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Fluoro-containing Heterocycles: VI.* New Derivatives of 1,3,4-Thiadiazino[6,5,4-i,j]quinoline**

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Abstract—A series of new tricyclic fluoroquinolones was prepared by replacing fluorine atoms in derivatives of 2-R-8-Y-7-oxo-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-i,j]quinoline-6-carboxylic acids. In acids and esters containing a hydrogen atom in position 8 occurred replacement of F^{10} by amine rests, and in compounds with a fluorine in position 8 was substituted either F^8 or F^{10} and F^8 depending on the amine character.

We formerly described a synthesis of ethyl 2-R-8-Y-7-oxo-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-i,j]-quinoline-6-carboxylates [2]. These compounds may be regarded as key intermediates for preparation of new derivatives of tricyclic fluoroquinolones that belong to an important class of antibacterial substances [3, 4]. The polycyclic fluoroquinolonecarboxylic acids containing a cycloalkylamine moiety are known to possess high antibacterial activity and also the other types of biological activity (antiviral, antitumor) [5–7].

Aiming to obtain new tricyclic fluoroquinolones we prepared in this study 2-R-8-Y-7-oxo-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-i,j]quinoline-6-carboxylic2-R-8-Y-7-oxo-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-i,j]quinoline-6-carboxylic2-R-8-Y-7-oxo-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-i,j]-quinoline-6-carboxylic acids **Ia–d** and investigated the fluorine substitution in the compounds. The acids **Ia–d** were obtained by hydrolysis of the corresponding ethyl esters by boiling for 3 h in a mixture of acetic and hydrochloric acids at 4:1 ratio. The structure of compounds **Ia–d** was confirmed by ^{1}H and ^{19}F NMR spectra (Table 1). In the ^{1}H NMR spectra are present the signals from the protons of the carboxy group, R substituent, and also a singlet from H^5 in the 8.5–8.6 ppm region; in the spectra of acids **Ia, c** (Y = H) the signal of H^8 appears as a doublet of doublets in the 9.0 ppm region. In the ^{19}F NMR spectra of acids **Ia, c** appear two signals of fluorine atoms in the form of doublet of doublets, and in the ^{19}F NMR spectra of compounds **Ib, d** are present three doublets of doublets. Note the difference in the vicinal coupling constants ^3J(F,F) in the ^{19}F spectra of these compounds: $^3J(F^{10}, F^9)$ = 23.2 Hz, $^3J(F^8, F^9)$ = 20.1 Hz.

The substitution of fluorine in acids **Ia, c** by amine rests was carried out for 2–4 h in boiling pyridine or at heating for 2–4 h in acetonitrile in the presence of catalytic quantities of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1). The structure of aminoacids **IIa–f** obtained was confirmed by ^{1}H and ^{19}F NMR spectra (Table 2) and also by mass spectra. In the ^{19}F NMR spectra of acids **IIa–f** appears a signal from one fluorine atom in the 118.6–119.9 ppm region with the vicinal coupling constant ^3J 11.5–12.2 Hz that corresponds to the replacement of F^{10} atom by an amine moiety. In the ^{1}H NMR spectra of compounds **IIa–f** the signal of H^8 atom is observed as a doublet with a coupling constant ^3J 11.5–12.5 Hz in the region 7.55–7.70 ppm. In the mass spectra of substituted acids **IIa, c, e, f** the peak of maximum intensity is $[M–CO_2]^+$, and in the mass spectrum of ethoxycarbonyl derivative **IId** it is the peak $[M–COOC_2H_4]^+$ (Table 3).

In the similar reaction of trifluoro-containing acids **Ib, d** two fluorine atoms F^8 and F^{10} are substituted by amines. This finding is consistent with the published data on simultaneous substitution of F^5 and F^7 atoms by amine rests in the esters of N^1-substituted tetrafluoroquinolone-3-carboxylic acids [8]. In the ^{1}H NMR spectra of disubstituted acids **IV** are observed proton signals from two cycloalkylamine rests (Table 4), and in their ^{19}F NMR spectra the only fluorine atom appears as a singlet in 131.0– 132.0 ppm region. The mass spectra of acids **IV** are also consistent with the assumed structure (Table 5).

* For communication V, see [1].

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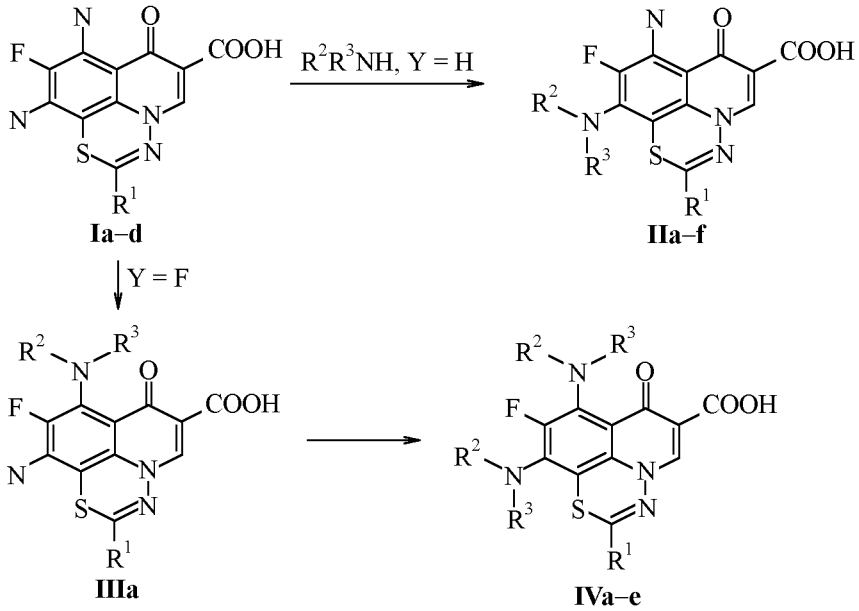
Scheme 1.



I, R^1 = pyrrolidin-1-yl (**a, b**), cyclohexylamino (**c, d**); **Y = H (a, c**), F (**b, d**); **II**, R^1 = pyrrolidin-1-yl (**a**–**d**), cyclohexylamino (**e, f**); NR^2R^3 = pyrrolidin-1-yl (**a, e**), 4-methylpiperazin-1-yl (**b**), morpholino (**c, f**), 4-ethoxycarbonylpiperazin-1-yl (**d**); **IIIa**, R^1 = pyrrolidin-1-yl, NR^2R^3 = morpholino; **IV**, R^1 = pyrrolidin-1-yl (**a**–**d**), cyclohexylamino (**e**); NR^2R^3 = pyrrolidin-1-yl (**a, e**), morpholino (**b**), 4-ethoxycarbonylpiperazin-1-yl (**c**), Me$©2N(CH$_2$)$_3$NH (**d**).

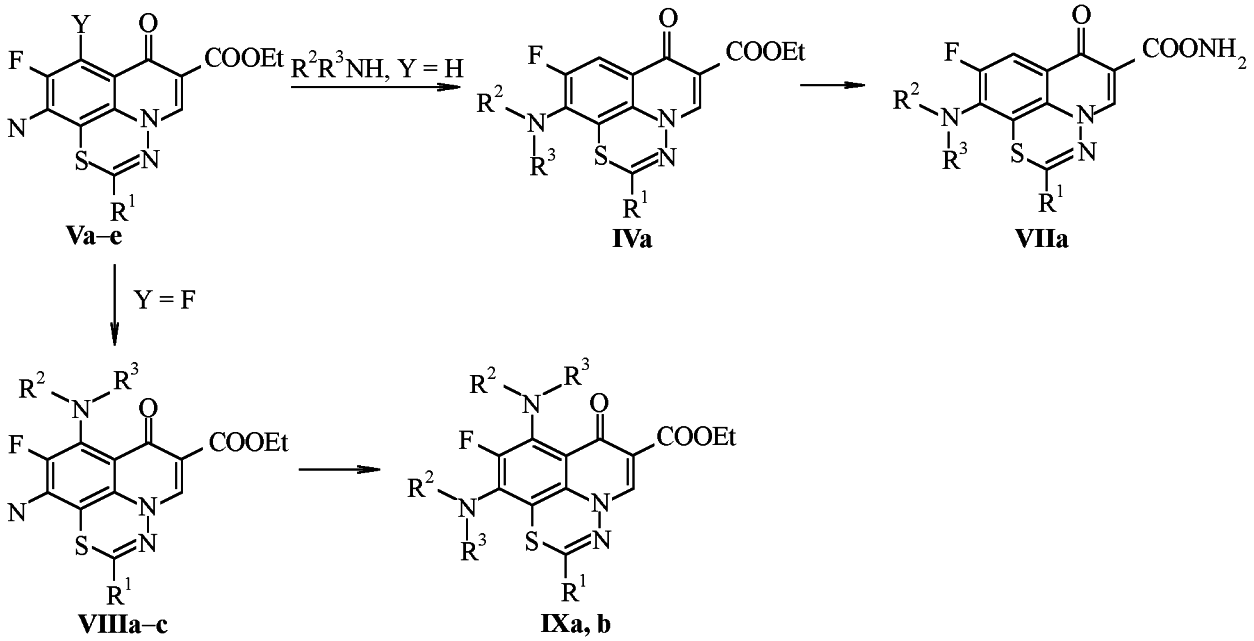
Table 1. ^{1}H and ^{19}F NMR spectra of 7-oxo-2-R-9-fluoro-10-Y-7*H*-1,3,4-thiadiazino[6,5,4-*i*,*j*]quinoline-6-carboxylic acids **Ia**–**d**

Compd. no.	^{1}H NMR spectrum, δ, ppm, coupling constant, Hz				^{19}F NMR spectrum, δ_F, ppm, d.d (coupling constant, Hz)
	H^5, s	H^8	COOH, br.s	R	
Ia	8.54	7.94 d.d $^3J(H^8, F^9)$ 10.3, $^4J(H^8, F^{10})$ 8.6	14.45	1.99 m [4H, $(CH_2)_2$], 3.58 m [4H, $N(CH_2)_2$]	135.17 [F^9, $^3J(F^9, F^{10})$ 21.4, $^3J(F^9, H^8)$ 10.3], 129.03 [F^{10}, $^3J(F^{10}, F^9)$ 21.4, $^4J(F^{10}, H^8)$ 8.6]
Ib	8.60	–	14.6	2.0 m [4H, $(CH_2)_2$], 3.6 m [4H, $N(CH_2)_2$]	159.86 [F^9, $^3J(F^9, F^{10})$ 23.2, $^3J(F^9, F^8)$ 20.1], 138.60 [F^8, $^3J(F^8, F^9$] 20.1, $^4J(F^8, F^{10})$ 10.4], 126.66 [F^{10}, $^3J(F^{10}, F^9)$ 23.2, $^4J(F^{10}, F^8)$ 10.4]
Ic	8.50	8.0 d.d $^3J(H^8, F^9)$ 10.4, $^4J(H^8, F^{10})$ 7.9	14.7	1.2 m [4H, $(CH_2)_2$], 1.9 m [6H, $(CH_2)_3$], 3.81 m [1H, CHNH], 7.8 d [1H, NH]	154.26 [F^{10}, $^3J(F^{10}, F^9)$ 22.0, $^4J(F^{10}, H^8)$ 7.9], 134.51 [F^9, $^3J(F^9, F^{10})$ 22.0, $^3J(F^9, H^8)$ 10.4]
Id	8.54	–	14.56	1.15 m [4H, $(CH_2)_2$], 20.1], 1.9 m [6H, $(CH_2)_3$], 3.77 m [1H, CHNH], 8.03 d [1H, NH, ^3J 7.0]	160.09 [F^9, $^3J(F^9, F^{10})$ 23.2, $^3J(F^9, F^8)$ 20.1] 139.34 [F^8, $^3J(F^8, F^9)$ 20.1, $^4J(F^8, F^{10})$ 9.8], 126.98 [F^{10}, $^3J(F^{10}, F^9)$ 23.2, $^4J(F^{10}, F^8)$ 9.8]

Table 2. ^{1}H NMR spectra of 2-R-7-oxo-10-Z-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i*,*j*]quinoline-6-carboxylic acids **IIa**–**f**

Compd. no.	Chemical shift, δ, ppm, coupling constant, Hz				
	H^5, s	H^8, d [$^3J(H^8, F^9)$]	COOH, br.s	R	Z
IIa	8.43	7.66 [12.2]	15.0	1.95 m [4H, $(CH_2)_2$], 3.53 m [4H, $N(CH_2)_2$]	1.95 m [4H, $(CH_2)_2$], 3.22 m [4H, $N(CH_2)_2$]
IIb	8.45	7.61 [11.9]	14.9	2.02 m [4H, $(CH_2)_2$], 3.57 m [4H, $N(CH_2)_2$]	2.85 s (3H, NCH_3), 3.37 m [4H, $N(CH_2)_2$], 3.57 m [4H, $N(CH_2)_2$]
IIc	8.45	7.68 [11.9]	14.9	1.96 m [4H, $(CH_2)_2$], 3.76 m [4H, $N(CH_2)_2$]	3.12 m [4H, $N(CH_2)_2$], 3.55 m [4H, $O(CH_2)_2$]
IId	8.38	7.55 [11.6]	14.4	2.02 m [4H, $(CH_2)_2$], 3.55 m [4H, $N(CH_2)_2$]	1.26 t (3H, CH_3), 3.07 m [4H, $N(CH_2)_2$], 3.55 m [4H, $N(CH_2)_2$], 4.10 q (2H, OCH_2)
IIe	8.50	7.64 [12.2]	14.81	1.30 m [6H, $(CH_2)_3$], 1.76 m (2H, CH_2), 1.95 m (2H, CH_2), 3.81 m (1H, CHNH), 7.59 m (1H, NH)	1.95 m [4H, $(CH_2)_2$], 3.25 m [4H, $N(CH_2)_2$]
IIf	8.51	7.70 [12.2]	14.89	1.30 m [6H, $(CH_2)_3$], 1.74 m (2H, CH_2), 1.99 m (2H, CH_2), 3.75 m (1H, CHNH), 7.84 d (1H, NH, ^3J 7.0)	3.27 m [4H, $N(CH_2)_2$], 3.75 m [4H, $O(CH_2)_2$]

Scheme 2.



V, R^1 = pyrrolidin-1-yl (**a, b**), morpholino (**c**), hexamethyleneimino (**d**); Y = H (**a**), F (**b**–**d**); **VIa, VIIa**, R^1 = NR^2R^3 = pyrrolidin-1-yl; Y = H; **VIII**, NR^2R^3 = morpholino, R^1 = pyrrolidin-1-yl (**a**), morpholino (**b**), hexamethyleneimino (**c**); **IX**, R^1 = pyrrolidin-1-yl; NR^2R^3 = pyrrolidin-1-yl (**a**), $Me_2N(CH_2)_3NH$ (**b**).

Table 3. ^{19}F NMR and mass spectra of 2-R-7-oxo-10-Z-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]-quinoline-6-carboxylic acids **IIa**–**f**

Compd. no.	δ_F, ppm [$J(F^9, H^8)$, Hz]	Mass spectrum, *m/z* (I_{rel}, %)
IIa	118.61 d [12.2]	402 (84), M^+, 358 (100), 325 (3), 288 (5), 261 (12), 234 (21)
IIb	119.73 d [12.0]	431 (41), M^+, 417 (10), 387 (27), 307 (10), 271 (13), 235 (20), 221 (11), 220 (11), 207 (21), 114 (13), 106 (18), 97 (27), 96 (35), 95 (37), 85 (26), 83 (31), 78 (22), 72 (100), 57 (62)
IIc	119.73 d [12.0]	419 (82), M^+, 375 (100), 317 (27), 279 (11), 248 (12), 220 (28), 192 (25)
IId	119.89 d [11.5]	517 (1), M^+, 489 (96), 445 (100), 247 (26), 219 (31)
IIe	118.92 d [12.1]	430 (81), M^+, 386 (100), 304 (31), 271 (66), 261 (20), 258 (14), 234 (26)
IIf	119.82 d [12.0]	446 (58), M^+, 403 (25), 402 (100), 320 (63), 287 (16), 262 (52), 235 (15), 221 (18), 220 (58), 192 (37), 63 (82), 55 (95)

With morpholine is first replaced atom F^8 to afford derivative **IIIa**, and at prolonged process and amine excess forms disubstituted quinolone **IVa**. The structure of 8-monosubstituted aminoacid **IIIa** was confirmed by the data of ^1H and ^{19}F NMR and mass spectra. In the ^{19}F NMR spectrum of compound **IIIa** the signals from two fluorine atoms appear as doublets with ^3J 22.0–22.5 Hz corresponding to a vicinal coupling constant $^3J(F^9, F^{10})$. This pattern indicates that F^8 atom is substituted by an amine rest.

It should be noted that in bicyclic 5,6,7,8-tetrafluoro-containing esters of 4-oxo-1,4-dihydroquinoline-3-carboxylic acids the amine replaces first of all F^5 atom. In this connection we decided to study the substitution of fluorine atoms in esters **V** by amines (Scheme 2).

The atom F^{10} in ethyl 2-(pyrrolidin-1-yl)-9,10-difluoro-7-oxo-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]-quinoline-6-carboxylate (**Va**) was substituted by pyrrolidine at boiling in acetonitrile for 2 h in the presence of the catalytic quantity of DBU. The structure of the substituted ester **VIa** was confirmed by ^1H and ^{19}F NMR and mass spectra (Table 6). From ester **VIa** was prepared hydrazide **VIIa** whose structure was also proved by the spectral data (Table 6). In the ^1H NMR spectrum are present the proton signals from groups $C(O)NHNH_2$, R', NR^2R^3, and singlet from H^5 atom at 8.43 ppm.

Table 4. ^1H NMR spectra of 2-R-8,10-Z_2-7-oxo-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylic acids **IVa**–**e**

Compd. no.	Chemical shift, δ, ppm			
	H^5, s	COOH, br.s	R	Z
IVa	8.33	15.55	1.91 m [4H, $(CH_2)_2$], 3.47 m [4H, $N(CH_2)_2$]	1.91 m [8H, $2(CH_2)_2$], 3.18 m [4H, $N(CH_2)_2$], 3.37 m [4H, $N(CH_2)_2$]
IVb	8.42	15.59	1.96 m [4H, $(CH_2)_2$], 3.76 m [4H, $N(CH_2)_2$]	3.10 m [4H, $N(CH_2)_2$], 3.24 m [4H, $N(CH_2)_2$], 3.56 m [4H, $O(CH_2)_2$], 3.75 m [4H, $O(CH_2)_2$]
IVc	8.69	15.45	2.01 m [4H, $(CH_2)_2$], 3.65 m [4H, $N(CH_2)_2$]	1.29 t (6H, $2CH_3$), 3.09 m [4H, $N(CH_2)_2$], 3.21 m [4H, $N(CH_2)_2$], 3.55 m [4H, $N(CH_2)_2$], 3.59 m [4H, $N(CH_2)_2$], 4.18 q (4H, $2OCH_2$)
IVd[a]	8.45	15.1	2.00 m [4H, $(CH_2)_2$], 3.51 m [4H, $N(CH_2)_2$]	1.79 m (2H, CH_2), 1.82 m (2H, CH_2), 2.23 s [6H, $N(CH_3)_2$], 2.29 s [6H, $N(CH_3)_2$], 2.38 m (2H, CH_2), 2.48 m (2H, CH_2), 3.45 m (2H, CH_2), 3.60 m (2H, CH_2), 5.93 br.s (1H, NH), 9.30 br.s (1H, NH)
IVe	8.48	15.57	1.28 m [4H, $(CH_2)_2$], 1.61 m [6H, $(CH_2)_3$], 3.82 m (1H, CHNH), 8.1 d (1H, NH, ^3J 7.0 Hz)	1.97 m [8H, $2(CH_2)_2$], 3.25 m [4H, $N(CH_2)_2$], 3.51 m [4H, $N(CH_2)_2$]

[a] ^1H NMR spectrum was recorded in $CDCl_3$.

In the spectra of compounds **VIa** and **VIIa** the signal of H^8 proton appears as a doublet at 7.6 ppm with the coupling constant $^3J(H^8, F^9)$ 12.5 Hz. In the ^{19}F NMR spectra of ester **VIa** and hydrazide **VIIa** the signal of F^9 atom is a doublet in the region 120.8 ppm. The mass spectra of these compounds contain characteristic peaks *m/z* 385 $[M-OC_2H_5]^+$ for ester and $[M-NHNH_2]^+$ for hydrazide.

In reactions with esters **V** (Y = F) as with acids **Ib, d** the amines replace both F^8 and F^{10} providing diamino derivatives **IX**. Using morpholine we succeeded in isolating 8-monosubstituted derivatives **VIII**. The structure of compounds **VIII, IX** was confirmed by ^1H and ^{19}F NMR and mass spectra (Table 6). In the ^{19}F NMR spectra of monosubstituted esters **VIII** are observed two fluorine signals as doublets in the region 149 and 132 ppm with the coupling constants $^3J(F^9,F^{10})$ 23.0–23.4 Hz. It is interesting that 8-morpholino-substituted compounds **VIIIa, b, IIIa** in the mass spectra have a peak of maximum intensity *m/z* 322 corresponding to $[M-COOC_2H_4-R]^+$ for esters **VIII**, and $[M-CO_2-R]^+$ for acid IIIa. Compounds **II–IV, VI–IX** synthesized in the course of this investigation are potential biologically active substances.

EXPERIMENTAL

^1H and ^{19}F were registered on spectrometers Bruker WP-250 and Bruker WP-80-SY at operating frequencies 250.135 MHz for protons and 75.38 MHz for fluorine from solutions in DMSO-d_6; internal reference for protons was TMS, for fluorine hexafluorobenzene. Mass spectra were measured on Finnigan MAT-8200 instrument.

Table 5. ^{19}F NMR and mass spectra of 2 2-R-8,10-Z_2-7-oxo-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i*,*j*]quinoline-6-carboxylic acids **IVa–e**

Compd. no.	δ_F, ppm (1F, F^9)	Mass spectrum, *m/z* (I_{rel}, %)
IVa	131.36 s	471 (18), M^+, 375 (85), 358 (70), 347 (60), 306 (20), 288 (25), 262 (100), 234 (54)
IVb	132.02 s	503 (23), M^+, 485 (14), 444 (13), 390 (44), 389 (88), 374 (53), 348 (49), 343 (21), 304 (31), 286 (15), 243 (29), 220 (100), 192 (27)
IVc	131.11 s	645 (11), M^+, 601 (11), 556 (12), 543 (16), 517 (18), 505 (28), 499 (26), 473 (28), 460 (86), 447 (68), 421 (36), 403 (21), 235 (21), 96 (29), 56 (100)
IVd	151.76 s	533 (3), M^+, 475 (9), 457 (22), 86 (13), 85 (27), 84 (79), 72 (30), 70 (13), 59 (16), 58 (100)
IVe	131.11 s	499 (3), M^+, 375 (66), 358 (28), 347 (24), 332 (27), 329 (22), 306 (31), 288 (18), 262 (100), 234 (37)

Table 6. ^1H and ^{19}F NMR spectra and mass spectra of compounds **VI–IX**

Compd. no.	Chemical shift, δ, ppm in ^1H NMR spectra			
	OCH_2CH_3 ($NHNH_2$)	H^5, s	R, m (4H)	Z
VIa	1.33 t (3H, CH_3) 4.22 q (2H, OCH_2)	8.30	1.97 $[(CH_2)_2]$, 3.49 $[N(CH_2)_2]$	1.97 m [4H, $(CH_2)_2$], 3.16 m [4H, $N(CH_2)_2$]
VIIa	4.40 br.s (2H, NH_2) 10.48 s (1H, CONH)	8.43	1.98 $[(CH_2)_2]$, 3.52 $[N(CH_2)_2]$	1.98 m [4H, $(CH_2)_2$], 3.17 m [4H, $N(CH_2)_2$]
VIIIa	1.31 t (3H, CH_3), 4.21 q (2H, OCH_2)	8.21	1.97 $[(CH_2)_2$, 3.72 $[N(CH_2)_2]$	3.17 m [4H, $N(CH_2)_2$], 3.53 m [4H, $O(CH_2)_2$]
VIIIb	1.32 t (3H, CH_3), 4.22 q (2H, OCH_2)	8.24	3.52 $[N(CH_2)_2]$, 3.71 $[O(CH_2)_2]$	3.18 m [4H, $N(CH_2)_2$], 3.69 m [4H, $O(CH_2)_2$]
VIIIc	1.33 t (3H, (CH_3), 4.22 q (2H, OCH_2)	8.20	1.58 $[(CH_2)_2]$, 1.79 $[(CH_2)_2]$, 3.73 $[N(CH_2)_2]$	3.18 m [4H, $N(CH_2)_2$], 3.62 m [4H, $O(CH_2)_2$]
IXa	1.35 t (3H, CH_3), 4.33 q (2H, OCH_2)	8.36	1.97 $[(CH_2)_2]$, 3.54 $[N(CH_2)_2]$	1.97 m [8H, $2(CH_2)_2$], 3.21 m [4H, $N(CH_2)_2$], 3.54 · [4H, $N(CH_2)_2$]
IXb	1.31 t (3H, CH_3), 4.19 q (2H, OCH_2)	8.11	1.97 $[(CH_2)_2]$, 3.52 $[N(CH_2)_2]$	1.69 m (2H, CH_2), 1.72 m (2H, CH_2), 2.15 s (6H, NMe_2), 2.20 s (6H, NMe_2), 2.30 m (2H, CH_2), 2.37 m (2H, CH_2), 3.28 m (2H, CH_2), 3.39 m (2H, CH_2), 5.65 br.s (1H, NH), 10.05 br.s (1H, NH)

Table 6. (Contd.)

Compd. no.	Chemical shift in ^{19}F NMR spectra, δ_F, ppm (J, Hz)	Mass spectrum, *m/z* (I_{rel}, %)
VIa[a]	120.78 d [1F, F^9, $^3J(F^9, H^8)$ 12.4]	430 (48), M^+, 385 (5), 358 (100), 261 (11), 234 (16), 70 (11)
VIIa[b]	120.78 d [1F, F^9, $^3J(F^9, H^8)$ 12.4]	416 (56), M^+, 386 (32), 385 (100), 289 (28), 243 (19), 192 (11)
VIIIa	149.27 d [1F, F^9, $^3J(F^9, F^{10})$ 23.4], 132.55 d [1F, F^{10}, $^3J(F^{10}, F^9)$ 23.4]	464 (5), M^+, 369 (12), 368 (60), 323 (25), 322 (100), 307 (26), 294 (28), 238 (19), 209 (13)
VIIIb	149.45 d [1F, F^9, $^3J(F^9, F^{10})$ 22.9], 132.56 d [1F, F^{10}, $^3J(F^{10}, F^9)$ 23.4]	–
VIIIc	149.19 d [1F, F^9, $^3J(F^9, F^{10})$ 23.4], 132.34 d [1F, F^{10}, $^3J(F^{10}, F^9)$ 23.3]	492 (3), M^+, 369 (12), 368 (62), 335 (12), 323 (27), 322 (100), 294 (24), 238 (16), 223 (12)
IXa	134.79 s (1F, F^9)	499 (5), M^+, 403 (46), 386 (14), 375 (28), 374 (48), 360 (20), 358 (26), 346 (14), 334 (26), 306 (19), 263 (17), 262 (100)
IXb	148.82 d.d [1F, F^9, $^4J(F^9, NH)$ 1.0]	561 (1), M^+, 503 (14), 457 (26), 375 (10), 266 (11), 85 (13), 84 (72), 72 (27), 59 (15), 58 (100)

δ (H^8): [a] 7.56 d [$J(H^8, F^9)$ 12.5 Hz], [b] 7.57 d [$J(H^8, F^9)$ 12.6 Hz].

Yields, melting points and elemental analyses of compounds **I–IV, VI–IX** are listed in Table 7.

2-R-8-Y-Ethyl 7-oxo-2,10-bis(pyrrolidin-1-yl)-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylate-7-oxo-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylic acids I. To 1.1 g (2.9 mmol) of ethyl 7-oxo-2-(pyrrolidin-1-yl)-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylate (**Va**) was added 25 ml of a mixture HCl–AcOH (1:4). The reaction mixture was boiled for 3 h, cooled, diluted with water, the precipitate of acid **Ia** was filtered off and recrystallized from DMSO. Yield 0.75 g (74%).

In a similar way were prepared acids **Ib–d**. Mass spectrum of compound **Ib** [*m/z* (I_{rel}, %]: 369 (100), M^+, 325 (93), 256 (12), 226 (16), 201 (22), 178 (17), 157 (14).

2-R-10-Z-7-Oxo-9-fluoro-7*H*-1,3,4-thiadiazino-[6,5,4-*i,j*]quinoline-6-carboxylic acids II. (a) To a solution of 0.7 g (2 mmol) of 7-oxo-2-(pyrrolidin-1-yl)-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylic acid (**Ia**) in 8 ml of pyridine was added 0.6 ml)8 mmol) of pyrrolidine, and the mixture was boiled for 3 h. After cooling the precipitate was filtered off and washed with ether. To the precipitate was added 4 ml of 2 N HCl and 4 ml of methanol, the mixture was boiled for 30 min, the precipitate of compound **IIa** was filtered off and recrystallized from DMSO. Yield 0.4 g (50%). Similarly was prepared compound **IIc**. (b) To a dispersion of 0.85 g (2.42 mmol) of acid **Ia** in 15 ml of anhydrous acetonitrile was added 1,15 ml (7.26 mmol) of ethoxycarbonylpiperazine and 4 drops of DBU. The mixture was boiled for 3 h, on cooling the precipitate of compound **IId** was filtered off and recrystallized from ethanol. Yield 0.65 g (55%).

Compounds **IIb, c, e, f** were prepared similarly and recrystallized from DMSO.

8-Morpholino-7-oxo-2-(pyrrolidin-1-yl)-9,10-difluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylic acid (IIIa). To 0.45 g (1.2 mmol) of acid **Ib** in 15 ml of anhydrous acetonitrile was added 0.21 ml (2.4 mmol) of morpholine and 3 drops of DBU. The reaction mixture was boiled for 1 h, cooled, the precipitate was filtered off and recrystallized from DMSO. Yield 0.35 g (67%). ^{1}H NMR spectrum (DMSO-d_6, δ, ppm): 1.95 m [4H, $(CH_2)_2$], 3.27 m [4H, $N(CH_2)_2$], 3.52 m [4H, $O(CH_2)_2$], 3.75 m [4H, $N(CH_2)_2$], 8.42 s (1H, H^5), 15.28 br.s (1H, COOH). ^{19}F NMR spectrum (DMSO-d_6, δ_F, ppm): 147.73 d [F^9, $^3J(F^9, F^{10})$ 22.5 Hz], 129.14 d [F^{10}, $^3J(F^{10}, F^9)$ 22.0 Hz]. Mass spectrum [*m/z* (I_{rel}, %)]: 436 (5), M^+, 340 (48), 322 (100), 307 (11), 294 (25), 238 (15).

2-R-8,10-Z_2-7-Oxo-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylic acids IV. (a) To a dispersion of 0.8 g (2.2 mmol) of acid **Ib** in 10 ml of anhydrous acetonitrile was added 0.6 ml (9 mmol) of pyrrolidine and 5 drops of DBU. The reaction mixture was boiled for 2 h, cooled, the precipitate was filtered off. To the precipitate was added 5 ml of 2 N HCl, the mixture was boiled for 30 min, the precipitate was filtered off and recrystallized from DMSO, Yield 0.7 g (68%).

Similarly were prepared derivatives **IVb–e**; compounds **IVc, d** were recrystallized from ethanol. In the synthesis of compound **IVb** the reaction time was prolonged to 6 h. (b) To 0.5 g (1.15 mmol) of acid **IIIa** in 12 ml of anhydrous acetonitrile was

Table 7. Yields, melting points[a], and elemental analyses of compounds synthesized

Compd. no.	mp, °C	Yield, %	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Ia	>260	74	51.14	3.10	11.88	$C_{15}H_{11}F_2N_3O_3S$	51.28	3.16	11.96
Ib	240–242	78	47.96	2.78	11.34	$C_{15}H_{10}F_3N_3O_3S$	48.78	2.73	11.38
Ic	258–260	69	53.62	4.16	11.08	$C_{17}H_{15}F_2N_3O_3S$	53.82	3.99	11.08
Id	>260	71	51.19	3.76	9.76	$C_{17}H_{14}F_3N_3O_3S$	51.38	3.55	10.57
IIa	230–232	50	56.70	4.77	13.55	$C_{19}H_{19}FN_4O_3S$	56.71	4.76	13.92
IIb	246–248	24	55.90	4.98	16.11	$C_{20}H_{22}FN_5O_3S$	55.67	5.14	16.23
IIc	>260	68	54.33	4.90	13.0	$C_{19}H_{19}FN_4O_3S$	54.54	4.58	13.39
IId	254–256	55	53.87	4.79	14.02	$C_{22}H_{24}FN_5O_5S$	53.98	4.94	14.31
IIe	>260	72	58.21	5.12	12.86	$C_{21}H_{23}FN_4O_3S$	58.59	5.38	13.02
IIf	>260	74	55.80	4.99	12.71	$C_{21}H_{23}FN_4O_4S$	56.49	5.19	12.55
IIIa	251–253	67	52.03	4.31	13.02	$C_{19}H_{18}F_2N_4O_4S$	52.29	4.16	12.84
IVa	245–247	62	58.18	5.63	14.80	$C_{23}H_{26}FN_5O_3S$	58.58	5.56	14.85
IVb	279–281	76	54.33	4.9	13.73	$C_{23}H_{26}FN_5O_5S$	54.86	5.20	13.91
IVc[b]	216–218	80	53.70	5.86	15.16	$C_{29}H_{36}FN_7O_7S$	53.94	5.62	15.18
IVd[b]	121–123	43	55.78	6.56	18.58	$C_{25}H_{36}FN_7O_3S$	56.27	6.80	18.37
IVe	>260	57	59.80	6.27	13.86	$C_{25}H_{30}FN_5O_3S$	60.10	6.05	14.02
VIa	235–237	61	58.41	5.29	12.97	$C_{21}H_{23}FN_4O_3S$	58.59	5.38	13.01
VIIa	246–248	92	54.61	4.99	20.00	$C_{19}H_{21}FN_6O_2S$	54.79	5.08	20.18
VIIIa[b]	166–168	65	54.13	4.59	12.28	$C_{21}H_{22}F_2N_4O_4S$	54.30	4.77	12.06
VIIIb[b]	218–220	52	52.21	4.49	11.85	$C_{21}H_{22}F_2N_4O_4S$	52.49	4.62	11.66
VIIIc[b]	188–190	49	58.85	5.15	11.51	$C_{23}H_{26}F_2N_4O_4S$	56.09	5.32	11.38
IXa	240–242	72	59.64	6.09	13.76	$C_{25}H_{30}FN_5O_3S$	60.10	6.05	14.02
IXb[b]	206–208	77	57.61	7.02	17.61	$C_{27}H_{40}FN_7O_3S$	57.73	7.18	17.45

Solvent for crystallization: [a] DMSO, [b] ethanol.

added 1 ml (11.5 mmol) of morpholine and 8 drops of DBU. The reaction mixture was boiled for 6 h, on cooling the precipitate of compound **IVb** was filtered off and recrystallized from DMSO. Yield 0.45 g (83%).

Ethyl 7-oxo-2,10-bis(pyrrolidin-1-yl)-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylate (VIa). To 0.65 g (1.72 mmol) of ethyl ester **Va** in 8 ml of anhydrous acetonitrile was added 0.37 ml (5.1 mmol) of pyrrolidine and 3 drops of DBU. The reaction mixture was boiled for 2 h. On cooling the precipitate of compound **VIa** was filtered off and recrystallized from DMSO. Yield 0.45 g (61%).

Hydrazide of 2-(pyrrolidin-1-yl)-7-oxo-10-(pyrrolidin-1-yl)-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylic acid (VIIa). To 0,2 g (0.47 mmol) of ethyl ester **VIa** in 3 ml of pyridine was added 1.2 ml of 70% hydrazine hydrate. The reaction mixture was heated to 80°C for 1.5 h. On cooling the hydrazide **VIIa** precipitate was filtered off and recrystallized from DMSO. Yield 0.18 g (92%).

Ethyl 2-R-8-(morpholin-1-yl)-7-oxo-9,10-di-7fluoro-*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxyates VIII. To 0.2 g (0.5 mmol) of ester **Vb** in 8 ml of anhydrous acetonitrile was added 0.2 ml (2 mmol) of morpholine and 3 drops of DBU. The reaction mixture was boiled for 2 h. On cooling the precipitate of compound **VIIIb** was filtered off and recrystallized from ethanol. Yield 0.12 g (52%). Compounds **VIIIa,c** were obtained by the similar procedure.

Ethyl 7-oxo-2-(pyrrolidin-1-yl)-8,10-Z_2-9-fluoro-7*H*-1,3,4-thiadiazino[6,5,4-*i,j*]quinoline-6-carboxylates IX. To 0.4 g (1 mmol) of ester **Vb** in 5 ml of anhydrous acetonitrile was added 0.15 ml (2.2 mmol) of pyrrolidine and 3 drops of DBU. The reaction mixture was boiled for 2 h. On cooling the precipitate of compound **IXa** was filtered off and recrystallized from ethanol. Yield 0.4 g (80%).

Compound **IXb** was obtained similarly.

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