**,**d**,**e**, **6a**, and **7a** (DMSO-d_6)

Compound	δ, J/Hz						
	H(5) (s)	H(8)	R	R(10)	NH (br.s, 1 H)	COOEt	COOH (br.s)
5a	8.28	7.25 (dd, ^3J = 10.7, ^4J = 7.5)	7.59 (m, 3 H, H(3′), H(4′), H(5′)), 7.83 (m, 2 H, H(2′), H(6′))	—	10.6	1.26 (t, 3 H, Me), 4.18 (q, 2 H, OCH_2)	—
5b	8.22		7.52 (m, 3 H, H(3′), H(4′), H(5′)), 7.83 (m, 2 H, H(2′), H(6′))	—	10.4	1.26 (t, 3 H, Me), 4.18 (q, 2 H, OCH_2)	—
5d	8.30	7.26 (dd, ^3J = 10.7, ^4J = 8.1)	8.09 (d, 2 H, H(2′), H(6′), ^3J = 8.8), 8.35 (d, 2 H, H(3′), H(5′), ^3J = 8.8)	—	10.4	1.27 (t, 3 H, Me), 4.18 (q, 2 H, OCH_2)	—
5e	8.22	7.23 (dd, ^3J = 11.0, ^4J = 8.2)	2.4 (s, 3 H, SMe)	—	11.0	1.26 (t, 3 H, Me), 4.19 (q, 2 H, OCH_2)	—
6a	8.45	7.43 (dd, ^3J = 10.7, ^4J = 7.6)	7.58 (m, 3 H, H(3′), H(4′), H(5′)), 7.89 (m, 2 H, H(2′), H(6′))	—	11.1	—	14.9
7a	8.15	6.46 (d, ^3J = 10.5)	7.54 (m, 3 H, H(3′), H(4′), H(5′)), 7.89 (m, 2 H, H(2′), H(6′))	1.92 (m, 4 H, $(CH_2)_2$)	10.6	—	15.8

trometer (376 MHz for ^{19}F). The internal standards were tetramethylsilane (for ^{1}H) and hexafluorobenzene (for ^{19}F). Mass spectra were obtained on a Varian MAT 311A instrument equipped with a direct inlet system at an accelerating voltage of 3 kV, a cathode emission current of 300 μA, and an ionizing electron energy of 70 eV.

The starting benzamidrazones were synthesized from corresponding imidate hydrochlorides following the known procedure.[9]

Ethyl 3-(4-R-benzimidoylhydrazino)-2-(polyfluorobenzoyl)acrylates (3a,b,d). To 1 g (5.6 mmol) of *p*-nitrobenzamidrazone **2c** in ethanol (15 mL), 3-ethoxy-2-tetrafluoro-

Table 4. ^{19}F NMR spectral parameters (DMSO-d_6) and mass spectra of compounds **5a**,**d**,**e**, **6a**, and **7a**

Compound	δ_F, J/Hz		Mass spectrum, m/z (I_{rel} (%))
	F(9)	F(10) (dd)	
5a	136.38 (dd, $^3J_{F,F}$ = 21.8, $^3J_{H,F}$ = 10.9)	152.12 ($^3J_{F,F}$ = 21.8, $^4J_{F,H}$ = 6.6)	369 $[M]^+$ (43), 324(19), 298(20), 297(100)
5d	136.12 (dd, $^3J_{F,F}$ = 22.0, $^3J_{F,H}$ = 10.9)	152.02 ($^3J_{F,F}$ = 22.0, $^4J_{F,H}$ = 7.5)	414 $[M]^+$ (94), 369(33), 367(78), 343(19), 342(100), 323(13), 322(11), 296(42), 295(13), 284(33), 266(18), 238(21), 136(21)
5e	136.57 (dd, $^3J_{F,F}$ = 22.1, $^3J_{F,H}$ = 11.0)	153.43 ($^3J_{F,F}$ = 22.1, $^4J_{F,H}$ = 7.8)	
6a	133.85 (dd, $^3J_{F,F}$ = 21.7, $^3J_{H,F}$ = 10.7)	150.15 ($^3J_{F,F}$ = 21.7, $^4J_{F,H}$ = 6.5)	341 $[M]^+$ (37), 298(20), 297(100), 296(27), 104(15), 77(17), 53(14)
7a	140.92 (d, $^3J_{H,F}$ = 10.5)		392 $[M]^+$ (100), 348(60), 279(17), 245(45), 196(14)

benzoylacrylate **1a** (1.8 g, 5.6 mmol) was added. The reaction mass was stirred for 2 h at room temperature, the bright yellow precipitate of compound **3d** was filtered off and recrystallized from ethanol. The yield was 2.1 g (84%), m.p. 158—160 °C. ^1H NMR (DMSO-d_6, δ, J/Hz): 1.14 (t, 3 H, $OCH_2C\underline{H}_3$); 4.03 (q, 2 H, $OC\underline{H}_2CH_3$); 7.15 (m, 1 H, H(6″)); 7.35 (br.s, 2 H, NH); 8.14 (d, 2 H, H(2′), H(6′), J = 8.8); 8.26 (d, 2 H, H(3′), H(5′), J = 8.8); 8.39 (s, 1 H, H(3)); 12.8 (br.s, 1 H, NH). Found (%): C, 50.53; H, 3.08; N, 12.40. $C_{19}H_{14}F_4N_4O_5$. Calculated (%): C, 50.22; H, 3.08; N, 12.33.

Compounds **3a**,**b** were synthesized analogously.

Compound **3a**, yield 63%, m.p. 138—140 °C. ^1H NMR (DMSO-d_6, δ): 1.13 (t, 3 H, $OCH_2C\underline{H}_3$); 4.01 (q, 2 H, $OC\underline{H}_2CH_3$); 7.01 (m, 1 H, H(6″)); 7.12 (br.s, 2 H, NH); 7.43 (m, 3 H, H(3′), H(4′), H(5′)); 7.86 (m, 2 H, H(2′), H(6′)); 8.37 (s, 1 H, H(3)); 12.9 (br.s, 1 H, NH). Found (%): C, 55.40; H, 3.57; N, 10.17. $C_{19}H_{15}F_4N_3O_3$. Calculated (%): C, 55.75; H, 3.69; N, 10.27.

Compound **3b**, yield 65%, m.p. 104—106 °C. ^1H NMR (DMSO-d_6, δ, J/Hz): 1.15 (t, 3 H, $OCH_2C\underline{H}_3$); 4.03 (q, 2 H, $OC\underline{H}_2CH_3$); 7.16 (br.s, 2 H, NH); 7.44 (m, 3 H, H(3′), H(4′), H(5′)); 7.87 (m, 2 H, H(2′), H(6′)); 8.37 (d, 1 H, H(3), J = 11.6); 13.0 (br.d, 1 H, NH, J = 11.6). Found (%): C, 53.68; H, 3.26; N, 9.62. $C_{19}H_{14}F_5N_3O_3$. Calculated (%): C, 53.40; H, 3.30; N, 9.83.

5-X-1-(4-*R*-Benzimidoylamino)-3-ethoxycarbonyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinolines (4a—e). *A.* A solution of acrylate **3a** (0.4 g, 0.98 mmol) in anhydrous toluene (10 mL) was refluxed for 2 h. After cooling the reaction mass, the colorless precipitate of compound **4a** was filtered off and recrystallized from DMSO. The yield was 0.32 g (89%), m.p. 252—254 °C. Found (%): C, 61.75; H, 3.56; N, 11.57. $C_{19}H_{14}F_3N_3O_3$. Calculated (%): C, 61.79; H, 3.55; N, 11.38.

Compounds **4b**,**d** were synthesized analogously

Compound **4b**, yield 82%, m.p. 238—240 °C. Found (%): C, 55.96; H, 3.07; N, 10.03. $C_{19}H_{13}F_4N_3O_3$. Calculated (%): C, 56.03; H, 3.22; N, 10.32.

Compound **4d**, yield 89%, m.p. 226—228 °C. Found (%): C, 52.69; H, 3.45; N, 12.60. $C_{19}H_{13}F_3N_4O_5$. Calculated (%): C, 52.53; H, 3.00; N, 12.90.

B. To *p*-methoxybenzamidrazone **2b** (1 g, 6.1 mmol) in ethanol (15 mL), 3-ethoxyacrylate **1a** (1.9 g, 6.1 mmol) was added. The reaction mass was stirred for 3 h at ~20 °C. The precipitate was filtered off, anhydrous toluene (15 mL) was added, and the mixture was refluxed for 4 h. After cooling the solution, the colorless precipitate of compound **4c** was filtered off and recrystallized from DMSO. The yield was 2.0 g (79%), m.p. 220—222 °C. Found (%): C, 57.06; H, 4.40; N, 9.60. $C_{20}H_{16}F_3N_3O_4$. Calculated (%): C, 57.23; H, 3.82; N, 10.02.

C. To *S*-methylisothiosemicarbazide hydroiodide, **2d**·HI, (0.85 g, 3.6 mmol) in anhydrous toluene (15 mL), pyridine (0.6 mL, 7.2 mmol) and 3-ethoxyacrylate **1a** (1.2 g, 3.6 mmol) was added. The reaction mass was kept for 30 min at ~20 °C and then refluxed for 3 h. After cooling, the colorless precipitate of compound **4e** was filtered off, washed with ethanol, and recrystallized from DMSO. The yield was 0.95 g (73%), m.p. 239—241 °C. Found (%): C, 46.86; H, 3.31; N, 11.59. $C_{14}H_{12}F_3N_3O_3S$. Calculated (%): C, 46.75; H, 3.34; N, 11.69.

Ethyl 2-R-8-X-9,10-difluoro-7-oxo-1,7-dihydro-1,2,4-triazino[5,6,1-*i*,*j*]quinoline-6-carboxylates (5a,b,d,e). A solution of compound **4a** (0.3 g, 0.8 mmol) in acetic anhydride (6 mL) was refluxed for 2 h. After cooling, the light-yellow precipitate of compound **5a** was filtered off and recrystallized from DMSO. The yield was 0.2 g (68%), m.p. >250 °C. Found (%): C, 61.79; H, 3.51; N, 11.34. $C_{19}H_{13}F_2N_3O_3$. Calculated (%): C, 61.79; H, 3.55; N, 11.38.

Compounds **5b**,**d** were synthesized analogously. To obtain the tricyclic derivative **5e**, a solution of quinolone **4e** in acetic anhydride was kept at 110 °C for 10 h.

Compound **5b**, yield 62%, m.p. 223—225 °C. Found (%): C, 59.23; H, 3.32; N, 10.61. $C_{19}H_{12}F_3N_3O_3$. Calculated (%): C, 58.91; H, 3.10; N, 10.88.

Compound **5d**, yield 81%, m.p. >250 °C. Found (%): C, 54.92; H, 2.76; N, 13.21. $C_{19}H_{12}F_2N_4O_5$. Calculated (%): C, 55.04; H, 2.90; N, 13.52.

Compound **5e**, yield 76%, m.p. 245—247 °C. Found (%): C, 49.15; H, 3.47; N, 11.96. $C_{14}H_{11}F_2N_3O_3S$. Calculated (%): C, 49.56; H, 3.24; N, 12.39.

9,10-Difluoro-7-oxo-2-phenyl-1,7-dihydro-1,2,4-triazino[5,6,1-*i*,*j*]quinoline-6-carboxylic acid (6a). A solution of ester **5a** (0.5 g, 1.4 mmol) in 15 mL of HCl—AcOH (1 : 4) mixture was refluxed for 3 h. After cooling, water (25 mL) was added to the reaction mass and the precipitate was filtered off and recrystallized from DMSO. The yield was 0.35 g (76%), m.p. >250 °C. Found (%): C, 59.82; H, 2.70; N, 12.17. $C_{17}H_9F_2N_3O_3$. Calculated (%): C, 59.82; H, 2.64; N, 12.32.

9-Fluoro-7-oxo-2-phenyl-10-(pyrrolidin-1-yl)-1,7-dihydro-1,2,4-triazino[5,6,1-*i*,*j*]quinoline-6-carboxylic acid (7a). To compound **6a** (0.2 g, 0.6 mmol) in anhydrous pyridine (5 mL), pyrrolidine (0.3 g, 4.2 mmol) was added, and the reaction mass was refluxed for 6 h. After cooling, the precipitate was filtered off, 2 *M* HCl (1.5 mL) and ethanol (1.5 mL) was added, and the mixture was stirred for 2 h at ~20 °C. The precipitate of compound **7a** was filtered off and recrystallized from DMSO. The yield was 0.15 g (64%), m.p. >250 °C. Found (%): C, 64.02; H, 4.25; N, 13.98. $C_{21}H_{17}FN_4O_3$. Calculated (%): C, 64.28; H, 4.37; N, 14.28.

Ethyl 1-(*N*,*N*-diacetylamino)-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (8). A solution of compound **4c** (1.2 g, 2.9 mmol) in acetic anhydride (15 mL) was refluxed for 2.5 h. The reaction mass was cooled and concentrated, and ethanol (10 mL) was added to the residue. The colorless precipitate was filtered off and recrystallized from ethanol. The yield was 0.8 g (73%), m.p. 180—182 °C. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 1.30 (t, 3 H, $OCH_2C\underline{H}_3$); 2.43 (s, 6 H, 2 $COCH_3$); 4.26 (q, 2 H, $OC\underline{H}_2CH_3$); 8.04 (ddd, 1 H, H(5), J = 10.3, 8.2, 1.5); 8.92 (s, 1 H, H(2)). Mass spectrum (*m*/*z*, I_{rel} (%)): 370 $[M]^+$ (5), 328 (69), 313 (10), 283 (13), 282 (19), 267 (20), 263 (11), 257 (13), 256 (100), 225 (15), 214 (17). Found (%): C, 51.41; H, 3.71; N, 7.46. $C_{16}H_{13}F_3N_2O_5$. Calculated (%): C, 51.85; H, 3.51; N, 7.56.

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