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SYNTHESIS OF NEW FLUORINATED DERIVATIVES OF QUINOLINECARBOXYLIC ACIDS

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Ethyl esters of 1-(7-Z-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbamoyl)-5-X-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids (X = H, F; Z = pyrrolidino-, piperidino-, hexamethylenimino-, morpholino-, thiomorpholino-) have been synthesized by the interaction of quinolone-3-carboxylic acid hydrazides with ethyl esters of 3-ethoxy-2-(polyfluorobenzoyl)acrylic acid . It was shown possible to cyclize intramolecularly the esters obtained with the formation of 1,3,4-oxadiazino[6,5,4-i,j]quinoline derivatives.

Keywords: quinolone-3-carboxylic acid hydrazides, 1,3,4-oxadiazino[6,5,4-*i,j*]quinolines, reactivity, spectral characteristics.

In previous publications [1,2] we have reported the synthesis of 1,3,4-oxadiazino[6,5,4-*i,j*]quinoline derivatives by the cyclization of ethyl esters of 3-(2-acyl-1-hydrazino)-2-[tetra(penta)fluorobenzoyl]acrylic acid.

In the present communication the synthesis is described of new derivatives of this system, *viz*. compounds **1, 2**, containing a substituted quinolone residue in position 2 (see Scheme). The ethyl esters of 1-(7-Z-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbamoyl)-5-X-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **6a-e** and **7a-e** were obtained in 78-95% yield by heating the ethyl esters of 3-ethoxy-2-(polyfluorobenzoyl)acrylic acids **3** and **4** with the hydrazides of substituted quinolone-3-carboxylic acids **5a-e** in toluene (2-3 h). The initial hydrazides **5a-e** were synthesized in 67-94% yield from the corresponding ethyl esters of 7-Z-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acids and hydrazine hydrate. The ^{1}H NMR spectra of compounds 5 are given in Table 1.

The ^{1}H NMR spectra of esters **6** and **7**, containing two quinolone residues (Table 2), are characterized by the presence of singlet signals for the NH group proton at 13.0-13.2 and a singlet for 2-H at 8.4-8.5 ppm. A characteristic multiplet for the 5-H proton with a center at 7.9-8.0 ppm was observed in the spectra of compounds **6a-e**. The chemical shifts of the protons in positions 2', 5', and 8' for esters **6** and **7** were close to those for the initial hydrazides **5**. The ^{19}F NMR spectrum of compound **7a** contains five signals for fluorine atoms (see Experimental).

It might have been supposed that hydrolysis of compounds **6** and **7** would occur at both the ester and amide groups. However on boiling esters **6a** and **7b** in an acidic medium (HCl–CH_3COOH, 1:4) their amide groups were retained and the corresponding acids **8** and **9** were obtained, the structures of which were confirmed by data of ^{1}H NMR spectra (Table 3). In the case of compound **8** replacement occurred of the 7-F atom by a residue of cyclic amine (pyrrolidine, 4-methylpiperazine) and products **10a,b** were obtained (Table 3).

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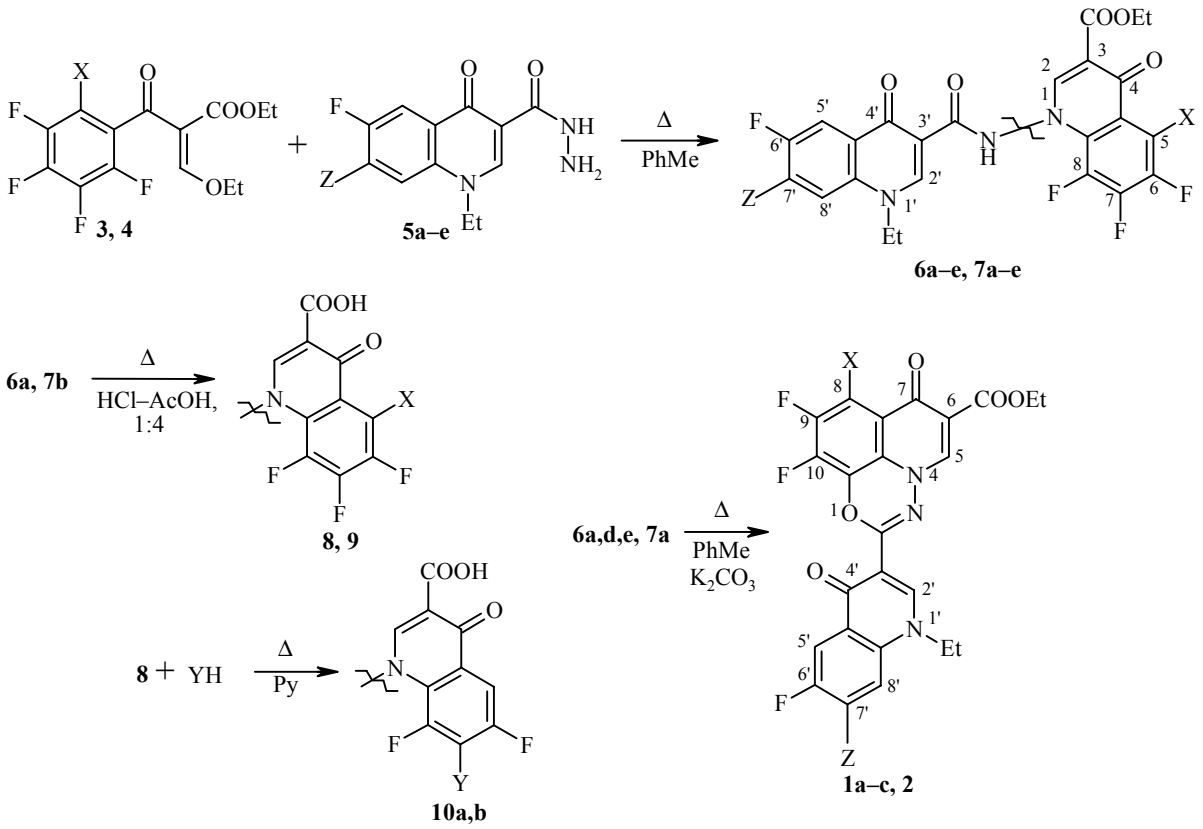

1a-c, 3, 6a-e, **8** X = H; **2**, **4, 7a-e, 9** X = F; **1a, 2, 5a-7a**, **8, 10a,b** Z = pyrrolidino-; **5b-7b, 9** Z = piperidino-; **5c–7c** Z = hexamethylenimino-; **1b, 5d-7d** Z = morpholino-; **1c**, **5e-7e** Z = thiomorpholino-; **10 a** Y = pyrrolidino-; **b** Y = 4-methylpiperazino-

TABLE 1. ^{1}H NMR Spectra of Hydrazides **5a-e**

Com-pound	Chemical shifts, δ, ppm, coupling constants (*J*), Hz							
	NH, br. s	2-H, s	5'-H	8'-H, d	NH_2, br. s	NCH_2, q, *J* = 7.2	$CH_2\underline{CH_3}$, t, *J* = 7.2	Z, m
5a	10.73	8.65	7.75, $^{3}J_{HF}$ = 14.8	6.57, $^{4}J_{HF}$ = 7.6	4.51	4.41	1.39	1.9-2.1 (4H, $2CH_2$), 3.4-3.6 (4H, $N(CH_2)_2$)
5b	10.66	8.74	7.84, $^{3}J_{HF}$ = 13.4	7.06, $^{4}J_{HF}$ = 7.3	4.54	4.49	1.39	1.6-1.7 (6H, $3CH_2$), 3.2-3.3 (4H, $N(CH_2)_2$)
5c	10.74	8.68	7.79, $^{3}J_{HF}$ = 15.3	6.79, $^{4}J_{HF}$ = 7.6	4.52	4.44	1.38	1.5-1.6 (4H, $2CH_2$), 1.8-1.9 (4H, $2CH_2$), 3.5-3.6 (4H, $N(CH_2)_2$)
5d	10.64	8.76	7.88, $^{3}J_{HF}$ = 13.7	7.09, $^{4}J_{HF}$ = 7.3	4.55	4.50	1.40	3.2-3.3 (4H, $N(CH_2)_2$), 3.7-3.8 (4H, $O(CH_2)_2$)
5e	10.64	8.75	7.87, $^{3}J_{HF}$ = 13.4	7.13, $^{4}J_{HF}$ = 7.3	4.54	4.50	1.39	2.7-2.8 (4H, $S(CH_2)_2$), 3.3-3.5 (4H, $N(CH_2)_2$)

TABLE 2. ^{1}H NMR Spectra of Hydrazides **5a-e**

Com-pound	Chemical shifts, δ, ppm, coupling constants (*J*), Hz										
	NH, s	2'-H, s	2-H, s	5-H	5'-H, d	8'-H, d	OCH_2, q	$CH_2\underline{CH_3}$, t	NCH_2, q	$CH_2\underline{CH_3}$, t	Z, m
6a	13.18	8.76	8.76	7.96, ddd, ^3J = 10.2, ^4J = 8.2, ^5J = 1.8	7.75, ^3J = 14.7	6.60, ^4J = 7.6	4.20, *J* = 7.0	1.26, *J* = 7.0	4.45, *J* = 7.0	1.41, *J* = 7.0	1.8-2.0 (4H, $2CH_2$), 3.5-3.7 (4H, $N(CH_2)_2$)
6b	13.16	8.85	8.85	7.97, m	7.86, ^3J = 13.4	7.09, ^4J = 7.0	4.22, *J* = 7.0	1.27, *J* = 7.0	4.52, *J* = 7.0	1.44, *J* = 7.0	1.6-1.7 (2H, CH_2), 1.7-1.8 (4H, $2CH_2$), 3.2-3.3 (4H, $N(CH_2)_2$)
6c	13.15	8.80	8.80	7.95, m	7.75, ^3J = 15.3	6.81, ^4J = 7.6	4.21, *J* = 7.0	1.26, *J* = 7.0	4.46, *J* = 7.0	1.41, *J* = 7.0	1.5-1.6 (4H, $2CH_2$), 1.8-1.9 (4H, $2CH_2$), 3.5-3.7 (4H, $N(CH_2)_2$)
6d	13.03	8.88	8.88	7.97, ddd, ^3J = 10.3, ^4J = 8.3, ^5J = 1.8	7.88, ^3J = 13.7	7.14, ^4J = 7.3	4.21, *J* = 7.0	1.26, *J* = 7.0	4.52, *J* = 7.0	1.43, *J* = 7.0	3.3-3.4 (4H, $N(CH_2)_2$), 3.8-3.9 (4H, $O(CH_2)_2$)
6e	13.03	8.88	8.50	7.97, m	7.86, ^3J = 13.4	7.17, ^4J = 7.3	4.21, *J* = 7.0	1.26, *J* = 7.0	4.53, *J* = 7.0		2.7-2.9 (4H, $S(CH_2)_2$), 3.5-3.7 (4H, $N(CH_2)_2$)
7a	13.12	8.76	8.41	—	7.75, ^3J = 14.2	6.61, ^4J = 7.7	4.20, *J* = 7.0	1.26, *J* = 7.0	4.45, *J* = 7.0	1.41, *J* = 7.0	1.8-2.0 (4H, $2CH_2$), 3.5-3.6 (4H, $N(CH_2)_2$)
7b	13.00	8.85	8.41	—	7.85, ^3J = 13.6	7.10, ^4J = 7.3	4.21, *J* = 7.3	1.26, *J* = 7.3	4.52, *J* = 7.1	1.42, *J* = 7.1	1.6-1.7 (2H, CH_2), 1.7-1.8 (4H, $2CH_2$), 3.2-3.3 (4H, $N(CH_2)_2$)
7c	13.09	8.79	8.40	—	7.77, ^3J = 15.2	6.82, ^4J = 7.5	4.21, *J* = 7.0	1.26, *J* = 7.0	4.48, *J* = 7.0	1.41, *J* = 7.0	1.5-1.6 (4H, $2CH_2$), 1.8-1.9 (4H, $2CH_2$), 3.5-3.7 (4H, $N(CH_2)_2$)
7d	12.97	8.87	8.42	—	7.90, ^3J = 14.6	7.14, ^4J = 7.6	4.21, *J* = 7.1	1.26, *J* = 7.1	4.52, *J* = 7.0	1.43, *J* = 7.0	3.2-3.4 (4H, $N(CH_2)_2$), 3.8-3.9 (4H, $O(CH_2)_2$)
7e	12.98	8.87	8.41	—	7.86, ^3J = 13.4	7.18, ^4J = 7.1	4.20, *J*= 7.1	1.26, *J* = 7.1	4.53, *J* = 7.0	1.43, *J* = 7.0	2.7-2.9 (4H, $S(CH_2)_2$), 3.5-3.6 (4H, $N(CH_2)_2$)

TABLE 3. ^{1}H NMR Spectra of Quinolonecarboxylic Acids **8**, **9**, and **10a,b**

Compound	Chemical shifts, δ, ppm, coupling constants (*J*), Hz										
	COOH, s	NH, s	2'-H, s	2-H, s	5-H	5'-H, d	8'-H, d	Y	NCH_2, q	$CH_2\underline{CH_3}$, t	Z, m
8	13.93	13.41	8.80	8.77	8.12, m	7.71, ^3J = 14.7	6.60, ^4J = 7.6	—	4.46, J = 7.0	1.41, J = 7.0	1.99 (4H, $2CH_2$), 3.57 (4H, $N(CH_2)_2$)
9	13.82	13.23	8.86	8.76	—	7.82, ^3J = 13.4	7.10, ^4J = 7.3	—	4.53, J = 7.0	1.42, J = 7.0	1.65 (2H, CH_2), 1.71 (4H, $2CH_2$), 3.24 (4H, $N(CH_2)_2$)
10a	13.74	13.25	8.73	8.37	7.65, dd, ^3J = 14.0; ^5J = 1.5	7.69, ^3J = 14.2	6.57, ^4J = 7.5	1.85 (4H, m, $2CH_2$), 3.59 (4H, m, $N(CH_2)_2$)	4.43, J = 7.0	1.44, J = 7.0	2.03 (4H, $2CH_2$), 3.59 (4H, $N(CH_2)_2$)
10b	13.65	13.12	8.65	8.34	8.00, dd, ^3J = 13.7; ^5J = 1.4	7.42, ^3J = 12.2	6.84, ^4J = 7.3	2.36 (3H, s, NCH_3), 2.64 (4H, m, $N(CH_2)_2$), 3.75 (4H, m, $N(CH_2)_2$)	4.80, J = 6.7	1.53, J = 6.7	2.07 (4H, $2CH_2$), 3.35 (4H, $N(CH_2)_2$)

TABLE 4. ^{1}H NMR Spectra and Mass Spectra of the Tricyclic Condensed Esters **1a-c** and **2**

Compound	Chemical shifts, δ, ppm, coupling constants (*J*), Hz										*m/z* (*I*, %)
	5-H, s	2'-H, s	8-H	5'-H, d	8'-H, d	NCH_2, q	$CH_2\underline{CH_3}$, t	OCH_2, q	$CH_2\underline{CH_3}$, t	Z, m	
1a	8.16	8.30	7.44, m	7.55, ^3J = 11.6	6.46, ^4J = 7.2	4.46, J = 7.1	1.58, J = 7.1	4.24, J = 7.1	1.32, J = 7.1	1.9-2.1 (4H, $2CH_2$), 3.4-3.6 (4H, $N(CH_2)_2$)	M^+ 552 (85), 507 (9), 480 (49), 284 (100), 240 (34), 223(19), 201 (14)
1b	8.38	8.53	7.56, dd, ^3J = 10.5; ^4J = 7.4	7.80, ^3J = 13.4	7.05, ^4J = 7.0	4.43, J = 7.0	1.44, J = 7.0	4.24, J = 7.0	1.30, J = 7.0	3.2-3.3 (4H, $N(CH_2)_2$), 3.8-3.9 (4H, $O(CH_2)_2$)	M^+ 568 (31), 523 (5), 496 (37), 301 (27), 243 (100)
1c	8.37	8.53	7.57, m	7.78, ^3J = 13.4	7.08, ^4J = 7.0	4.42, J = 6.9	1.44, J = 6.9	4.24, J = 7.0	1.30, J = 7.0	2.7-2.9 (4H, $S(CH_2)_2$), 3.5-3.7 (4H, $N(CH_2)_2$)	M^+ 584 (31), 539 (4), 512 (33), 438 (11), 317 (16), 243 (100)
2	8.22	8.38	—	7.62, ^3J = 12.3	6.44, ^4J = 7.1	4.33, J = 6.8	1.42, J = 6.8	4.21, J = 7.0	1.29, J = 7.0	1.9-2.0 (4H, $2CH_2$), 3.4-3.6 (4H, $N(CH_2)_2$)	M^+ 570 (28), 525 (3), 498 (20), 285 (100)

On boiling amides **6a,d,e** and **7a** in toluene in the presence of K_2CO_3 (3-4 h) an intramolecular cyclization occurs with the participation of the amide group oxygen atom, leading to the formation of an oxadiazine ring (yields of the corresponding products were 75-94%). The obtained ethyl esters of 2-(7-Z-1-ethyl-6-fluoro-4-oxo-3-quinolinyl)-8-X-9,10-difluoro-7-oxo-7H-1,3,4-oxadiazino[6,5,4-*ij*]quinoline-6-carboxylic acids **1a-c** and **2** may be considered as a new type of substituted tricyclic fluoroquinolone containing a second quinolone fragment.

The data of the ^{1}H NMR spectra of compounds **1** and **2** (Table 4) indicate the closing of the oxadiazine ring. The signal for the NH group proton is absent, the signals of the protons in positions 5 and 2' are displaced towards high field by 0.3-0.4 ppm, and the signal of the 8-H proton is displayed as a doublet of doublets (^3J = 10.5, ^4J = 7.4 Hz), in difference to the initial esters **6** and **7** in which this signal has the shape of a doublet of doublets of doublets.

TABLE 5. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{28}H_{23}F_3N_4O_5 \cdot H_2O$	59.34 / 58.95	4.42 / 4.42	9.80 / 9.82	>250	94
1b	$C_{28}H_{23}F_3N_4O_6 \cdot H_2O$	57.70 / 57.34	4.30 / 4.30	9.38 / 9.55	>250	80
1c	$C_{28}H_{23}F_3N_4O_5S \cdot H_2O$	55.17 / 55.81	4.15 / 4.18	8.78 / 9.30	>250	75
2	$C_{28}H_{22}F_4N_4O_5 \cdot H_2O$	56.46 / 57.15	3.89 / 4.11	10.02 / 9.52	>250	82
5a	$C_{16}H_{19}FN_4O_2$	60.15 / 60.37	6.07 / 6.02	17.64 / 17.60	259-261	91
5b	$C_{17}H_{21}FN_4O_2$	61.33 / 61.43	6.27 / 6.37	17.03 / 16.86	255-257	94
5c	$C_{18}H_{23}FN_4O_2$	62.29 / 62.41	6.57 / 6.69	16.00 / 16.17	226-228	73
5d	$C_{16}H_{19}FN_4O_3$	57.42 / 57.48	5.74 / 5.73	16.68 / 16.76	250-252	69
5e	$C_{16}H_{19}FN_4O_2S$	54.78 / 54.84	5.45 / 5.47	16.33 / 15.99	246-248	67
6a	$C_{28}H_{24}F_4N_4O_5$	58.31 / 58.74	4.53 / 4.23	10.06 / 9.79	178-180	78
6b	$C_{29}H_{26}F_4N_4O_5 \cdot H_2O$	57.30 / 57.62	4.73 / 4.67	9.34 / 9.27	179-182	89
6c	$C_{30}H_{28}F_4N_4O_5 \cdot H_2O$	58.18 / 58.25	4.93 / 4.89	9.16 / 9.06	>250	87
6d	$C_{28}H_{24}F_4N_4O_6 \cdot H_2O$	55.05 / 55.45	4.38 / 4.32	9.20 / 9.24	178-179	89
6e	$C_{28}H_{24}F_4N_4O_5S \cdot H_2O$	54.28 / 54.02	4.16 / 4.21	9.16 / 9.00	172-174	87
7a	$C_{28}H_{23}F_5N_4O_5$	57.46 / 56.95	3.76 / 3.93	9.26 / 9.49	197-200	95
7b	$C_{29}H_{25}F_5N_4O_5$	57.56 / 57.62	4.37 / 4.17	9.21 / 9.27	178-179	91
7c	$C_{30}H_{27}F_5N_4O_5 \cdot H_2O$	56.76 / 56.60	4.72 / 4.59	8.90 / 8.80	267-268	93
7d	$C_{28}H_{23}F_5N_4O_6 \cdot 2H_2O$	51.75 / 52.34	4.19 / 4.24	9.18 / 8.72	198-200	91
7e	$C_{28}H_{23}F_5N_4O_5S$	54.68 / 54.02	4.01 / 3.72	9.00 / 9.00	>250	89
8	$C_{26}H_{20}F_4N_4O_5 \cdot 0.5H_2O$	56.46 / 56.44	3.89 / 3.82	10.02 / 10.13	>250	83
9	$C_{27}H_{21}F_5N_4O_5 \cdot H_2O$	53.78 / 54.55	3.71 / 3.90	9.06 / 9.42	>250	70
10a	$C_{30}H_{28}F_3N_5O_5 \cdot H_2O$	59.18 / 58.72	4.79 / 4.93	11.36 / 11.41	>250	64
10b	$C_{31}H_{31}F_3N_6O_5 \cdot 2H_2O$	55.79 / 56.36	5.22 / 5.34	12.59 / 12.72	>250	78

The chemical shifts of the 5'-H and 8'-H protons and of the protons of the cyclic amine residue were changed insignificantly. The mass spectra of compounds **1** and **2** were characterized by the presence of intense peaks for the molecular ions. The presence of $[M-45]^+$ and $[M-72]^+$ peaks is caused by fission of ethoxy and carbethoxy groups. Further fragmentation occurs with breaking of the oxadiazine ring.

In conclusion, new derivatives of bi- and tricyclic fluoroquinolones have been obtained. Acids **8** are not only intermediates for the synthesis of new tricyclic fluoroquinolones but are of separate interest, since under defined conditions two reactive fluoroquinolone fragments may be released, which may possibly lead to a change in the spectrum of biological activity.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker WP-250 (250 MHz) instrument, solvent was DMSO-d_6, internal standard TMS. The ^{19}F NMR spectra were taken on a Bruker WP-80 (80 MHz) instrument, solvent was DMSO-d_6, internal standard hexafluorobenzene. The mass spectra were recorded on a Varian MAT 311A spectrometer. Plotting conditions: accelerating voltage 3 kV, cathode emission current 300 μA, energy of ionizing electrons 70 eV, samples were inserted directly into the ion source.

Hydrazides of 7-Z-1-Ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids (5a-e). A suspension of 7-Z-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-3-quinoline-carboxylic acid ethyl ester (6 mmol) and hydrazine hydrate (4.5 ml) in pyridine (10 ml) was maintained for 1 h at 80°C. The reaction mixture was cooled to room temperature, dissolved in distilled water (40 ml), and acetic acid added to pH 5-6. The precipitated solid was filtered off, washed with water, with ethanol, and with ether.

Ethyl Esters of 1-(7-Z-1-Ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbamoyl)-5-X-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids (6a-e, 7a-e). Ethyl ester **3** or **4** (0.95 mmol) was added to a suspension of hydrazide **5a-e** (0.94 mmol) in absolute toluene (8 ml). The reaction mixture was boiled for 2 h, then cooled. The precipitate of **6** or **7** was filtered off and recrystallized from acetonitrile. ^{19}F NMR spectrum of compound **7a**, δ, ppm: 161.41 (1F, m); 155.29 (1F, m); 149.80 (1F, m); 143.69 (1F, m); 128.31 (1F, m).

Ethyl Esters of 2-(7-Z-1-Ethyl-6-fluoro-4-oxo-1,4-dihydroquinolinyl)-8-X-9,10-difluoro-7-oxo-7H-1,3,4-oxadiazino[6,5,4-*i,j*]quinoline-6-carboxylic Acids (1a-c, 2). Calcined potassium carbonate (1.1 mmol) was added to a suspension of amide **6a,d,e** or **7a** (0.85 mmol) in absolute toluene (15 ml). The reaction mixture was boiled for 3-4 h and cooled. The solid product **1** or **2** was filtered off, washed with water, and recrystallized from DMSO.

1-(7-Z-1-Ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carbamoyl)-5-X-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids (8, 9). A solution of compound **6a** or **7b** (1 mmol) in a mixture (25 ml) of hydrochloric and acetic acids (1:4) was boiled for 3 h. The reaction mixture was cooled, diluted with water, the solid product **8** or **9** was filtered off, and recrystallized from DMSO.

1-(1-Ethyl-6-fluoro-4-oxo-7-pyrrolidino-1,4-dihydroquinoline-3-carbamoyl)-7-Y-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids (10a,b). Pyrrolidine or 4-methylpiperazine (6 mmol) was added to a solution of acid **8** (0.55 g, 1.05 mmol) in pyridine (6 ml). The reaction mixture was boiled for 4 h, then cooled. The solid product **10a** or **10b** was filtered off, and recrystallized from DMSO.

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