1,3,4-Oxa(thia)diazino [*i,j*]-annelated quinolines: a new type of key intermediate in the synthesis of tricyclic fluoroquinolones

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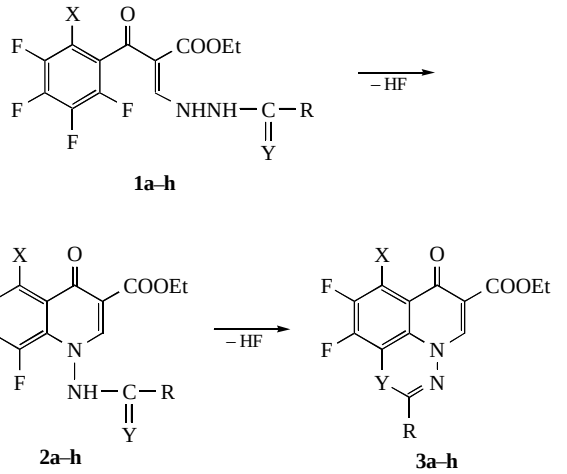
The synthesis of new derivatives of 1,3,4-oxa(thia)diazino[6,5,4-*i,j*]quinolines, which have a structure that is very similar to the ofloxacin skeleton, by intramolecular cyclizations of ethyl 3-(R-carbonylhydrazino)- and 3-(R-thiocarbonylhydrazino)-substituted 2-polyfluorobenzoyl acrylates, is described.

6-Fluoroquinolones are a well-known class of fully synthetic antibacterials. During the last decade an enormous amount of data on their structural modifications have been accumulated in the literature.[1–4] Condensed derivatives of 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid are of special interest since some of them possess not only antibacterial, but also antiviral and anticancer activity.[1,5–7] The most important representatives of condensed fluoroquinolones are ofloxacin and its active enantiomer levofloxacin which are characterized chemically by a tricyclic structure of 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*d,e*][1,4]benzoxazine-6-carboxylic acid.[2–4]

We have recently described a new approach to the synthesis of pentacyclic fluoroquinolones which is based on intramolecular cyclizations of 3-(azol-2-yl)hydrazino substituted 2-(polyfluorobenzoyl)acrylates.[8,9] In continuation of our studies on the reactions of 3-hydrazino substituted 2-(polyfluorobenzoyl)-acrylates we wish to report on the synthesis of novel derivatives of 9,10-difluoro-7-oxo-7*H*-pyrido[1,2,3-*d,e*][1,3,4]-benzoxa(thia)-diazine-6-carboxylic acids. These tricyclic 1,3,4-oxadiazino- and 1,3,4-thiadiazino[6,5,4-*i,j*] annelated quinolines have a very similar skeleton to ofloxacin and can be regarded as aza- and thia-analogues. Moreover, derivatives of 1,3,4-thiadiazino[*i,j*] fused quinolines represent a new heterocyclic system, and seem to be a new type of key intermediate in the synthesis of tricyclic fluoroquinolones.

We have found that heating ethyl 3-hydrazino-2-polyfluoro-benzoyl acrylates **1a**–**h**, bearing pyridin-3-carbonyl, pyridin-4-carbonyl or cycloalkylaminocarbonyl substituents at N(2), in toluene or acetonitrile in the presence of KF for 1–3 h, is sufficient to cause nucleophilic displacement of two fluorine atoms, thus affording derivatives of 7-oxo-7*H*-pyrido[1,2,3-*d,e*][1,3,4]-benzoxa(thia)diazine-6-carboxylic acids **3a**–**h** in 48–87% yields (Scheme 1).† Starting materials **1a**–**h** were obtained in high yields (70–90%) from the reaction of ethyl 3-ethoxy-2-[tetra(penta)fluorobenzoyl]acrylates with hydrazides of nicotinic or isonicotinic acids and cycloalkylamino-substituted thiosemicarbazides in dry toluene or ethanol at room temperature. All compounds **1a**–**h** gave satisfactory elemental analysis, NMR and mass spectroscopic data.



a X = H, Y = O, R = pyridin-4-yl
b X = H, Y = O, R = pyridin-3-yl
c X = F, Y = O, R = pyridin-4-yl
d X = F, Y = O, R = pyridin-3-yl
e X = H, Y = S, R = hexamethylenimin-1-yl
f X = H, Y = S, R = pyrrolidin-1-yl
g X = F, Y = S, R = hexamethylenimin-1-yl
h X = F, Y = S, R = pyrrolidin-1-yl

Scheme 1

Tricyclic compounds **3a**–**h** are formed through the intermediate bicyclic fluoroquinolones **2a**–**h**. This path is substantiated by ^{1}H and ^{19}F NMR studies which revealed the formation of mixtures of **2a**–**d** and **3a**–**d** during the course of the reaction. Individual quinolone **2a** (X = H, Y = O, R = pyridin-4-yl) could be isolated in 40% yield only in one case, *i.e.* on heating acrylate **1a** in toluene for 1 h.‡ Refluxing **2a** in toluene for 2 h gave tricyclic derivative **3a** in 85% yield. However, we failed to obtain compounds **2e**–**h** since their cyclizations into tricyclic quinolones **3e**–**h** proceed much faster than those of **1a**–**d**.

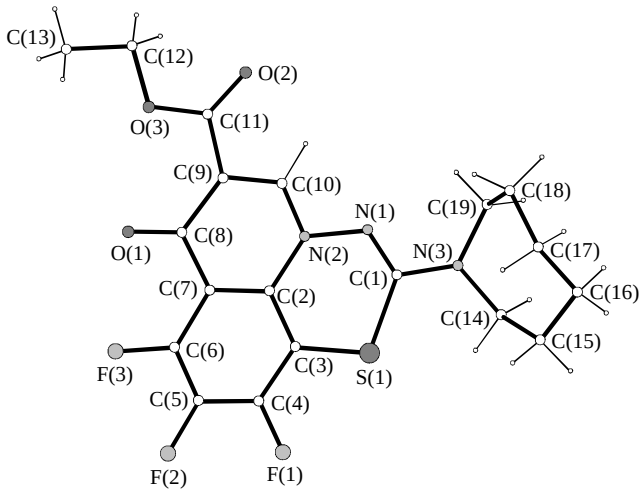


Figure 1 Molecular structure of compound **3g**. Numeration of atoms does not correspond to the IUPAC nomenclature. Selected bond lengths/Å and angles/° for compound **3g**: S(1)–C(1) 1.77(1), S(1)–C(3) 1.74(1), F(1)–C(4) 1.35(1), F(2)–C(5) 1.33(1), F(3)–C(6) 1.34(1), O(1)–C(8) 1.24(1), N(1)–C(1) 1.27(1), N(2)–C(2) 1.40(1), N(2)–C(10) 1.34(1), N(3)–C(1) 1.38(1), C(2)–C(3) 1.42(1), C(2)–C(7) 1.40(1), C(3)–C(4) 1.40(1), C(4)–C(5) 1.38(1), C(5)–C(6) 1.35(1), C(6)–C(7) 1.42(1), C(7)–C(8) 1.49(1), C(8)–C(9) 1.46(1), C(9)–C(10) 1.37(1), C(9)–C(11) 1.49(1); C(1)–S(1)–C(3) 99.1(5), C(2)–N(2)–C(10) 120.1(7), C(1)–N(3)–C(14) 123.3(8), S(1)–C(1)–N(1) 128.7(7), S(1)–C(1)–N(3) 113.1(7), N(1)–C(1)–N(3) 118.1(9), N(2)–C(2)–C(3) 118.5(8), N(2)–C(2)–C(7) 119.4(8), C(3)–C(2)–C(7) 122.1(8), S(1)–C(3)–C(2) 125.3(7), S(1)–C(3)–C(4) 118.5(7), C(2)–C(3)–C(4) 116.1(9), F(1)–C(4)–C(3) 116.4(9), F(1)–C(4)–C(5) 120.3(9), C(3)–C(4)–C(5) 123.2(9), F(2)–C(5)–C(4) 117.8(9), F(2)–C(5)–C(6) 123.2(9), C(4)–C(5)–C(6) 119.0(9), F(3)–C(6)–C(5) 116.0(8), F(3)–C(6)–C(7) 121.4(8), C(5)–C(6)–C(7) 122.5(9), C(2)–C(7)–C(6) 116.9(8), C(2)–C(7)–C(8) 122.4(8), C(6)–C(7)–C(8) 120.7(8), O(1)–C(8)–C(7) 122.1(9), O(1)–C(8)–C(9) 124.6(9), C(7)–C(8)–C(9) 113.3(8), C(8)–C(9)–C(10) 120.3(8), C(8)–C(9)–C(11) 125.7(8), C(10)–C(9)–C(11) 114.0(8), N(2)–C(10)–C(9) 124.5(8).

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

X-Ray analysis of compound **3g**¶ revealed that it represents a fused tricyclic system bearing three fluorine atoms, ethoxycarbonyl and azacycloheptane substituents (Figure 1). The tricyclic system is nearly planar, the dihedral angle between planes of the quinoline fragment and the fused six-membered thiadiazine ring being 3.1°. The azacycloheptane fragment adopts a chair conformation, with the N(3), C(14), C(16) and C(17) atoms almost coplanar and deviations of the C(15), C(18) and C(19) atoms from this average plane of –0.64, 0.89 and 1.17 Å, respectively.

† *General procedure for the synthesis of* 9,10-*difluoro*-7-*oxo*-7*H*-2-[*pyridin*-3(4)-*yl*]*pyrido*[1,2,3-*d*,*e*][1,3,4]-*benzoxa*(*thia*)*diazine*-6-*carboxylic acid* **3a–d**: (*a*) A solution of ethyl 3-[(pyridin-4-yl)-hydrazido]-2-(tetrafluorobenzoyl)acrylate **1a** (0.5 g, 1.2 mmol) in dry toluene (20 ml) was kept under reflux for 2 h. The reaction solution was filtered at the end of the reaction. The filtrate was evaporated and the precipitate obtained was recrystallized from propan-2-ol to yield **3a** (0.25 g, 56%), mp 244–246 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.30 (t, 3H, Me), 4.23 (q, 2H, OC*H*$_2$CH$_3$), 7.63 (dd, 1H, 8-H, ^3J 11 Hz, ^4J 7.5 Hz), 7.88 (dd, 2H, 2′,6′-H, ^3J 4.5 Hz, ^4J 1.5 Hz), 8.56 (s, 1H, 5-H), 8.85 (dd, 2H, 3′,5′-H, ^3J 4.5 Hz, ^4J 1.5 Hz); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 154.24 (dd, 1F, 10-F, $^3J_{FF}$ 22 Hz, $^4J_{FH}$ 7.5 Hz), 134.51 (dd, 1F, 9-F, $^3J_{FF}$ 22 Hz, $^3J_{FH}$ 11 Hz); *m*/*z*: 371 (50%, M$^+$), 326 (51), 299 (100).

3b, mp 216–218 °C (propan-2-ol). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.30 (t, 3H, Me), 4.23 (q, 2H, OC*H*$_2$CH$_3$), 7.64 (dd, 1H, 8-H, ^3J 10.4 Hz, ^4J 7.6 Hz), 7.67 (ddd, 1H, 5′-H, $^3J_{5'\text{-H},6'\text{-H}}$ 8.1 Hz, $^3J_{5'\text{-H},4'\text{-H}}$ 4.9 Hz, $^5J_{5'\text{-H},2'\text{-H}}$ 0.8 Hz), 8.32 (ddd, 1H, 6′-H, $^3J_{6'\text{-H},5'\text{-H}}$ 8.1 Hz, $^4J_{6'\text{-H},4'\text{-H}}$ 2.3 Hz, $^4J_{6'\text{-H},2'\text{-H}}$ 1.5 Hz), 8.57 (s, 1H, 5-H), 8.85 (dd, 1H, 4′-H, $^3J_{4'\text{-H},5'\text{-H}}$ 4.9 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ 2.3 Hz), 9.14 (dd, 1H, 2′-H, $^5J_{2'\text{-H},5'\text{-H}}$ 0.8 Hz, $^4J_{2'\text{-H},6'\text{-H}}$ 1.5 Hz); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 154.24 (dd, 1F, 10-F, $^3J_{FF}$ 22 Hz, $^4J_{FH}$ 7.6 Hz), 134.66 (dd, 1F, 9-F, $^3J_{FF}$ 22 Hz, $^3J_{FH}$ 10.4 Hz); *m*/*z*: 371 (82%, M$^+$), 326 (73), 299 (100).

3c, mp 238–240 °C (acetonitrile). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.28 (t, 3H, Me), 4.22 (q, 2H, OC*H*$_2$CH$_3$), 7.85 (dd, 2H, 2′,6′-H, ^3J 4.6 Hz, ^4J 1.5 Hz), 8.47 (s, 1H, 5-H), 8.84 (dd, 2H, 3′,5′-H, ^3J 4.6 Hz, ^4J 1.5 Hz); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 160.59 (dd, 1F, 9-F, ^3J 20.2 Hz, ^3J 21.4 Hz), 151.43 (dd, 1F, 10-F, ^3J 21.4 Hz, ^4J 6.0 Hz), 146.19 (dd, 1F, 8-F, ^3J 20.2 Hz, ^4J 6.0 Hz); *m*/*z*: 389 (40%, M$^+$), 344 (45), 317 (100), 240 (36), 213 (34), 185 (34).

(*b*) A solution of **1d** (0.5 g, 1.17 mmol) and KF (0.14 g, 2.33 mmol) in acetonitrile (10 ml) was kept under reflux for 2 h. The precipitate of **3d** obtained after cooling the reaction solution to room temperature was filtered off, washed with water and recrystallized from ethanol (0.35 g, 76%), mp 226–228 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.29 (t, 3H, Me), 4.23 (q, 2H, OC*H*$_2$CH$_3$), 7.65 (ddd, 1H, 5′-H, $^3J_{5'\text{-H},6'\text{-H}}$ 8.1 Hz, $^3J_{5'\text{-H},4'\text{-H}}$ 4.8 Hz, $^5J_{5'\text{-H},2'\text{-H}}$ 0.9 Hz), 8.32 (ddd, 1H, 6′-H, $^3J_{6'\text{-H},5'\text{-H}}$ 8.1 Hz, $^4J_{6'\text{-H},4'\text{-H}}$ 2.3 Hz, $^4J_{6'\text{-H},2'\text{-H}}$ 1.5 Hz), 8.50 (s, 1H, 5-H), 8.86 (dd, 1H, 4′-H, $^3J_{4'\text{-H},5'\text{-H}}$ 4.8 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ 2.3 Hz), 9.12 (dd, 1H, 2′-H, $^5J_{2'\text{-H},5'\text{-H}}$ 0.9 Hz, $^4J_{2'\text{-H},6'\text{-H}}$ 1.5 Hz); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 160.77 (dd, 1F, 9-F, ^3J 20.2 Hz, ^3J 21.3 Hz), 151.42 (dd, 1F, 10-F, ^3J 21.3 Hz, ^4J 5.5 Hz), 146.31 (dd, 1F, 8-F, ^3J 20.2 Hz, ^4J 5.5 Hz); *m*/*z*: 389 (34%, M$^+$), 344 (30), 317 (100), 240 (29), 213 (33), 185 (27).

General procedure for the synthesis of 2R-*substituted ethyl* 9,10-*difluoro*-8-X-7-*oxo*-7*H*-*pyrido*[1,2,3-*d*,*e*][1,3,4]-*benzothiadiazine*-6-*carboxylates* **3e–h**. A solution of **1f** (0.8 g, 1.9 mmol) in dry toluene (10 ml) was kept under reflux for 1 h. The precipitate of **3f** obtained after cooling the reaction solution to room temperature was filtered off and recrystallized from DMSO (0.36 g, 48%), mp 250–251 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.29 (t, 3H, Me), 1.85–2.10 (m, 4H, 3′,4′-H), 3.40–3.65 (m, 4H, 2′,5′-H), 4.24 (q, 2H, OC*H*$_2$CH$_3$), 7.80 (dd, 1H, 8-H, ^3J 10.8 Hz, ^4J 8.5 Hz), 8.37 (s, 1H, 5-H); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 137.8 (dd, 1F, 9-F, $^3J_{FF}$ 22.3 Hz, $^3J_{FH}$ 10.8 Hz), 132.2 (dd, 1F, 10-F, $^3J_{FF}$ 22.3 Hz, $^4J_{FH}$ 8.5 Hz); *m*/*z*: 379 (73%, M$^+$), 334 (15), 308 (17), 307 (100), 238 (25).

3e, mp 172–175 °C (acetone). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.29 (t, 3H, Me), 1.69–1.73 (m, 4H, 4′,5′-H), 1.73–1.90 (m, 4H, 3′,6′-H), 3.56–3.70 (m, 4H, 2′,7′-H), 4.24 (q, 2H, OC*H*$_2$CH$_3$), 7.78 (dd, 1H, 8-H, ^3J 10.8 Hz, ^4J 9.0 Hz), 8.37 (s, 1H, 5-H); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 137.8 (dd, 1F, 9-F, $^3J_{FF}$ 23.5 Hz, $^3J_{FH}$ 10.8 Hz), 132.1 (dd, 1F, 10-F, $^3J_{FF}$ 23.5 Hz, $^4J_{FH}$ 9.0 Hz); *m*/*z*: 407 (100%, M$^+$), 362 (22), 335 (86), 265 (11), 238 (49).

3g, mp 171–173 °C (acetone). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.28 (t, 3H, Me), 1.61–1.75 (m, 4H, 4′,5′-H), 1.75–1.90 (m, 4H, 3′,6′-H), 3.56–3.70 (m, 4H, 2′,7′-H), 4.22 (q, 2H, OC*H*$_2$CH$_3$), 8.33 (s, 1H, 5-H); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 162.41 (dd, 1F, 9-F, $^3J_{9\text{-F},8\text{-F}}$ 20.2 Hz, $^3J_{9\text{-F},10\text{-F}}$ 23.2 Hz), 140.93 (dd, 1F, 8-F, $^3J_{8\text{-F},9\text{-F}}$ 20.2 Hz, $^4J_{8\text{-F},10\text{-F}}$ 9.8 Hz), 129.63 (dd, 1F, 10-F, $^3J_{10\text{-F},9\text{-F}}$ 23.2 Hz, $^4J_{10\text{-F},8\text{-F}}$ 9.8 Hz); *m*/*z* 425 (100%, M$^+$), 380 (15), 353 (67), 283 (11), 256 (57).

3h, mp 230–231 °C (ethanol). ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.28 (t, 3H, Me), 1.85–2.01 (m, 4H, 3′,4′-H), 3.40–3.57 (m, 4H, 2′,5′-H), 4.22 (q, 2H, OC*H*$_2$CH$_3$), 8.24 (s, 1H, 5-H); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 163.69 (dd, 1F, 9-F, $^3J_{9\text{-F},8\text{-F}}$ 20.4 Hz, $^3J_{9\text{-F},10\text{-F}}$ 23.2 Hz), 142.12 (dd, 1F, 8-F, $^3J_{8\text{-F},9\text{-F}}$ 20.4 Hz, $^4J_{8\text{-F},10\text{-F}}$ 9.3 Hz), 131.05 (dd, 1F, 10-F, $^3J_{10\text{-F},9\text{-F}}$ 23.2 Hz, $^4J_{10\text{-F},8\text{-F}}$ 9.3 Hz); *m*/*z* 397 (63%, M$^+$), 352 (12), 324 (100), 256 (24).

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‡ *Ethyl* 1-(*pyridin*-4-*carbonyl*)*amino*-6,7,8-*trifluoro*-4-*oxo*-1,4-*dihydro-quinolin*-3-*carboxylate* **2a**. A solution of ethyl 3-[2-(pyridin-4-carbonyl)-hydrazino-1]-2-(tetrafluorobenzoyl)acrylate **1a** (0.8 g, 1.9 mmol) in dry toluene (12 ml) was refluxed for 1 h. The reaction solution was then immediately filtered, evaporated and the precipitate obtained recrystallized from propan-2-ol to yield quinolone **2a** (0.3 g, 40%), mp 142–144 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.30 (t, 3H, Me), 4.26 (q, 2H, OC*H*$_2$CH$_3$), 7.87 (dd, 2H, 2′,6′-H, ^3J 4.4 Hz, ^4J 1.5 Hz), 8.04 (ddd, 1H, 5-H, $^3J_{HF}$ 10.2 Hz, $^4J_{HF}$ 8.0 Hz, $^5J_{HF}$ 2.1 Hz), 8.81 (s, 1H, 2-H), 8.87 (dd, 2H, 3′,5′-H, ^3J 4.4 Hz, ^4J 1.5 Hz); ^{19}F NMR ([^{2}H$_6$]DMSO) δ: 151.13 (ddd, 1F, 7-F, $^3J_{7\text{-F},6\text{-F}}$ 23.2 Hz, $^3J_{7\text{-F},8\text{-F}}$ 19.2 Hz, $^4J_{FH}$ 8.0 Hz), 148.66 (ddd, 1F, 8-F, $^3J_{8\text{-F},7\text{-F}}$ 19.2 Hz, $^4J_{8\text{-F},6\text{-F}}$ 4.6 Hz, $^5J_{FH}$ 2.1 Hz), 136.32 (ddd, 1F, 6-F, $^3J_{6\text{-F},7\text{-F}}$ 23.2 Hz, $^3J_{FH}$ 10.2 Hz, $^4J_{6\text{-F},8\text{-F}}$ 4.6 Hz).

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¶ Experimental X-ray crystallographic data for **3g** were obtained on a Syntex-P2$_1$ diffractometer (λ MoKα, graphite monochromator, $\theta/2\theta$-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 using programs SHELX-93 to R = 0.076 (wR_2 = 0.187) for 2128 independent reflections with $F^2 > 3\sigma(I)$; GOOF = 1.203. Empirical formula $C_{19}H_{18}F_3N_3O_3S$, monoclinic crystals, space group $P2_1/c$, a = 6.913(5) Å, b = 12.532(8) Å, c = 21.32(2) Å, β = 91.06(6)°, V = 1847(3) Å^3, d_{calc} = 1.530 g cm^{-3}, Z = 4, μ = 0.232 mm^{-1}. Full lists of bond angles, bond lengths and thermal parameters have been deposited at the Cambrige Crystallographic Data Centre (CCDC). For detail, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 1998. Any request to the CCDC should quote full literature citation and the reference number 1135/27.