Novel pentacyclic fluoroquinolones

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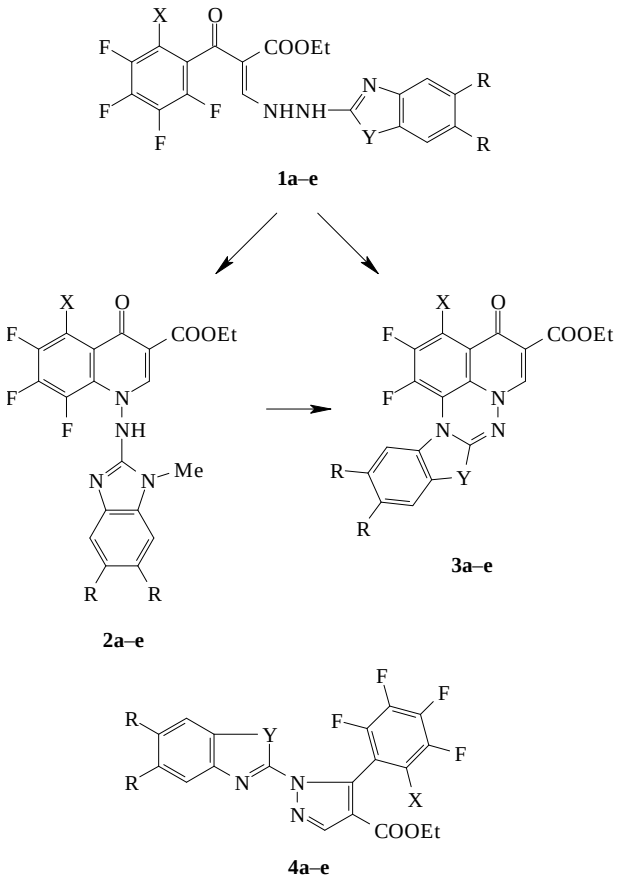
Heating of ethyl 3-[β-(benzazol-2-yl)hydrazino]-2-(polyfluorobenzoyl)acrylates in acetonitrile with DBU yields derivatives of 4-oxo-4*H*-benzazolo[2′,3′:3,4][1,2,4]triazino[5,6,1-*i*,*j*]quinoline-5-carboxylic acids, representing a novel heterocyclic system.

A whole number of papers have recently appeared dedicated to tetracyclic derivatives of the so-called 'fluoroquinolone' family of antibacterials;[1–4] some of these compounds have proved to be more active than ofloxacin and seem to be rather promising antibacterial actives, in particular the compound KB-5246.[1] Pentacyclic fluoroquinolones have not hitherto been described in the literature.

We have suggested that modifying the position N-1 in 8-fluoro-substituted 4-oxoquinoline-3-carboxylic acids with residues of 2-amino-1-azaheterocycles capable of amino–imino tautomerism may be a prerequisite for further intramolecular cyclizations leading to [*i*,*j*]-condensed quinolones. In order to reach this goal 3-[β-(benzazol-2-yl)hydrazino]-2-(polyfluorobenzoyl)acrylates **1** were prepared and their plausible cyclizations in refluxing acetonitrile in the presence of potassium fluoride or triethylbenzylammonium chloride (TEBA) were studied. It has already been reported, however,[5] that under these conditions compounds **1** are converted into 2-(5-polyfluorophenyl-4-ethoxycarbonyl-pyrazol-1-yl)benzimidazoles; in addition, benzimidazo[1,2-*a*]-pyrazolo[1,5-*c*]quinazoline derivatives are formed provided the imidazole fragment in **1** bears an NH moiety (Y = NH). From these data it follows that in order to convert acrylates **1** into [*i*,*j*] condensed fluoroquinolones the following conditions need to be fulfilled: i, the possibility for closure of the pyrazole ring has to be excluded, which is true if Y in **1** is either an NR (R ≠ H) substituent or other heteroatom; ii, a proper base facilitating intramolecular substitution of F-8 has to be found.



Scheme 1

In this paper we wish to report that we have succeeded in finding appropriate conditions for the synthesis of pentacyclic fluoroquinolones **3a**–**e**. When compounds **1a**–**e** (Y = NCH_3 or S) were refluxed in acetonitrile for 1 h with diazabicycloundec-7-ene (DBU), derivatives of a novel heterocyclic system of 4-oxo-4*H*-benzazolo[2′,3′:3,4][1,2,4]triazino[5,6,1-*i*,*j*]quinolin-5-carboxylic acid **3a**–**e** were obtained in 50–72% yields (Scheme 1).† It has been suggested that compounds **3** are derived from intramolecular cyclization of bicyclic fluoroquinolones **2**. Indeed, reflux of acrylates **1a**–**e** in dry acetonitrile or dioxane in the presence of base was found to give mixtures of **2** and **3** (Table 1). Individual 1-aminobenzazolyl-substituted quinolone **2a** (X = F, Y = NCH_3 and R = F) was successfully isolated in 58% yield only in one case, *i.e.* on heating **1a** in acetonitrile in the presence of TEBA.‡ Reflux of **2a** in acetonitrile for 1 h in the presence of DBU gave pentacyclic derivative **3a** in 88% yield. It should also be noted that transformation of **1** into **2** and **3** is always accompanied by the formation of 2-(5-polyfluorophenyl-4-ethoxycarbonyl-pyrazol-1-yl)benzazoles **4** (10–30%), described earlier.[5]

Evidence for the structure of compounds **3a**–**e** is provided by ^1H and ^{19}F NMR and mass spectrometric data as well as by the X-ray analysis performed for **3d**.§

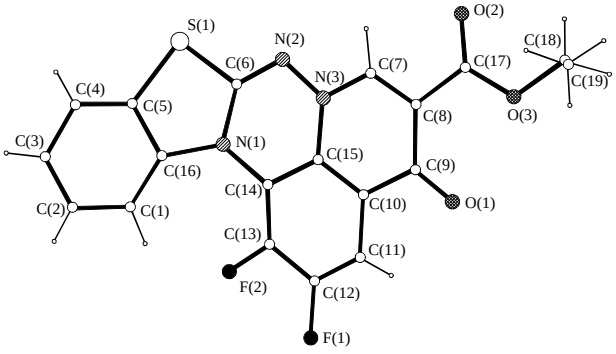


Figure 1 Molecular structure and numbering of atoms for the compound **3d**.

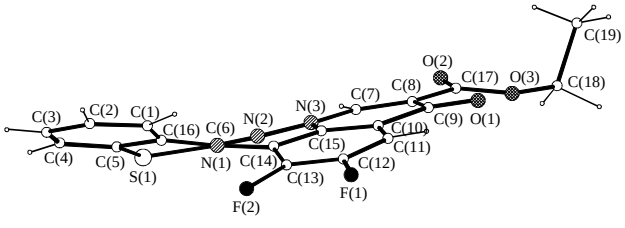


Figure 2 Projection of the molecule **3d** into the plane which is normal to the averaged plane of the polycyclic system.

X-ray analysis of compound **3d**¶ has revealed that it consists of 5 unsaturated rings (Figure 1). Unlike other condensed aromatic systems, the planarity of **3d** is destroyed considerably, so that all condensed rings are not coplanar to each other. Indeed, the benzene ring A and the thiazole ring B planes conform to an angle of 5.9°; the triazine ring C is fused with the pyridone fragment D and the benzene ring E, forming dihedral angle of 3.7 and 10.3°, respectively; the dihedral angle between the rings D and E of the quinolone fragment is 6.7°. The mutual orientation of these planes is clearly seen in Figure 2, which shows a projection of the molecule into the plane which is normal to the averaged plane of the polycyclic system. It is obvious that the reason for such deviations from planarity in the polycyclic system **3d** is steric hindrance between the hydrogen atom at C(1) and the fluorine atom at C(13). If the rings A and E were planar, the distance between F(2) and H(1) would be too small (< 2.0 Å), which is not admissable. Violation of the planarity in **3d** (the angle between the rings A and E is 28.8°) extends the distance F(2)–H(1) to a normal value (2.32 Å). Other geometrical parameters for the molecule **3d** proved to be quite normal for such heterocyclic systems.[6]

† *General procedure for the synthesis of fluorinated derivatives of* 4-*oxo*-4*H*-*benzazolo*[2′,3′:3,4][1,2,4]*triazino*[5,6,1-*i*,*j*]*quinoline*-5-*carboxylic acid* **3a**–**e**.

(*a*) A solution of ethyl 3-[β-(1-methyl-5,6-difluorobenzimidazol-2-yl)-hydrazino]-2-(pentafluorobenzoyl) acrylate **1a** (1.5 g, 3 mmol) and DBU (1 ml, 6 mmol) in acetonitrile (50 ml) was kept under reflux for 1 h. The precipitate of **3a** obtained after cooling the reaction solution to room temperature was filtered off and recrystallized from DMF. Yield 0.7 g (51%), mp > 250 °C. Mass spectrum, *m*/*z* 450 (100%), 405 (8), 378 (54), 363 (35), 294 (11); ^{1}H NMR ([$^2H_6$]DMSO): δ 1.25 (t, 3H, CH_3), 3.3 (s, 3H, N–CH_3), 4.2 (q, 2H, OCH_2CH_3), 7.3–7.7 (m, 2H, arom.), 8.2 (s, 1H, 6-H); ^{19}F NMR ([$^2H_6$]DMSO): δ 161.8 (m, 1F), 146.2 (m, 2F), 143.1 (m, 1F), 135.6 (m, 1F). Some physical characteristics for other compounds (melting point, solvent for recrystallization, and NMR spectral data) are given below: **3b**, 262–264 °C, acetonitrile, ^{1}H NMR ([$^2H_6$]DMSO): δ 1,26 (t, 3H, CH_3), 4.18 (q, 2H, OCH_2CH_3), 7.2–7.8 (m, 4H, arom.), 8.27 (s, 1H, 6-H); ^{19}F NMR ([$^2H_6$]DMSO): δ 160.5 (m, 1F), 146.0 (m, 1F), 124.5 (m, 1F); **3c**, > 300 °C, DMF, ^{1}H NMR ([$^2H_6$]DMSO): δ 1.38 (t, 3H, CH_3), 3.43 (s, 3H, N–CH_3), 4.34 (q, 2H, OCH_2CH_3), 7.03–8.02 (m, 3H, arom.), 8.55 (s, 1H, 6-H); ^{19}F NMR ([$^2H_6$]DMSO): δ 144.2 (m, 1F), 141.0 (m, 1F), 137.4 (m, 1F), 132.8 (m, 1F); **3d**, 248–250 °C, DMF, ^{1}H NMR ([$^2H_6$]DMSO): δ 1.33 (t, 3H, CH_3), 4.2 (q, 2H, OCH_2CH_3), 7.19–7.81 (m, 5H, arom.), 8.34 (s, 1H, 6-H); ^{19}F NMR ([$^2H_6$]DMSO): δ 134.6 (m, 1F), 130.4 (m, 1F); **3e**, 268–270 °C, DMF, ^{1}H NMR ([$^2H_6$]DMSO): δ 1.6 (t, 3H, CH_3), 3.68 (s, 3H, N–CH_3), 4.75 (q, 2H, OCH_2CH_3), 7.3–8.1 (m, 5H, arom.), 8.95 (s, 1H, 6-H); ^{19}F NMR ([$^2H_6$]DMSO): δ 137.3 (m, 1F), 133.1 (m, 1F).

(*b*) A solution of **1a** (1.7 g, 3.5 mmol) and KF (0.2 g, 35 mmol) in acetonitrile (60 ml) was kept under reflux for 4 h. The precipitate of **3a** obtained after cooling the reaction solution to room temperature was filtered off, washed with water and recrystallized from DMF (0.65 g, 42%), mp 245 °C. The reaction solution was diluted with water (60 ml), and the precipitate obtained was filtered off and recrystallized from ethanol affording 1-methyl-5,6-difluoro-2-(5-pentafluorophenyl-4-ethoxy-carbonyl-pyrazol-1-yl)benzimidazole **4a** (0.55 g, 35%), mp 134 °C.

(*c*) A solution of ethyl 1-(1′-methyl-5′,6′-difluorobenzimidazol-2′-yl)-amino-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **2a** (0.5 g, 1.06 mmol) and DBU (0.35 ml, 2.1 mmol) in acetonitrile (20 ml) was kept under reflux for 1 h. Cooling to room temperature gave a precipitate of **3a** which was filtered off and recrystallized from DMF yielding 0.42 g (88%), mp > 250 °C.

1,2-*Difluoro*-4-*oxo*-4*H*-*benzthiazolo*[2′,3′:3,4][1,2,4]*triazino*[5,6,1-*i*,*j*]-*quinoline*-5-*carboxylic acid.* To a suspension of ethyl 3-[β-(benzthiazol-2-yl)-hydrazino]-2-(2,3,4,5-tetrafluorobenzoyl) acrylate **3d** (2.5 g, 5.7 mmol) in dry dioxane (25 ml) was added, portionwise, a 50% suspension of NaH in oil (0.75 g, 15.6 mmol) at room temperature. The reaction mixture was heated and kept under reflux for 4 h. After being cooled to room temperature 0.5 ml of ethanol and 25 ml of water were added. Some acetic acid was then added to the reaction mixture to reach pH 6–7. The precipitate obtained was filtered off, washed with water and recrystallized from DMF to yield 1.5 g (71.5%) of 1,2-difluoro-4-oxo-4*H*-benzthiazolo-[2′,3′:3,4][1,2,4]triazino[5,6,1-*i*,*j*]quinoline-5-carboxylic acid, mp 300 °C. ^{1}H NMR ([$^2H_6$]DMSO): δ 7.3–7.95 (m, 5H, arom.), 8.53 (s, 1H, H-6), 14.70 (s, 1H, COOH). ^{19}F NMR ([$^2H_6$]DMSO): δ 131.75 (m, 1F), 127.6 (m, 1F).

‡ *Ethyl* 1-(1′-*methyl*-5′,6′-*difluorobenzimidazol*-2′-*yl*)*amino*-5,6,7,8-*tetra-fluoro*-4-*oxo*-1,4-*dihydroquinoline*-3-*carboxylate* **2a**. A solution of ethyl 3-[β-(1-methyl-5,6-difluorobenzimidazol-2-yl)hydrazino]-2-(pentafluoro-benzoyl) acrylate **1a** (2 g, 4 mmol) and triethylbenzylammonium chloride (1.8 g, 8 mmol) in acetonitrile (40 ml) was refluxed for 4 h. After being cooled to room temperature the precipitate obtained was filtered off, washed with water and recrystallized from DMF to yield 1.1 g (58%) of **2a**, mp 242–244 °C. Mass spectrum, *m*/*z* 470 (M^+, 12%), 450 (10), 397 (28), 378 (14), 333 (30), 289 (40), 243 (100), 187 (27), 168 (29); ^{1}H NMR ([$^2H_6$]DMSO): δ 1.3 (t, 3H, CH_3), 3.3 (s, 3H, N–CH_3), 4.2 (q, 2H, OCH_2CH_3), 6.9–7.6 (m, 2H, arom.), 8.3 (s, 1H, H-2), 11.5 (s, 1H, NH); ^{19}F NMR ([$^2H_6$]DMSO): δ 162.3 (m, 1F), 152.6 (m, 1F), 150.3 (m, 1F), 147.5 (m, 1F), 146.7 (m, 1F), 144.4 (m, 1F). The reaction solution was diluted with water (40 ml), affording a precipitate which was filtered off and recrystallized from ethanol to yield 1-methyl-5,6-difluoro-2-pentafluorophenyl-4-ethoxycarbonyl-pyrazol-1-yl)benzimidazole **4a** (0.35 g, 18%), mp 134 °C. Mass spectrum, *m*/*z* 472 (M^+, 100%), 453 (60), 443 (15), 427 (15), 425 (25); ^{1}H NMR ([$^2H_6$]DMSO): δ 1.29 (t, 3H, CH_3), 3.86 (s, 3H, N–CH_3), 4.3 (q, 2H, OCH_2CH_3), 7.19–7.43 (m, 2H, arom.), 8.36 (s, 1H, H-3).

Table 1 Reaction conditions and yields of fluoroquinolones **2** and **3** resulting from ethyl 3-[β-(benzazol-2-yl)hydrazino]-2-(polyfluorobenzoyl) acrylates **1** on reflux in acetonitrile or dioxane.

Starting material	Base used	Solvent	Reaction time/h	Products (yields,%)
1a	KF	MeCN	4	**3a** (42) + **4a** (35)
	TEBA	MeCN	4	**2a** (58) + **4a** (18)
	DBU	MeCN	1	**3a** (51)
1b	DBU	MeCN	1	**3b** (67)
1c	DBU	MeCN	1	**3c** (19) + **4c** (56)
	NaH	dioxane	2	**2c** (56)+ **3c** (25)
1d	DBU	MeCN	2	**3d** (11) + **4d** (62)
	NaH	dioxane	4	**3d** (72)[a]
1e	DBU	MeCN	2	**3e** (44)
	NaH	dioxane	2	**2e** (42)+ **3e** (36)

[a]Product was isolated as 1,2-difluoro-4-oxo-4*H*-benzthiazolo[2′,3′:3,4]-triazino[5,6,1-*i*,*j*]quinoline-5-carboxylic acid.

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¶ Experimental X-ray crystallographic data for **3d** were obtained at 20 °C on a 'CAD-4' diffractometer (λ MoKα, graphite monochromator, ω-scan, $2\theta_{max}$ = 60°). The structure was solved by a direct method and refined by a full-matrix least-squares method in an anisotropic approximation (isotropic – for hydrogen atoms) using programs SHELX-76 to R = 0.060 (R_w = 0.064) for 3146 independent reflections with $F^2 > 3\sigma I$; $F(000)$ = 408, largest diff. peak and hole are 0.711 and –0.545 e Å^{-3}, respectively. The Lorentz polarisation correction was applied. Empirical formula $C_{19}H_{11}F_2N_3O_3S$, triclinic crystals, space group $P\bar{1}$, a = 8.262(1) Å, b = 8.857(3) Å, c = 11.746(5) Å, α = 105.50(3)°, β = 93.82(3)°, γ = 95.67(3)°, V = 820.3(9) Å^3, d_{calc} = 1.617 g cm^{-3}, Z = 2. Full lists of bond angles, bond lengths and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1997, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/15.