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Fused fluoroquinolones: synthesis and ^{1}H and ^{19}F NMR studies

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Abstract

New derivatives of fused fluoroquinolones bearing five aromatic rings have been obtained. The ^{19}F NMR spectra of these pentacyclic fluoroquinolones demonstrate unusual through space ^{1}H–^{19}F and ^{19}F–^{19}F spin–spin interactions with coupling constants $^{6}J(F, H) = 2.0$–3.0 Hz, $^{7}J(F, F) = 3.5$–4.0 Hz and $^{9}J(F, H) = 3.0$–3.5 Hz. Relative reactivities of fluorine atoms in pentacyclic fluoroquinolones in the amino-defluorination reactions are also different relative to bi- and tricyclic fluoroquinolones. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Fused fluoroquinolones; ^{1}H and ^{19}F NMR spectra; Long range coupling constants; Amino-defluorination

1. Introduction

Synthetic antibacterials of the ''fluoroquinolone'' family, derivatives of 4-oxo-1,4-dihydro-3-quinolinecarboxylic acid, have found wide application in medicine and veterinary medicine [1–5]. Besides introduction of substituents into the basic quinolone structures, the synthesis of fused polycyclic compounds is a widely used approach for structural modification of fluoroquinolones [6]. Indeed, derivatives of fused fluoroquinolones were found to exhibit not only high antibacterial but also antiviral activity, in particular against hepatitis B and human immuno-deficiency (HIV) viruses [7–9], as well as anticancer and other kinds of activity [10–13]. The most promising derivatives are [*i,j*]-fused fluoroquinolones presented by the well-known ofloxacine, levofloxacine and marbofloxacine (Scheme 1) [14].

We have recently described the synthesis of [*i,j*]-fused fluoroquinolones forming a new pentacyclic aromatic system of benzazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinolines (Scheme 2) [15,16]. It was shown by X-ray analysis that planarity of this system is considerably destroyed, probably due steric hindrance between F1 and H12. In this paper, we wish to discuss the ^{1}H and ^{19}F NMR spectral data for derivatives of 4-oxo-4H-benzazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline-5-carboxylic acid (**1**)–(**10**) and to report on the synthesis of some new derivatives of fused fluoroquinolones (**11**)–(**15**) (Schemes 2 and 3).

2. Results and discussion

Studying the ^{19}F NMR spectra of compounds (**1**)–(**10**) we have found that the signals of F1 and F2 are of different multiplicity. Whereas the F2 resonance appears as double doublet with ^{3}J(F2–F1) 20.7–21.8 Hz and ^{3}J(F2–H3) 10.1–10.7 Hz (as in the ^{19}F NMR spectra of tricyclic fluoroquinolones [17]), the signal of F1 has a more complicated structure of ddd for compounds (**5**)–(**8**), (**10**) or dddd — for compounds (**1**)–(**4**), (**9**) (Table 1).

The multiplicity of F1 in the ^{19}F NMR spectra of compounds (**1**)–(**10**) indicates that F1 is coupled with not only F2 and F3 (H3) of the quinolone moiety, but also with H12 of the annelated fragment, and with H11 and H12 in the case of the compound (**9**). Long-range coupling constants ^{6}J(F1–H12) 2.0–3.8 Hz have been measured for all compounds, while additional ^{7}J(F1–H11) 2.9 Hz was observed in the ^{19}F and ^{1}H NMR spectra of the compound (**9**) (Tables 1 and 2).

In the ^{1}H NMR spectra of compounds (**1**)–(**4**), the signals of H9 and H12 can easily be distinguished due to their different multiplicities. The H9 resonance signal appears as a double doublet with ^{3}J(H9–F10) 10.3–10.5 Hz and ^{4}J(H9–F11) 7.3–7.5 Hz, while the signal of H12 has a more complicated multiplicity of ddd, since in addition to ^{3}J(H12–F11) and ^{4}J(H12–F10) the coupling constant ^{6}J(H12–F1) 2.0–3.8 Hz is observed (Table 2). Compounds (**1**)–(**4**) are also characterized by different multiplicities of the ^{19}F resonance signals of the benzimidazole fragment: ddd for F10 and dddd for F11 due to the long-range coupling constant ^{7}J(F11–F1) 3.5–4.0 Hz (Table 2). A feature of the

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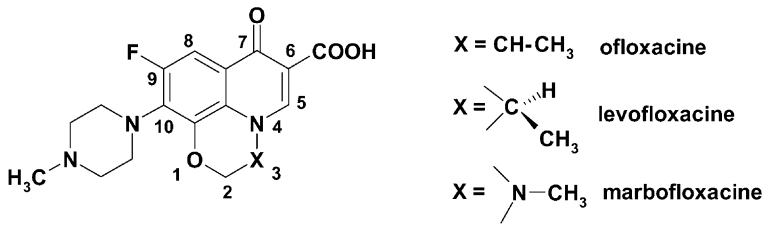
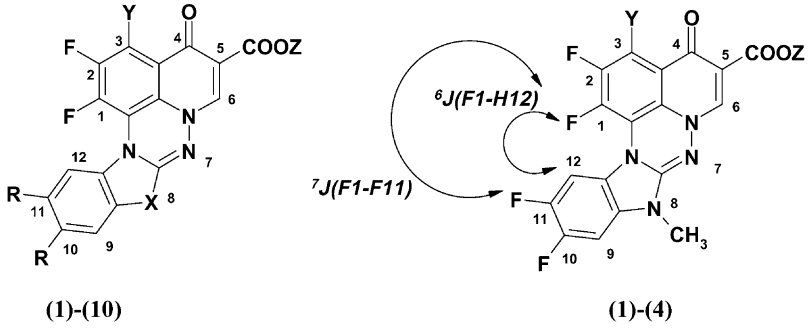


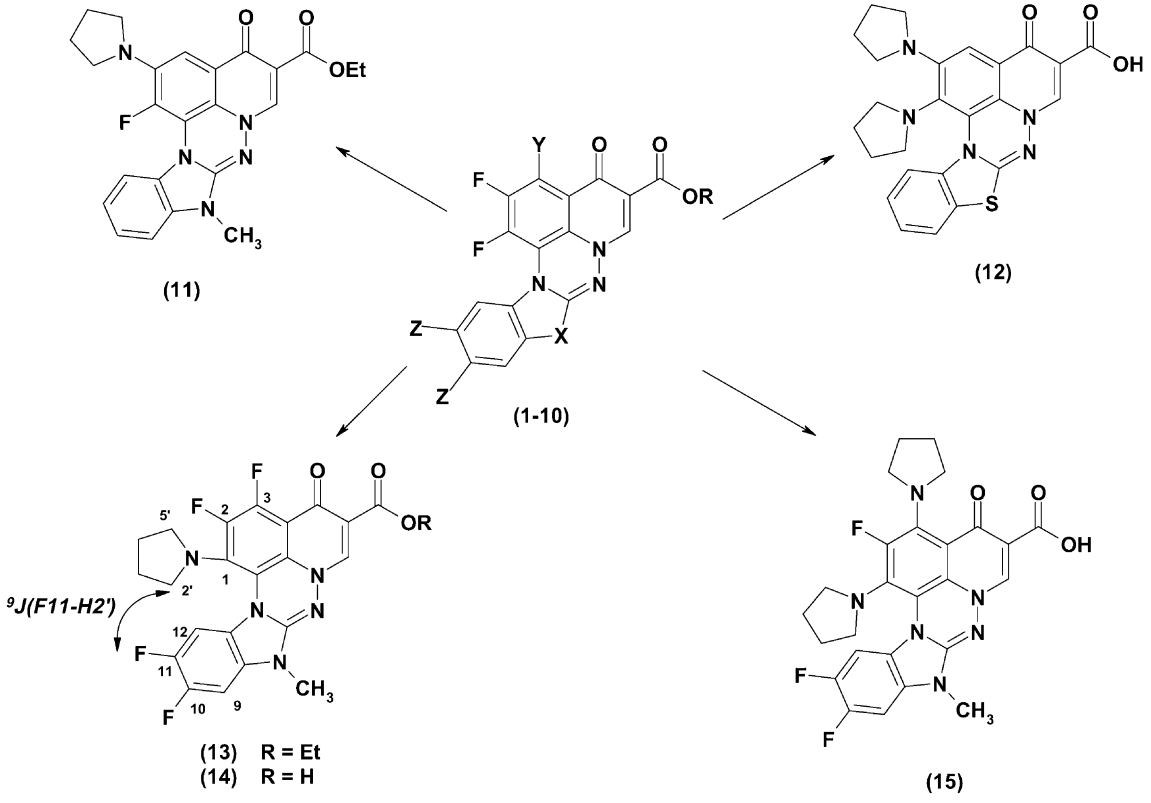
Scheme 1.



Scheme 2.

^{1}H NMR spectra of compounds (**5**)–(**10**) is that the ^{1}H signals of H9–H12 are observed as poorly resolved multiplets, thus, the coupling constant ^6J(H12–F1) cannot be measured.

Analyzing the ^{1}H and ^{19}F NMR spectral data for benzazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinolines (**1**)–(**10**) one can suggest that long-range spin–spin interactions between F1, F11 and H12 are realized through space due to



Scheme 3.

Table 1
^{1}H NMR spectral data for fused quinolones (**1**)–(**10**) in DMSO-d_6

Compounds	X	Y	Z	R	Characteristics, δ (ppm), ^nJ (Hz)			
					H3	H9	H12	Other
1	NCH_3	F	Et	F	–	7.48 dd ^3J(H9–F10) 10.5 ^4J(H9–F11) 7.5	7.46 ddd ^3J(H12–F11) 10.5 ^4J(H12–F10) 7.5 ^6J(H12–F1) 2.5	1.29 t (3H, CH_3) 3.35 s (3H, NCH_3) 4.22 q (2H, OCH_2) 8.20 s (1H, H6)
2	NCH_3	H	Et	F	7.62 dd ^3J(H3–F2) 10.5 ^4J(H3–F1) 8.0	7.49 dd ^3J(H9–F10) 10.5 ^4J(H9–F11) 7.5	7.52 ddd ^3J(H12–F11) 10.5 ^4J(H12–F10) 7.5 ^6J(H12–F1) 2.0	1.30 t (3H, CH_3) 3.37 s (3H, NCH_3) 4.24 q (2H, OCH_2) 8.30 s (1H, H6)
3	NCH_3	F	H	F	–	7.65 dd ^3J(H9–F10) 10.4 ^4J(H9–F11) 7.5	7.58 ddd ^3J(H12–F11) 11.2 ^4J(H12–F10) 7.5 ^6J(H12–F1) 3.8	3.39 s (3H, NCH_3) 8.39 s (1H, H6) 14.93 br. s (1H, COOH)
4	NCH_3	H	H	F	7.74 dd ^3J(H3–F2) 10.1 ^4J(H3–F1) 8.0	7.66 dd ^3J(H9–F10) 10.3 ^4J(H9–F11) 7.3	7.62 ddd ^3J(H12–F11) 11.6 ^4J(H12–F10) 7.1 ^6J(H12–F1) 2.6	3.39 s (3H, NCH_3) 8.38 s (1H, H6) 14.95 br. s (1H, COOH)
5	NCH_3	H	Et	H	7.60 dd ^3J(H3–F2) 10.5 ^4J(H3–F1) 8.0	7.14 m (1H), 7.28 m (2H), 7.52 m (1H)		1.28 t (3H, CH_3) 3.39 s (3H, NCH_3) 4.21 q (2H, OCH_2) 8.32 s (1H, H6)
6	NCH_3	H	H	H	7.77 dd ^3J(H3–F2) 10.2 ^4J(H3–F1) 7.9	7.18 m (1H), 7.26 m (1H), 7.37 m (1H) 7.62 m (1H)		3.63 s (3H, NCH_3) 8.47 s (1H, H6) 15.1 s (1H, COOH)
7	S	F	Et	H	–	7.3 m (3H), 7.7 m (1H)		1.26 t (3H, CH_3) 4.18 q (2H, OCH_2) 8.27 s (1H, H6)
8	S	H	Et	H	7.63 m	7.32 m (3H), 7.73 m (1H)		1.33 t (3H, CH_3) 4.20 q (2H, OCH_2) 8.34 s (1H, H6)
9	S	H	H	H	7.80 dd ^3J(H3–F2) 9.2 ^4J(H3–F1) 7.7	7.32 m (1H), 7.43 m (2H), 7.78 m (1H)		8.53 s (1H, H6) 14.7 s (1H, COOH)
10	O	H	H	H	7.82 dd ^3J(H3–F2) 10.0 ^4J(H3–F1) 7.9	7.38 m (2H), 7.58 m (1H), 7.66 m (1H)		8.52 s (1H, H6) 14.8 s (1H, COOH)

the vicinity of these nuclei. It is worth noting that similar through space couplings have been reported in the ^{19}F NMR spectra of ethyl 1-(2-NR^1R^2-3,3,3-trifluoropropyl)-6,7,8-trifluoro-4-oxoquinolin-3-carboxylates [18].

The ability of fluorine atoms F1–F3 in pentacyclic quinolones (**1**)–(**10**) to be displaced by nucleophiles proved to be different in comparison with that of bicyclic or tricyclic fluoroquinolones. In bicyclic 6,7-difluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acids position 7 is known to be the most vulnerable to nucleophilic attack; also in tricyclic 9,10-difluoro-7-oxo-1,7-dihydro-1,3,4-thiadiazino[6,5,4-*i,j*]quinolin-6-carboxylic acids F10 at the same position of the quinolone skeleton is first displaced on reacting with cycloalkylimines [3,19].

We have found that the reaction of 1,2-difluoro derivative of fused quinolone (**5**) with pyrrolidine in refluxing pyridine results in the formation of 2-substituted product (**11**) (Scheme 3), as shown by the ^{1}H NMR spectrum of (**11**) in which the H3 resonance signal is observed as a doublet with ^4J(H3–F1) 8.2 Hz (Table 3). It is also substantiated by the ^{19}F NMR spectrum of (**11**) in which the F1 signal is split into double doublet with ^4J(F1–H3) 8.0 Hz and ^6J(F1–H12) 3.1 Hz (Table 4).

The reaction of fluoroquinolone (**9**) bearing the annelated benzothiazole fragment with pyrrolidine in refluxing pyridine gave a 1,2-disubstituted product (**12**) (Scheme 3). Evidence for structure (**12**) is provided by ^{1}H NMR and mass-spectrometry data (Tables 3 and 4). The formation of (**11**) and (**12**) demonstrates the good leaving ability of F2, that is at the position which is not an activated one in bi- or tricyclic derivatives of fluoroquinolones. The reactions of (**6**) or (**9**) with 4-methylpiperazine and

Table 2
^{19}F NMR spectral data for fused quinolones (**1**)–(**10**) in DMSO-d_6

Compounds	Characteristics, δ_F (ppm), ^nJ (Hz)				
	F1	F2	F3	F10	F11
1	135.56 dddd ^3J(F1–F2) 21.5, ^4J(F1–F3) 5.8 ^6J(F1–H12) 2.5, ^7J(F1–F11) 4.0	161.72 dd ^3J(F2–F1) 20.4 ^3J(F2–F3) 20.4	145.99 dd ^3J(F3–F2) 19.7 ^4J(F3–F1) 5.8	146.20 ddd ^3J(F10–F11) 21.5 ^3J(F10–H9) 11.0 ^4J(F10–H12) 7.5	143.05 dddd ^3J(F11–F10) 21.5, ^3J(F11–H12) 10.5 ^4J(F11–H9) 7.5, ^7J(F11–F1) 4.0
2	138.65 dddd ^3J(F1–F2) 21.5, ^4J(F1–H3) 8.0 ^6J(F1–H12) 2.0, ^7J(F1–F11) 3.5	135.61 dd ^3J(F2–F1) 21.3 ^3J(F2–H3) 10.4	–	146.21 ddd ^3J(F10–F11) 22.0 ^3J(F10–H9) 10.5 ^4J(F10–H12) 7.5	145.85 dddd ^3J(F11–F10) 22.0 ^3J(F11–H12) 10.5 ^4J(F11–H9) 7.5 ^7J(F11–F1) 3.5
3	133.35 dddd ^3J(F1–F2) 21.2, ^4J(F1–F3) 5.8 ^6J(F1–H12) 2.0, ^7J(F1–F11) 3.3	158.85 dd ^3J(F2–F1) 20.6 ^3J(F2–F3) 20.6	144.05 dd ^3J(F3–F2) 20.0 ^4J(F3–F1) 5.8	145.48 ddd ^3J(F10–F11) 21.4 ^3J(F10–H9) 11.5 ^4J(F10–H12) 7.1	142.27 dddd ^3J(F11–F10) 21.7, ^3J(F11–H12) 10.8 ^4J(F11–H9) 6.8, ^7J(F11–F1) 3.6
4	136.50 dddd ^3J(F1–F2) 21.1, ^4J(F1–H3) 7.9 ^6J(F1–H12) 2.0, ^7J(F1–F11) 3.5	132.77 dd ^3J(F2–F1) 20.9 ^3J(F2–H3) 10.2	–	145.49 ddd ^3J(F10–F11) 21.5 ^3J(F10–H9) 11.5 ^4J(F10–H12) 7.2	142.05 dddd ^3J(F11–F10) 21.6, ^3J(F11–H12) 10.7 ^4J(F11–H9) 6.9, ^7J(F11–F1) 3.8
5	139.20 ddd ^3J(F1–F2) 21.8, ^4J(F1–H3) 7.6 ^6J(F1–H12) 3.1	133.73 dd ^3J(F2–F1) 21.6 ^3J(F2–H3) 10.7	–	–	–
6	137.10 ddd ^3J(F1–F2) 21.3, ^4J(F1–H3) 8.1 ^6J(F1–H12) 2.9	132.86 dd ^3J(F2–F1) 21.1 ^3J(F2–H3) 10.3	–	–	–
7	127.86 ddd ^3J(F1–F2) 21.5, ^4J(F1–F3) 8.1 ^6J(F1–H12) 2.5	160.62 dd ^3J(F2–F1) 20.7 ^3J(F2–F3) 19.9	146.70 dd ^3J(F3–F2) 19.9 ^4J(F3–F1) 8.1	–	–
8	130.5 ddd ^3J(F1–F2) 21.8, ^4J(F1–H3) 7.9 ^6J(F1–H12) 2.5	134.6 dd ^3J(F2–F1) 21.8 ^3J(F2–H3) 10.6	–	–	–
9	127.95 dddd ^3J(F1–F2) 20.9, ^4J(F1–H3) 8.9 ^6J(F1–H12) 3.4, ^7J(F1–H11) 2.9	131.93 dd ^3J(F2–F1) 20.9 ^3J(F2–H3) 10.2	–	–	–
10	138.94 ddd ^3J(F1–F2) 21.1, ^4J(F1–H3) 7.8 ^6J(F1–H12) 3.7	132.59 dd ^3J(F2–F1) 21.0 ^3J(F2–H3) 10.1	–	–	–

butylamine afforded mixtures of 1- and 2-monosubstituted products.

The behavior of 1,2,3-trifluoro derivatives of fused quinolones in amino-defluorination reactions is somewhat different, as exemplified by the reactions of (**1**) and (**3**) with pyrrolidine in refluxing pyridine. The ester (**1**) was transformed under these conditions into 1-pyrrolidinylsubstituted ethyl 8-methyl-2,3,10,11-tetrafluoro-4-oxo-4H-benzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline-5-carboxylate (**13**) and further into acid (**14**). It follows from the ^{19}F NMR spectra of compounds (**13**) and (**14**) in which the signal of F3 appears as a doublet with ^3J(F3–F2) 20.0 Hz, while the F2 resonance is observed as a double triplet with ^3J(F2–F3) 20.0 Hz and ^5J(F2–H5′) 3.0 Hz due to coupling of F2 with the CH_2 protons of the pyrrolidine moiety (Table 4). Also the ^{19}F NMR spectra of compounds (**13**) and (**14**) F11 is coupled with the pyrrolidine protons and appears as dddd, demonstrating an additional coupling constant ^9J(F11–H2′) 3.0–3.5 Hz, over the F10 signal (ddd) (Table 4). The reaction of (**3**) with pyrrolidine gave the diamino derivative (**15**), as shown unequivocally by its ^{19}F NMR spectrum in which the signal of F2 appears as a singlet (Table 4).

In conclusion, it is worth noting that annelation of the benzazolotriazine fragment to the fluoroquinolone skeleton affects both ^{1}H and ^{19}F NMR spectroscopic characteristics, as well as the relative reactivities of fluorine atoms in the amino-defluorination reactions.

Table 3
^{1}H NMR spectral data for new fluoroquinolones (**11**)–(**15**) in DMSO-d_6

Compounds	Characteristics, δ (ppm), ^nJ (Hz)					
	H6	H3	COOEt (COOH)	H9–H12	NCH_3	Pyrrolidine substituent
11	8.15 s	6.83 d ^4J(H3–F1) 8.2	1.31 t (3H, CH_3) 4.27 q (2H, OCH_2)	7.1 m (1H), 7.2 m (1H), 7.4 m (1H)	3.37 s	1.97 m (4H, $(CH_2)_2$) 3.43 m (4H, $N(CH_2)_2$)
12	8.23 s	6.99 s	15.6 br. s (1H, COOH)	7.3 m (4H)	–	1.85 m (4H, $(CH_2)_2$) 1.98 m (4H, $(CH_2)_2$) 3.35 m (4H, $N(CH_2)_2$) 3.59 m (4H, $N(CH_2)_2$)
13	7.99 s	–	1.26 t (3H, CH_3) 4.16 q (2H, OCH_2)	7.40 dd (2H, H9, H12) ^3J(H9–F10) 10.5, ^4J(H9–F11) 7.2	3.34 s	1.88 m (4H, $(CH_2)_2$) 3.27 m (4H, $N(CH_2)_2$)
14	8.16 s	–	15.4 br. s (1H, COOH)	7.43 dd (1H, H12) ^3J(H12–F11) 11.3, ^4J(H12–F10) 7.2; 7.45 dd (1H, H9) ^3J(H9–F10) 11.3, ^4J(H9–F11) 7.2	3.41 s	1.90 m (4H, $(CH_2)_2$) 3.36 m (4H, $N(CH_2)_2$)
15	8.23 s	–	15.8 br. s (1H, COOH)	7.07 dd (1H, H9) ^3J(H9–F10) 11.1, ^4J(H9–F11) 7.2; 7.67 ddd (1H, H12) ^3J(H12–F11) 11.1, ^4J(H12–F10) 7.2, ^8J(H12–H2′) 3.9	3.34 s	1.76 m (4H, $(CH_2)_2$) 1.95 m (4H, $(CH_2)_2$) 3.36 m (8H, $2N(CH_2)_2$)

Table 4
^{19}F NMR and mass-spectral data for new fluoroquinolones (**11**)–(**15**)

Compounds	Characteristics, δ_F (ppm) ^nJ, Hz in DMSO-d_6					m/z (I_{rel}, %)
	F1	F2	F3	F10	F11	
11	128.61 dd ^4J(F1–H3) 7.9 ^6J(F1–H12) 3.1	–	–	–	–	
12	–	–	–	–	–	473 (M^+, 100%) 429 (69), 400 (8) 360 (10), 333 (21)
13	–	137.69 dt ^3J(F2–F3) 19.6 ^5J(F2–H2′) 3.4	149.99 d ^3J(F3–F2) 20.3	146.78 ddd ^3J(F10–F11) 21.5 ^3J(F10–H9) 11.6 ^4J(F10–H12) 7.1	144.19 dddd ^3J(F11–F10) 21.5 ^3J(F11–H12) 11.1 ^4J(F11–H12) 7.0 ^9J(F11–H5′) 3.5	501 (M^+, 17%) 472 (14), 452 (38) 432 (33), 407 (32) 386 (72), 360 (100) 345 (50)
14	–	146.06 dt ^3J(F2–F3) 19.6 ^5J(F2–H2′) 2.5	135.05 d ^3J(F3–F2) 19.6	145.92 ddd ^3J(F10–F11) 21.3 ^3J(F10–H9) 11.4 ^4J(F10–H12) 7.2	143.12 dddd ^3J(F11–F10) 21.3 ^3J(F11–H12) 10.7 ^4J(F11–H9) 6.9 ^9J(F11–H5′) 3.3	473 (M^+, 28%) 453 (21), 407 (29) 387 (21), 386 (86) 360 (100), 345 (72) 305 (16), 228 (21)
15	–	129.97 s	–	147.61 ddd ^3J(F10–F11) 21.9 ^3J(F10–H9) 11.2 ^4J(F10–H12) 7.5	144.37 ddd ^3J(F11–F10) 21.9 ^3J(F11–H12) 10.4 ^4J(F11–H9) 7.2	

3. Experimental

The ^{1}H and ^{19}F NMR Spectra in DMSO-d_6 were recorded on Bruker WH-250, DRX-500 and DRX-400 spectrometers operating at 250 and 500 MHz (^{1}H), and 376 MHz (^{19}F), respectively. All spectral data are reported in ppm in the δ-scale relative to internal TMS (^{1}H NMR) or hexafluorobenzene (^{19}F NMR), respectively. Compounds (**1**)–(**10**) were described earlier [15,16].

*3.1. Preparation of ethyl 1-fluoro-2-(pyrrolidin-1-yl)-4-oxo-4H-8-methylbenzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-i,j]quinoline-5-carboxylate (**11**)*

Pyrrolidine (172 mg, 0.2 cm^3; 0.0028 mol) was added to a solution of compound (**5**) (150 mg, 0.0004 mol) in pyridine (5 cm^3). The reaction mixture was refluxed for 5 h and cooled. The precipitate obtained was filtered off and recrystallized from DMSO to give ethyl 1-fluoro-2-(pyrrolidin-

1-yl)-4-oxo-4H-8-methylbenzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline-5-carboxylate (**11**), (110 mg; 61%) mp > 250°C. Calculated for $C_{24}H_{22}FN_5O_3$, C (64.43), H (4.92), N (15.66)%, found C (64.21), H (4.67), N (15.85)%.

*3.2. 1,2-Bis(pyrrolidin-1-yl)-4-oxo-4H-benzthiazolo-[2′,3′:3,4]-1,2,4-triazino-[5,6,1-i,j]quinoline-5-carboxylic acid (**12**)*

Pyrrolidine (516 mg, 0.6 cm^3; 0.0085 mol) was added to a solution of quinolinecarboxylic acid (**9**) (500 mg, 0.00125 mol) in pyridine (15 cm^3). The reaction mixture was refluxed for 5 h and cooled and diluted with water (20 cm^3). The precipitate obtained was filtered off and recrystallized from DMSO to give 1,2-bis(pyrrolidin-1-yl)-4-oxo-4H-benzthiazolo-[2′,3′:3,4]-1,2,4-triazino-[5,6,1-*i,j*]quinoline-5-carboxylic acid (**12**), (500 mg, 85%) mp > 250°C. Calculated for $C_{25}H_{23}N_5O_3S$, C (63.41), H (4.90), N (14.79)%, found C (63.28), H (5.15), N (14.59)%.

*3.3. Preparation of ethyl 1-(pyrrolidin-1-yl)-2,3,10,11-tetrafluoro-8-methyl-4-oxo-4H-benzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-i,j]quinoline-5-carboxylate (**13**)*

Pyrrolidine (327 mg, 0.38 cm^3; 0.00443 mol) was added to a solution of (**1**) (650 mg, 0.00148 mol) in pyridine (10 cm^3). The reaction mixture was refluxed for 5 h and cooled. The precipitate obtained was filtered off, washed with ethanol and recrystallized from DMSO to give ethyl 1-(pyrrolidin-1-yl)-2,3,10,11-tetrafluoro-8-methyl-4-oxo-4H-benzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline-5-carboxylate (**13**), (600 mg, 81%) mp 268–270°C. Calculated for $C_{24}H_{19}F_4N_5O_3$, C (57.49), H (3.82), N (13.97)%, found C (57.22), H (4.03), N (13.78)%.

*3.4. 1-(Pyrrolidin-1-yl)-2,3,10,11-tetrafluoro-8-methyl-4-oxo-4H-benzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-i,j]quinoline-5-carboxylic acid (**14**)*

A solution of (**13**) (500 mg, 0.001 mol) in a mixture of HCl and acetic acid (1:4, 20 cm^3) was refluxed for 3 h, cooled and diluted with water (30 cm^3). The precipitate obtained was filtered off and recrystallized from DMF to give 1-(pyrrolidin-1-yl)-2,3,10,11-tetrafluoro-8-methyl-4-oxo-4H-benzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]-quinoline-5-carboxylic acid (**14**), (400 mg, 85%) mp 262–264°C. Calculated for $C_{22}H_{15}F_4N_5O_3$, C (55.82), H (3.19), N (14.80)%, found C (55.59), H (3.41), N (14.62)%.

*3.5. 1,3-Bis(pyrrolidin-1-yl)-2,10,11-trifluoro-8-methyl-4-oxo-4H-benzimidazolo[2′,3′:3,4]-1,2,4-triazino[5,6,1-i,j]quinoline-5-carboxylic acid (**15**)*

Pyrrolidine (138 mg, 0.16 cm^3; 0.00188 mol) was added to a solution of quinoloncarboxylic acid (**3**) (200 mg, 0.00047 mol) in pyridine (5 cm^3), and the reaction mixture was refluxed for 5 h. Removal of solvent gave a solid which was recrystallized from ethanol to yield 1,3-bis(pyrrolidin-1-yl)-2,10,11-trifluoro-8-methyl-4-oxo-4H-benzimidazolo-[2′,3′:3,4]-1,2,4-triazino[5,6,1-*i,j*]quinoline-5-carboxylic acid (**15**), (400 mg, 85%) mp 194–196°C. Calculated for $C_{26}H_{23}F_3N_6O_3$, C (59.54), H (4.56), N (16.23)%, found C (59.54), H (4.42), N (16.02)%.

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