Fluorinated benzimidazo[1,2-*a*]quinolones*

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The reactions of 2-cyanomethylbenzimidazole with polyfluorobenzoyl chlorides afforded 2-(1,3-dihydrobenzimidazol-2-ylidene)-3-oxo-3-polyfluorophenylpropionitriles. Refluxing of the latter compounds in acetonitrile in the presence of DBU or in dimethylformamide in the presence of amines gave rise to fluorine-containing derivatives of benzimidazo[1,2-*a*]quinolone.

Key words: 2-cyanomethylbenzimidazole, polyfluorobenzoyl chlorides, 2-(1,3-dihydrobenzimidazol-2-ylidene)-3-oxo-3-polyfluorophenylpropionitriles, benzimidazo[1,2-*a*]quinolones.

[*a*]-Annelated derivatives of fluoroquinolonecarboxylic acids are of considerable interest.[1] In particular, benzothia(oxa)zolo[3,2-*a*]quinolones possessing high antibacterial activity were prepared by condensation of ethyl 2,4-dichloro-5-fluorobenzoylacetate with 2-chlorobenzothia(oxa)zoles in the presence of sodium hydride.[2,3]

An alternative approach to [*a*]-annelated quinolones involves acylation of α-azahetarylacetonitriles with 2-haloarenecarboxylic acid chlorides followed by cyclization of *C*-acyl derivatives.[4,5] Benzimidazo[1,2-*a*]quinolone derivatives prepared according to this method exhibit antimicrobial activity.[6] There are also data on the use of acetonitrile derivatives in the synthesis of antibacterial agents, such as lomefloxacin and fleroxacin.[7—10]

In the present study, we prepared fluoro derivatives of benzimidazo[1,2-*a*]quinolone as part of continuing investigations on structural modifications of fluoroquinolones.[11—15]

It was demonstrated that acylation of 2-cyanomethylbenzimidazole (**1**) with polyfluorobenzoyl chlorides (**2a,b**) afforded 2-(1,3-dihydrobenzimidazol-2-ylidene)-3-oxo-3-polyfluorophenylpropionitriles (**3a,b**) (Scheme 1). The ^{1}H NMR spectra of compounds **3a,b** show signals for the protons of the benzimidazole fragment as two symmetrical multiplets at δ 7.3 and 7.6 and signals of two NH groups at δ 13.2 (broadened) as well as a multiplet for one proton of the tetrafluorobenzene fragment (in the case of derivative **3a**). The mass spectra of compounds **3a,b** have intense molecular ion peaks $[M]^+$ and $[M - 19]^+$.

Compounds **3a,b** underwent cyclization into tetracyclic derivatives **4a,b** in 66 and 85% yields, respectively, on refluxing in acetonitrile in the presence of DBU for 5 h. In the ^{1}H NMR spectra of compounds **4a,b**, the broadened one-proton singlet of one NH group is retained, whereas the signals of the benzimidazole fragment are manifested as unsymmetrical multiplets shifted downfield compared to those in the spectra of **3a,b**. The mass spectra of benzimidazoquinolones **4a,b** are characterized by molecular ion peaks with the highest intensity. The absence of other intense peaks is indicative of stability of the aromatic tetracyclic system. The ^{19}F NMR spectrum of compound **4a** has signals for three fluorine atoms. It should be noted that the signals for F(3) and F(2) are observed as doublets of doublets of doublets, whereas the signal for F(1) is characterized by a more complex multiplicity due, apparently, to the through-space coupling with the protons of the benzimidazole fragment.

Fused derivative **4a** was generated in 80% yield by refluxing compound **3a** in DMF for 6 h. Heating of compound **3a** with pyrrolidine, 4-methylpiperidine, 3-methylpiperidine, or morpholine in DMF led both to cyclization of **3a** and the replacement of one fluorine atom. The positions and multiplicities of the signals in the ^{1}H and ^{19}F NMR spectra of derivatives **5a—d** provide evidence that the F(2) atom is replaced. The ^{1}H NMR spectra of compounds **5a—d** have a doublet of doublets for the H(4) proton at δ 7.6—7.7 and signals of the NH group, the amine residue, and the protons of the benzimidazole fragment. The ^{19}F NMR spectrum of compound **5a** shows signals for two *meta*-fluorine atoms.

It should be noted that heating of **3a** with 1-ethoxycarbonylpiperazine in DMF afforded dimethylamino-substituted quinolone **5e**, *i.e.*, cyclization was accompanied by the replacement of the fluorine atom by the dimethylamine residue rather than by the ethoxycarbonylpiperazine residue (as could be expected). Due to the presence of two labile fluorine atoms in quinolone **3b**, the reaction of

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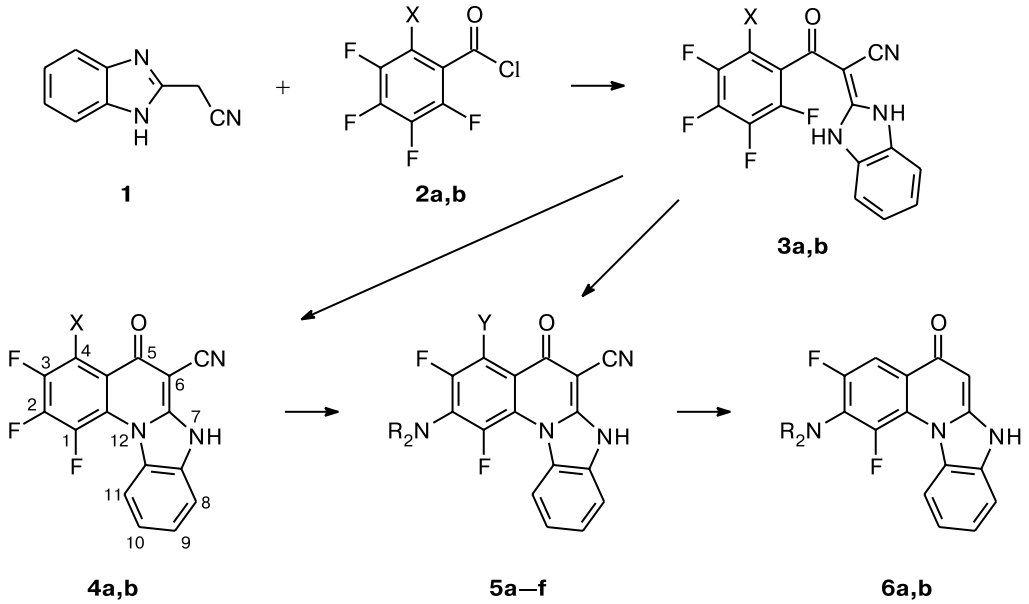
Scheme 1



2—4: X = H (**a**), F (**b**)
5: Y = H; NR_2 = pyrrolidin-1-yl (**a**), 4-methylpiperidin-1-yl (**b**), 3-methylpiperidin-1-yl (**c**), morpholin-4-yl (**d**), NMe_2 (**e**); Y = NR_2 = pyrrolidin-1-yl (**f**)
6: NR_2 = pyrrolidin-1-yl (**a**), 4-methylpiperidin-1-yl (**b**)

this compound with pyrrolidine in DMF involved both cyclization and the replacement of the F(2) and F(4) atoms with the amino residue.

Attempts to hydrolyze nitriles **5a,b** by heating in 30% sulfuric acid failed. The reactions with 60% sulfuric acid gave rise to compounds **6a,b**. Apparently, these reactions are accompanied by hydrolysis of the CN group but the resulting acids are unstable and are readily decarboxylated. The data from ^{1}H NMR spectroscopy and mass spectrometry of compounds **6a,b** are consistent with their structures. In the IR spectrum of compound **6b**, a stretching band of the nitrile group is absent, whereas the spectrum of compound **5b** has this band at 2200 cm^{-1}. The ^{1}H NMR spectra of compounds **6a,b** have a singlet of the H(6) proton at δ 6.2—6.3. These results are in agreement with the published data on the characteristic features of hydrolysis of quinoline-3-carbonitriles and the fact that the corresponding acids can be subjected to decarboxylation under drastic conditions.[16]

The new benzimidazo[1,2-*a*]quinolone derivatives synthesized in the present study are the first representatives of the series of fluorine-containing derivatives and are of interest as potential biologically active compounds.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250 MHz with Me_4Si as the internal standard. The ^{19}F NMR spectra were measured on a Bruker WP-80-SY spectrometer operating at 75.38 MHz with hexafluorobenzene as the internal standard. The mass spectra were obtained on a Varian MAT 311A spectrometer (accelerating voltage was 3 kV, cathode emission current was 300 μA, energy of ionizing electrons was 70 eV, direct inlet of the sample into the ion source). The IR spectra were measured on a Specord 751R instrument in KBr pellets.

2-Cyanomethylbenzimidazole was prepared by condensation of cyanoacetic ester with *o*-phenylenediamine according to a known procedure.[17]

2-(1,3-Dihydrobenzimidazol-2-ylidene)-3-oxo-3-(1,2,3,4-tetrafluorophenyl)propionitrile (3a). Tetrafluorobenzoyl chloride **2a** (1.5 mL, 15 mmol) was added to a suspension of 2-cyanomethylbenzimidazole **1** (1.5 g, 9.6 mmol) in toluene (15 mL). The reaction mixture was refluxed for 4 h and cooled. The precipitate of compound **3a** that formed was filtered off, washed with ethanol, and recrystallized from DMSO. The yield was 2.8 g (88%), m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 7.25 (m, 2 H, H(4), H(7)); 7.41 (m, 1 H, H(6′)); 7.56 (m, 2 H, H(5), H(6)); 13.09 (br.s, 2 H, NH). MS, *m/z* (I_{rel} (%)): 333 $[M]^+$ (98), 315 (19), 314 (100), 313 (33), 184 (22), 177 (26), 156 (18), 149 (19), 102 (13). Found (%): C, 57.60; H, 2.03; N, 12.75. $C_{16}H_7F_4N_3O$. Calculated (%): C, 57.67; H, 2.12; N, 12.61.

2-(1,3-Dihydrobenzimidazol-2-ylidene)-3-oxo-3-(perfluorophenyl)propionitrile (3b) was prepared analogously to compound **3a**. The yield was 83%, m.p. 238—240 °C. ^{1}H NMR (DMSO-d_6), δ: 7.27 (m, 2 H, H(4), H(7)); 7.57 (m, 2 H, H(5), H(6)); 13.19 (br.s, 2 H, NH). MS, *m/z* (I_{rel} (%)): 351 $[M]^+$ (100), 333 (16), 332 (85), 331 (53), 303 (18), 195 (18), 184 (26), 187 (13), 156 (22), 102 (16). Found (%): C, 54.42; H, 1.80;

N, 11.82. $C_{16}H_6F_5N_3O$. Calculated (%): C, 54.71; H, 1.72; N, 11.96.

1,2,3-Trifluoro-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (4a). ***A.*** 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.46 g, 3.0 mmol) was added to a solution of compound **3a** (1.0 g, 3.0 mmol) in dry MeCN (15 mL). The reaction mixture was refluxed for 3.5 h and concentrated. Water (25 mL) and AcOH (0.5 mL) were added to the residue. The precipitate of compound **4a** that formed was filtered off and recrystallized from DMSO. The yield was 0.8 g (85%), m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 7.35 (m, 1 H, H(4)); 7.44 (m, 1 H, H(8)); 7.54 (m, 1 H, H(9) or H(10)); 7.97 (m, 1 H, H(10) or H(9)); 8.02 (m, 1 H, H(11)); 13.82 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ_F: 153.17 (ddd, 1 F, F(2), $^3J_{F,F}$ = 23.2 Hz, $^3J_{F,F}$ = 19.5 Hz, $^4J_{F,H}$ = 7.9 Hz); 136.80 (ddd, 1 F, F(3), $^3J_{F,F}$ = 23.2 Hz, $^3J_{F,H}$ = 10.4 Hz, $^4J_{F,F}$ = 5.5 Hz); 132.08 (m, 1 F, F(1)). MS, *m/z* (I_{rel} (%)): 313 $[M]^+$ (100), 285 (16), 284 (12), 143 (12). Found (%): C, 61.32; H, 2.10; N, 13.45. $C_{16}H_6F_3N_3O$. Calculated (%): C, 61.39; H, 1.93; N, 13.42.

B. A solution of compound **3a** (0.4 g, 1.2 mmol) in DMF (4 mL) was refluxed for 5 h, cooled, and diluted with water. The precipitate of nitrile **4a** that formed was filtered off and recrystallized from DMSO. The yield was 0.3 g (80%).

1,2,3,4-Tetrafluoro-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (4b) was prepared according to procedure ***A*** analogously to compound **4a**. The yield was 66%, m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 7.36 (m, 1 H, H(8)); 7.50 (m, 2 H, H(9), H(10)); 8.44 (m, 1 H, H(11)); 13.6 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 331 $[M]^+$ (100), 303 (8), 302 (7), 165 (10). Found (%): C, 57.86; H, 1.32; N, 12.58. $C_{16}H_5F_4N_3O$. Calculated (%): C, 58.01; H, 1.52; N, 12.68.

1,3-Difluoro-5-oxo-2-pyrrolidino-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (5a). ***A.*** Pyrrolidine (0.3 mL, 0.26 g, 3.7 mmol) was added to a solution of compound **3a** (0.3 g, 1.0 mmol) in DMF (4 mL). The reaction mixture was refluxed for 5 h, cooled, and diluted with water. The precipitate of nitrile **5a** that formed was filtered off and recrystallized from DMSO. The yield was 0.27 g (74%), m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 1.98 (m, 4 H, $(CH_2)_2$); 3.75 (m, 4 H, $N(CH_2)_2$); 7.27 (m, 1 H, H(8)); 7.37 (m, 1 H, H(9) or H(10)); 7.47 (m, 1 H, H(10) or H(9)); 7.58 (dd, 1 H, H(4), ^3J = 13.8 Hz, ^5J = 1.3 Hz); 7.77 (m, 1 H, H(11)); 13.4 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ_F: 124.19 (m, 1 F, F(1)); 124.46 (dd, 1 F, F(3), $^3J_{F,H}$ = 13.8 Hz, $^5J_{F,H}$ = 1.3 Hz). MS, *m/z* (I_{rel} (%)): 364 $[M]^+$ (100), 363 (54), 338 (3), 322 (9), 294 (13), 280 (12), 266 (6), 182 (5). Found (%): C, 65.39; H, 4.00; N, 14.92. $C_{20}H_{14}F_2N_4O$. Calculated (%): C, 65.99; H, 3.87; N, 15.39.

B. Pyrrolidine (0.6 mL, 0.52 g, 7.2 mmol) was added to a solution of nitrile **4a** (0.6 g, 1.9 mmol) in DMF (5 mL). The reaction mixture was refluxed for 5 h, cooled, and diluted with water. The precipitate of compound **5a** that formed was filtered off and recrystallized from DMSO. The yield was 0.45 g (65%).

Compounds **5b—e** were prepared from compound **3a** using procedure ***A***.

1,3-Difluoro-2-(4-methylpiperidino)-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (5b). The yield was 71%, m.p. 252—254 °C. ^{1}H NMR (DMSO-d_6), δ: 1.02 (d, 3 H, Me, ^3J = 6.5 Hz); 1.40 (m, 2 H, CH_2); 1.50—1.70 (m, 1 H, CH); 1.76 (m, 2 H, CH_2); 3.22 (m, 2 H, NCH_2); 3.49 (m, 2 H, NCH_2); 7.32 (m, 1 H, H(8)); 7.41 (m, 1 H, H(9) or H(10)); 7.51 (m, 1 H, H(10) or H(9)); 7.70 (dd, 1 H, H(4), ^3J = 11.0 Hz, ^5J = 1.2 Hz); 7.86 (m, 1 H, H(11)); 13.6 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 392 $[M]^+$ (100), 391 (65), 338 (14), 322 (19), 313 (15), 294 (13), 266 (9). IR (KBr), ν/cm^{-1}: 2200 (CN). Found (%): C, 67.16; H, 4.33; N, 14.09. $C_{22}H_{18}F_2N_4O$. Calculated (%): C, 67.33; H, 4.62; N, 14.27.

1,3-Difluoro-2-(3-methylpiperidino)-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (5c). The yield was 58%, m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 0.96 (d, 3 H, Me, ^3J = 6.1 Hz); 1.10—1.30 (m, 1 H, CH); 1.83 (m, 4 H, 2 CH_2); 2.84 (m, 1 H, NCH); 3.11 (m, 1 H, NCH); 3.45 (m, 2 H, NCH_2); 7.32 (m, 1 H, H(8)); 7.41 (m, 1 H, H(9) or H(10)); 7.52 (m, 1 H, H(10) or H(9)); 7.70 (dd, 1 H, H(4), ^3J = 13.4 Hz, ^5J = 1.7 Hz); 7.85 (m, 1 H, H(11)); 13.6 (br.s, 1 H, NH). Found (%): C, 67.58; H, 4.41; N, 14.46. $C_{22}H_{18}F_2N_4O$. Calculated (%): C, 67.33; H, 4.62; N, 14.27.

1,3-Difluoro-2-morpholino-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (5d). The yield was 79%, m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 3.15 (m, 4 H, $N(CH_2)_2$); 3.40 (m, 2 H, OCH_2); 3.78 (m, 2 H, OCH_2); 7.31 (m, 1 H, H(8)); 7.40 (m, 1 H, H(9) or H(10)); 7.51 (m, 1 H, H(10) or H(9)); 7.71 (dd, 1 H, H(4), ^3J = 11.8 Hz, ^5J = 1.5 Hz); 7.86 (m, 1 H, H(11)); 13.5 (br.s, 1 H, NH). Found (%): C, 63.39; H, 3.65; N, 14.96. $C_{20}H_{14}F_2N_4O_2$. Calculated (%): C, 63.15; H, 3.71; N, 14.73.

2-Dimethylamino-1,3-difluoro-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (5e). The yield was 69%, m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 3.16 (s, 6 H, NMe_2); 7.31 (m, 1 H, H(8)); 7.40 (m, 1 H, H(9) or H(10)); 7.52 (m, 1 H, H(10) or H(9)); 7.69 (dd, 1 H, H(4), ^3J = 12.5 Hz, ^5J = 1.2 Hz); 7.86 (m, 1 H, H(11)); 13.6 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 338 $[M]^+$ (100), 337 (31), 322 (10), 294 (5), 155 (9). Found (%): C, 63.80; H, 3.24; N, 16.75. $C_{18}H_{12}F_2N_4O$. Calculated (%): C, 63.90; H, 3.57; N, 16.56.

1,3-Difluoro-5-oxo-2,4-dipyrrolidino-5,12-dihydrobenzimidazo[1,2-*a*]quinoline-6-carbonitrile (5f) was prepared analogously from nitrile **3b**. The yield was 65%, m.p. 244—246 °C. ^{1}H NMR (DMSO-d_6), δ: 1.95 (m, 4 H, $(CH_2)_2$); 2.08 (m, 2 H, CH_2); 2.20 (m, 2 H, CH_2); 3.32 (m, 2 H, NCH_2); 3.60 (m, 2 H, NCH_2); 3.79 (m, 4 H, $N(CH_2)_2$); 7.23 (m, 1 H, H(8)); 7.36 (m, 1 H, H(9) or H(10)); 7.65 (m, 1 H, H(10) or H(9)); 7.84 (m, 1 H, H(11)); 19.05 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 433 $[M]^+$ (100), 432 (23), 431 (35), 407 (7), 416 (5), 363 (5), 293 (3), 217 (8), 215 (4). Found (%): C, 66.57; H, 4.59; N, 16.15. $C_{24}H_{21}F_2N_5O$. Calculated (%): C, 66.50; H, 4.88; N, 16.15.

1,3-Difluoro-2-(4-methylpiperidino)-5-oxo-5,12-dihydrobenzimidazo[1,2-*a*]quinoline (6b). Water (6 mL) and concentrated H_2SO_4 (6 mL) were added to compound **5b** (1.3 g, 3.3 mmol). The reaction mixture was refluxed for 5.5 h and cooled. Then water (20 mL) was added. A solution of NH_3 was added to pH 8. The precipitate of derivative **6b** that formed was filtered off and recrytsallized from DMSO. The yield was 0.95 g (79%), m.p. 228—230 °C. ^{1}H NMR (DMSO-d_6), δ: 1.03 (d, 3 H, Me, ^3J = 6.5 Hz); 1.41 (m, 2 H, CH_2); 1.50—1.70 (m, 1 H, CH); 1.76 (m, 2 H, CH_2); 3.22 (m, 2 H, NCH_2); 3.43 (m, 2 H, NCH_2); 6.30 (s, 1 H, H(6)); 7.20 (m, 1 H, H(8)); 7.32 (m, 1 H, H(9) or H(10)); 7.50 (m, 1 H, H(10) or H(9)); 7.65 (dd, 1 H, H(4), ^3J = 10.9 Hz, ^5J = 1.2 Hz); 7.94 (m, 1 H, H(11)); 11.6 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 367 $[M]^+$ (100), 366 (47), 298 (11), 297 (12), 288 (12). Found (%): C, 68.98; H, 4.93; N, 11.69. $C_{21}H_{19}F_2N_3O$. Calculated (%): C, 68.65; H, 5.21; N, 11.43.

1,3-Difluoro-5-oxo-2-pyrrolidino-5,12-dihydrobenzimidazo[1,2-*a*]quinoline (6a) was prepared analogously to compound **6b** from compound **5a**. The yield was 72%, m.p. > 250 °C. ^{1}H NMR (DMSO-d_6), δ: 1.98 (m, 4 H, $(CH_2)_2$); 3.76 (m, 4 H, $N(CH_2)_2$); 6.22 (s, 1 H, H(6)); 7.21 (m, 1 H, H(8)); 7.30 (m, 1 H, H(9) or H(10)); 7.51 (m, 1 H, H(10) or H(9)); 7.68 (dd, 1 H, H(4), ^3J = 11.8 Hz, ^5J = 1.6 Hz); 7.87 (m, 1 H, H(11)); 11.4 (br.s, 1 H, NH). MS, *m*/*z* (I_{rel} (%)): 339 $[M]^+$ (100), 338 (52), 313 (24), 285 (18), 178 (15), 73 (23), 64 (84), 57 (32), 55 (29). Found (%): C, 67.54; H, 4.71; N, 12.09. $C_{19}H_{15}F_2N_3O$. Calculated (%): C, 67.24; H, 4.45; N, 12.38.

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