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SYNTHESIS OF FLUOROQUINOLONE–DI- AND TRI-(*N*-METHYLPYRROLE) CONJUGATES

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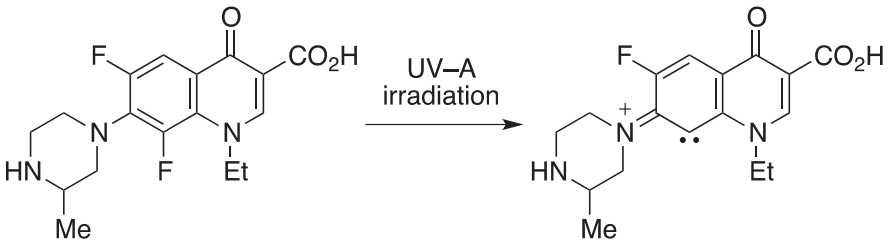
Abstract – Some FLQs, such as *lomefloxacin* and *fleroxacin,* having two fluorine atoms are known to generate an arylcarbene under photoirradiation conditions leading to DNA damage. We synthesized some conjugates between FLQs and di- and tri-(*N*-methylpyrrole) that are known as a DNA minor groove binder.

DNA photocleavers that cleave DNA with light in the UV region under mild conditions in the absence of any other additives such as metals, oxidants and reductants have attracted much attention because these agents can serve in the field of photochemotherapy.[1,2] Recent progress in the development of optical materials and laser technology has enabled the introduction of an intense UV beam into the depths of the human body more conveniently and safely, and photochemotherapy using a light of UV region is thus becoming increasingly important. We have recently been interested in phototoxities of fluoroquinolones (FLQs), which are widely used as broad-spectrum antimicrobial agents.[3] Some FLQs, such as *lomefloxacin* and *fleroxacin,* having two fluorine atoms are known to show potent photo mutagenic and photo carcinogenic activities.[4] These potent phototoxities of FLQs are thought to be mainly caused by an arylcarbene generated under irradiation conditions, and the arylcarbene is also known to cleave DNA by hydride abstraction from phosphate backbone of DNA, unlike commonly used photosensitizers in which phototoxicities and DNA damage are mainly attributed to singlet oxygen[5] (Scheme 1).



Scheme 1. Arylcarbene generation under irradiation conditions

In the course of our study[6] aimed at the development of agents that are applicable to photochemotherapy, we became interested in the possibility of combining a DNA binding molecule with an FLQ generating an arylcarbene to enhance the inherent DNA cleaving ability of FLQs under irradiation conditions. In this paper, we report the synthesis of FLQs having di- and tri-(*N*-methylpyrrole) moieties that interact with DNA (Figure 1).[7]

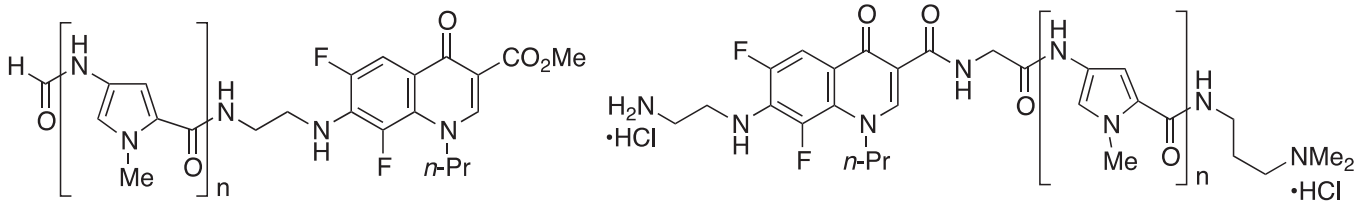
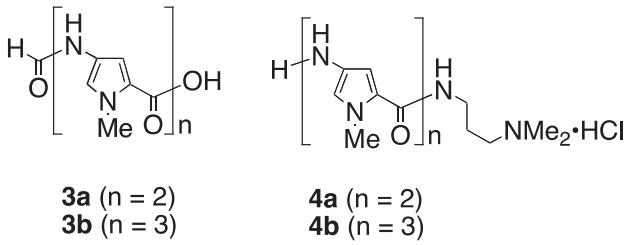


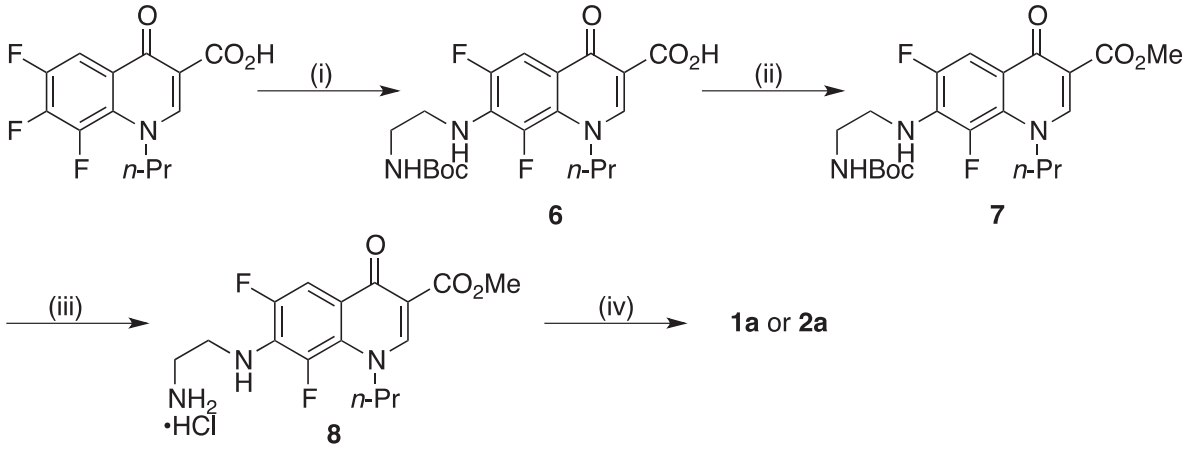
Figure 1. FLQ–di- and tri-(*N*-methylpyrrole) conjugates in this study

In the synthesis of FLQ–di- and tri-(*N*-methylpyrrole) conjugates **1a**, **1b**, **2a** and **2b**, di- and tri-(*N*-methylpyrrole) moieties **3a**, **3b**, **4a** and **4b** were prepared according to the procedures reported in the literature.[8]



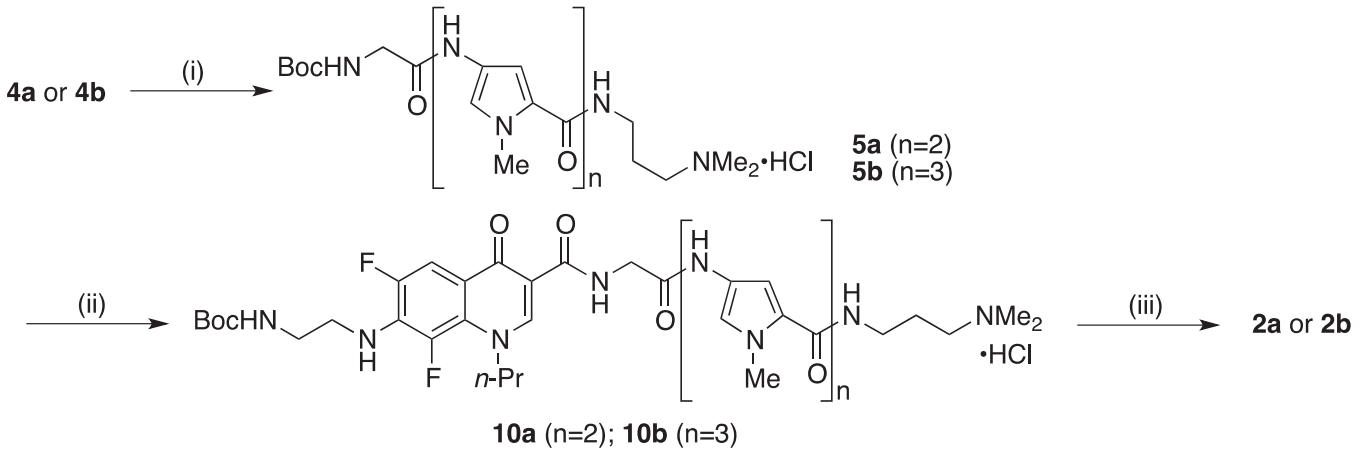
FLQ–di- and tri-(*N*-methylpyrrole) conjugates **1a** and **1b** were synthesized as shown in Scheme 2. 6,7,8-trifluoro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylic acid[9] was reacted with mono Boc-protected ethylenediamine in refluxing MeCN to give acid **6**, which is used as a common precursor. Acid **6** was converted to ester **7**, which was treated with HCl in MeOH-DCM (1:1) to afford hydrochloride **8**. Next, we examined coupling reaction between hydrochlorides **8** and **3a**. When *N*,*N*'–dicyclohexylcarbodiimide (DCC), *N*-[3-(dimethylamino)propyl]-*N*'-ethylcarbodiimide hydrochloride (EDC•HCl), and 1,1'–carbonyldiimidazole (CDI) were used as coupling reagents, the reactions did not proceeded at all, resulting in complete recovery of the starting materials, and when (benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) was used, inseparable residue of PyBOP prevented further purification. In the course of examining several conditions, we found that *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU) was a

suitable reagent for the coupling reaction between **8** and **3a**, and desired conjugate **1a** could be obtained even though yields were not so high. Conjugate **1b** was synthesized from **8** and **3b** in a similar manner.



Scheme 2. *Reagents and conditions*: (i) $BocHNCH_2CH_2NH_2$ (3 equiv.) / MeCN, reflux, 4 h, 97%. (ii) MeOH (excess), EDC•HCl (2 equiv.), DMAP (4 equiv.) / DCM, reflux, 4 h, 92%. (iii) HCl (1 mol/l) / MeOH-DCM (1:1), rt, 12 h, 95%. (iv) HBTU (1 equiv.), DIEA (3 equiv.), **3a** (for **1a**) or **3b** (for **1b**) / DMF, rt, 12 h, 47% for **1a** and 29% for **1b**

We also synthesized conjugates **2a** and **2b** as shown in Scheme 3. When we tried to couple acid **6** with di-(*N*-methylpyrrole) **4a** directly, the coupling reaction did not occur at all under any of the conditions examined, even when HBTU was used. We therefore decided to introduce glycine as a linker moiety between an FLQ and **4a** (or **4b**). Di- and tri-(*N*-methylpyrrole) **4a** and **4b** were reacted with *N*-Boc glycine in the presence of PyBOP and DIEA followed by removal of the Boc group under acidic conditions to afford *N*-Boc glycine-attached **5a** and **5b**.



Scheme 3. *Reagents and conditions*: *N*-Boc glycine (1 equiv.), PyBOP (1 equiv.), DIEA (2 equiv.) / DMF, rt, 12 h, 66% for **5a** and 11% for **5b**. (ii) HCl (1 mol/l)/ MeOH-DCM (1:1), rt, 12 h, then HBTU (1 equiv.), DIEA (3 equiv.), **6** / DMF, rt, 12 h. (iii) HCl (2 mol/l)/ MeOH–1,4-dioxane (1:1), rt, 12 h, 76% for **5a** (2 steps) and 61% for **5b** (2 steps)

Di-(*N*-methylpyrrole) **5a** was treated with methanolic HCl in DCM and a resulting hydrochloride was coupled with **6** using HBTU, giving desired conjugate **2a** in 76% yield. We could also obtain conjugate **2b** in 61% yield from **5b** by using a similar method. Although FLQs **6**, **7** and **8** were stable and could be handled under the light of fluorescent lamp, synthesized FLQ–di- and tri-(*N*-methylpyrrole) cojugates **1a**, **1b**, **2a** and **2b** were unexpectedly photosensitive, and gradually decomposed under the light of fluorescent lamp.[10] In conclusion, we synthesized four FLQ–di- and tri-(N-methylpyrrole) conjugates successfully. Photobiologocal studies of these compounds are now undergoing.

EXPERIMENTAL

General.

^{1}H-NMR spectra were taken on EOL JNM-AL400 (400 MHz) and JEOL JNM-AL300 (300 MHz) spectrometers in $CDCl_3$ with reference to $CHCl_3$ (7.26 ppm) or in DMSO-d_6 with reference to DMSO-d_6 (2.54 ppm) unless otherwise noted. ^{13}C-NMR were measured with JEOL AL400 (100 MHz) and JEOL JNM-AL300 (75 MHz) spectrometers in $CDCl_3$ with reference to $CDCl_3$ (77.0 ppm) and in DMSO-d_6 with reference to DMSO-d_6 (39.7 ppm). IR spectra were recorded on JASCO FT/IR-420 and Perkin-Elmer 1720 FT-IR spectrometer. Mass Spectra were obtained on a JEOL JMS-DX303 and JMS-SX102A. Melting points were obtained on YAMATO-MODEL20 melting point apparatus and were uncorrected. Column chromatography was performed on silicagel, KANTO KAGAKU N-60. Thin-layer chromatography was performed on precoated plates (0.25 mm, silicagel Merck Kieselgel 60 F254). All reactions were performed in oven-dried glassware under positive pressure of nitrogen, unless otherwise noted. Reaction mixtures were stirred magnetically.

Di-(*N*-methylpyrrole) 5a

To a stirred solution of **4a** (870 mg, 2.52 mmol) in 20 mL of DMF were added *N*-Boc-glycine (400 mg, 2.28 mmol), PyBOP (1.32 g, 2.52 mmol) and diisopropylethylamine (0.8 mL, 4.56 mmol) and the solution was stirred for 12 h at rt. The solvent was removed under reduced pressure and saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted three times with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified with column chromatography (SiO_2, 18% aq. NH_3/MeOH/$CHCl_3$ = 1/9/90 as an eluant), giving a desired product as pale yellow amorphous solid (850 mg, 66%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, br s), 7.82 (1H, br s), 7.77 (1H, br t, *J* = 5.0 Hz), 7.20 (1H, br d, *J* = 1.0 Hz), 6.92 (1H, br s), 6.48 (1H, br s), 6.44 (1H, br d, *J* = 1.0 Hz), 5.64 (1H, br s), 3.91 (2H, br d, *J* = 5.0 Hz), 3.87 (3H, s), 3.80 (3H, s), 3.44 (2H, q, *J* = 7.0 Hz), 2.43 (2H, t, *J* = 7.0 Hz), 2.27 (6H, s), 1.74 (2H, quint, *J* = 7.0 Hz) and 1.46 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 161.9 (C), 158.7 (C), 156.6 (C), 123.4 (C), 123.2 (C), 121.4 (C),

120.4 (C), 119.3 (CH), 118.5 (CH), 104.1 (CH), 102.9 (CH), 80.3 (C), 58.3 (CH_2), 45.3 (CH_3), 44.2 (CH_2), 38.7 (CH_2), 36.4 (CH_3), 36.3 (CH_3), 28.3 (CH_3) and 26.3 (CH_2); IR (KBr) ν 3296, 2976, 2941, 2820, 2779, 1682, 1641, 1579 and 1526 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{37}N_7O_5$ (M^+): 503.2856, found: 503.2849.

Tri-(*N*-methylpyrrole) 5b

5b was obtained in 11% yield from **4b** as pale yellow amorphous solid by the procedure employed for the synthesis of **5a**; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83 (1H, br s), 8.56 (1H, br s), 7.78 (1H, br s), 7.70 (1H, br t, *J* = 5.0 Hz), 7.25 (1H, s), 7.22 (1H, s), 6.83 (1H, br s), 6.65 (1H, br s), 6.40 (1H, br s), 6.21 (1H, br s), 3.94 (2H, br d, *J* = 5.0 Hz), 3.87 (3H, s), 3.82 (3H, s), 3.71 (3H, s), 3.44 (2H, br q, *J* = 7.0 Hz), 2.43 (2H, br t, *J* = 7.0 Hz), 2.25 (6H, s), 1.74 (2H, br quint, *J* = 7.0 Hz) and 1.43 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 162.0 (C), 159.0 (C), 158.7 (C), 156.7 (C), 123.4 (C), 123.1 (C), 122.8 (C), 121.8 (C), 121.3 (C), 120.4 (C), 119.6 (CH), 119.2 (CH), 118.7 (CH), 104.6 (CH), 103.4 (CH), 103.3 (CH), 80.3 (C), 58.1 (CH_2), 45.2 (CH_3), 44.2 (CH_2), 38.7 (CH_2), 36.4 (CH_3), 36.3 (CH_3), 28.2 (CH_3) and 26.2 (CH_2); IR (KBr) ν 3296, 3131, 2941, 2821, 1640, 1579 and 1525 cm^{-1}; HRMS (FAB+) calcd for $C_{30}H_{44}N_9O_6$ ($[M+H]^+$): 626.3336, found: 626.3431.

7-(2-((*tert*-Butoxycarbonyl)amino)ethyl)-6,8-difluoro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylic acid 6

To a stirred solution of **5** (1.0 g, 3.5 mmol) in 10 mL of MeCN was added *tert*-butyl (2-aminoethyl)carbamate (1.68 g, 10.5 mmol) and the solution was refluxed for 4 h. The reaction was quenched with 20% aqueous solution of AcOH and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated. Recrystallization of the residue from $CHCl_3$ afforded colorless needles (1.44g, 97%); mp 186-188 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, s), 7.92 (1H, d, $J_{H\text{-}F}$ = 12.5 Hz), 5.30 (1H, br s), 4.91 (1H, br s), 4.32 (2H, m), 3.68 (2H, br s), 3.46 (2H, br q, *J* = 5.0 Hz), 1.91 (2H, sext, *J* = 7.0 Hz), 1.45 (9H, s) and 1.00 (3H, t, *J* = 7.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.1 (C, t, $J_{C\text{-}F}$ = 3.1 Hz), 167.1 (C), 157.2 (C), 150.3 (CF, dd, $J_{C\text{-}F}$ = 6.8 and 240.5 Hz), 149.8 (CH), 139.6 (CF, dd, $J_{C\text{-}F}$ = 6.8 and 240.5 Hz), 132.7 (C, t, $J_{C\text{-}F}$ = 13.6 Hz), 126.9 (C, d, $J_{C\text{-}F}$ = 6.8 Hz), 116.0 (C, d, $J_{C\text{-}F}$ = 7.4 Hz), 107.8 (CH, dd, $J_{C\text{-}F}$ = 3.1 and 21.6 Hz), 107.0 (C), 80.1 (C), 60.6 (CH_2, d, $J_{C\text{-}F}$ = 16.1 Hz), 47.1 (CH_2), 40.7 (CH_2), 28.2 (CH_3), 24.0 (CH_2) and 10.7 (CH_3); IR (KBr) ν 3347, 3043, 2974, 2877, 1719, 1696, 1632 and 1538 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{25}F_2N_3O_5$ (M^+): 425.1762, found: 425.1767; Anal. calcd for $C_{20}H_{25}F_2N_3O_5$: C, 56.46; H, 5.92; N, 9.88. found: C, 56.12; H, 5.86; N, 9.82.

7-(2-((*tert*-Butoxycarbonyl)amino)ethyl)-6,8-difluoro-4-oxo-1-propyl-1,4-dihydroquinoline-3-

carboxylic acid, methyl ester 7

To a stirred solution of **7** (800 mg, 1.88 mmol) in 4 mL of CH_2Cl_2 were added MeOH (4 mL), 4-DMAP (920 mg, 7.52 mmol) and EDC•HCl (720 mg, 3.76 mmol) in this sequence. The mixture was refluxed for 4 h and the reaction was quenched with 20% aqueous solution of AcOH. The mixture was extracted three times with AcOEt, and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated. The residue was recrystallized from EtOH, affording colorless needles (960 mg, 92%); mp 148-150 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, s), 7.96 (1H, d, $J_{H\text{-}F}$ = 12.5 Hz), 4.88 (1H, br s), 4.86 (1H, br s), 4.22 (2H, m), 3.92 (3H, s), 3.62 (2H, br q, J = 5.0 Hz), 3.42 (2H, br q, J = 5.0 Hz), 1.88 (2H, sext, J = 7.0 Hz), 1.44 (9H, s) and 0.98 (3H, t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 166.1 (C), 156.9 (C), 150.9 (CH), 149.9 (CF, dd, $J_{C\text{-}F}$ = 6.8, 240.8 Hz), 139.8 (CF, dd, $J_{C\text{-}F}$ = 6.8, 240.8 Hz), 131.3 (C, t, $J_{C\text{-}F}$ = 13.6 Hz), 125.8 (C, d, $J_{C\text{-}F}$ = 6.8 Hz), 119.3 (C, d, $J_{C\text{-}F}$ = 8.0 Hz), 108.6 (C), 108.4 (CH, dd, $J_{C\text{-}F}$ = 3.8 and 21.6 Hz), 79.5 (C), 59.8 (CH_2, d, $J_{C\text{-}F}$ = 15.5 Hz), 51.9 (CH_3), 46.6 (CH_2), 40.6 (CH_2), 28.1 (CH_3), 23.7 (CH_2, d, $J_{C\text{-}F}$ = 4.4 Hz) and 10.6 (CH_3); IR (KBr) ν 3382, 3290, 2974, 2879, 1722, 1685, 1618 and 1592 cm^{-1}; HRMS (EI) calcd. for $C_{15}H_{15}F_4NO_3$ (M^+): 439.1919, found: 439.1907; Anal. calcd for $C_{15}H_{15}F_4NO_3$: C, 57.40; H, 6.19; N, 9.56. found: C, 57.44; H, 6.05; N, 9.44.

FLQ–di-(*N*-methylpyrrole) conjugate 1a

To a stirred solution of **7** (300 mg, 0.68 mmol) in 10 mL of CH_2Cl_2 was added methanolic solution of HCl (1 mol/l, 10 mL) and the mixture was stirred for 12 h at rt. The solution was concentrated under reduced pressure, giving **8** as pale yellow powder, which was used without further purification. Di-(*N*-methylpyrrole) **3a** (180 mg, 0.62 mmol) was dissolved in 15 mL of DMF, and to this solution were added HBTU (240 mg, 0.42 mmol), diisopropylethylamine (0.32 mL, 1.9 mmol). After stirring for 10 min, hydrochloride **8** was added to this solution and the mixture was stirred for 12 h at rt. The mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed with 5% aqueous solution of $KHSO_4$ and brine, dried over Na_2SO_4, evaporated. The residue was purified with preparative TLC ($CHCl_3$/MeOH = 5/1 was used as an eluant), giving a desired product **1a** as pale yellow solid (178 mg, 47% in 2 steps); mp 190-192 °C (decomp.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.05 (1H, brs), 9.85 (1H, brs), 8.49 (1H, s), 8.12 (1H, s), 8.11 (1H, t, J = 5.0 Hz), 7.65 (1H, d, $J_{H\text{-}F}$ = 12.5 Hz), 7.18 (1H, s), 7.15 (1H, s), 6.89 (1H, s), 6.88 (1H, s), 6.19 (1H, brs), 4.28 (2H, m), 3.83 (3H, s), 3.78 (3H, s), 3.73 (3H, s), 3.54 (2H, m), 3.41 (2H, m), 1.75 (2H, sext, J = 7.0 Hz) and 0.87 (3H, t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 170.6 (C, t, $J_{C\text{-}F}$ = 3.1 Hz), 165.0 (C), 161.8 (C), 158.3 (C), 157.9 (C), 151.1 (CH), 149.8 (d, $J_{C\text{-}F}$ = 232.5 Hz), 140.1 (C, dd, $J_{C\text{-}F}$ = 245.0 and 6.8 Hz), 131.2 (C, t, $J_{C\text{-}F}$ = 14.2 Hz), 126.2 (d, $J_{C\text{-}F}$ = 6.8 Hz), 123.0 (C), 122.8 (C), 122.1 (C), 120.8 (C), 118.4 (CH), 118.0 (CH, d,

$J_{C\text{-}F}$ = 6.8 Hz), 108.2 (CH), 107.2 (CH, d, $J_{C\text{-}F}$ = 22.3 Hz), 104.6 (CH), 104.0 (CH), 58.5 (CH_2, $J_{C\text{-}F}$ = 14.9 Hz), 51.3 (CH_3), 45.0 (CH_2), 39.3 (CH_2), 36.1 (CH_3), 35.9 (CH_3), 23.2 (CH_2, d, $J_{C\text{-}F}$ = 4.4 Hz) and 10.5 (CH_3); IR (KBr) ν 3280, 3116, 2951, 2872, 1721, 1675, 1631, 1579 and 1526 cm^{-1}; HRMS (FAB+) calcd. for $C_{29}H_{31}F_2N_7O_6$ ($[M+H]^+$): 612.2304, found: 612.2397.

FLQ–tri-(*N*-methylpyrrole) conjugate 1b

FLQ–conjugate **1b** was obtained in 29% yield from **3b** and **8** as pale yellow solid by the procedure employed for the synthesis of **1a**; mp 192 ˚C (decomp.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.07 (1H, brs), 9.90 (1H, br s), 9.87 (1H, br s), 8.49 (1H, s), 8.13 (1H, s), 8.12 (1H, br t, J = 5.0 Hz), 7.65 (1H, d, $J_{H\text{-}F}$ = 12.5 Hz), 7.23 (1H, d, J = 1.0 Hz), 7.19 (1H, d, J = 1.0 Hz), 7.16 (1H, d, J = 1.0 Hz), 7.04 (1H, d, J = 1.0 Hz), 6.93 (1H, d, J = 1.0 Hz), 6.90 (1H, d, J = 1.0 Hz), 6.20 (1H, brs), 4.28 (2H, m), 3.83 (6H, s), 3.79 (3H, s), 3.73 (3H, s), 3.55 (2H, m), 3.42 (2H, m), 2.76 (2H, sext, J = 7.0 Hz) and 0.85 (3H, t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 170.6 (C), 165.0 (C), 161.8 (C), 158.5 (C), 158.4 (C), 157.9 (C), 151.2 (CH), 149.6 (C, dd, $J_{C\text{-}F}$ = 247.5 and 8.0 Hz), 139.7 (C, dd, $J_{C\text{-}F}$ = 241.7 and 6.8 Hz), 131.2 (C, t, $J_{C\text{-}F}$ = 14.3 Hz), 126.2 (d, $J_{C\text{-}F}$ = 6.8 Hz), 123.0 (C), 122.9 (C), 122.7 (C), 122.3 (C), 122.1 (C), 120.8 (C), 118.5 (CH), 118.0 (CH, dd, $J_{C\text{-}F}$ = 6.8 Hz), 117.9 (CH), 108.2 (CH), 107.2 (d, $J_{C\text{-}F}$ =17.1 Hz), 104.9 (CH), 104.6 (CH), 58.5 (CH_2, d, $J_{C\text{-}F}$ =14.9 Hz), 51.3 (CH_3), 45.0 (CH_2), 39.3 (CH_2), 36.1 (CH_3), 35.9 (CH_3), 23.2 (CH_2, d, $J_{C\text{-}F}$ = 4.4 Hz) and 10.5 (CH_3); IR (KBr) ν 3308, 2948, 2872, 1718, 1655, 1616, 1581 and 1542 cm^{-1}; HRMS (FAB+) calcd. for $C_{35}H_{37}F_2N_9O_7$ ($[M+H]^+$): 734.2784; found: 734.2866.

FLQ–di-(*N*-methylpyrrole) conjugate 10a

To a stirred solution of **5a** (1.0 g, 1.99 mmol) in 5 mL of CH_2Cl_2 was added methanolic solution of HCl (1 mol/l, 10 mL) and the solution was stirred for 12 h at rt. The solution was concentrated under reduced pressure, giving as a hydrochloride as light brown amorphous solid, which was used without further purification. The hydrochloride was dissolved in 20 mL of DMF. To this solution were added acid **6** (1.0 g, 2.35 mmol), PyBOP (1.22 g, 2.35 mmol) and diisopropylethylamine (1.86 mL, 10.5 mmol) and the mixture was stirred for 4 h at 40 ˚C. The solution was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue was recrystallized from MeOH–Et_2O, giving **10a** as colorless powder (1.3 g, 76% in 2 steps); mp 176-178 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.23 (1H, br t, J = 5.0 Hz), δ 9.98 (1H, s), δ 9.85 (1H, s), δ 8.62 (1H, s), δ 8.13 (1H, br t, J = 5.0 Hz), 7.75 (1H, d, $J_{H\text{-}F}$ = 12.0 Hz), δ 7.16 (2H, s), δ 6.93 (2H, s), δ 6.90 (1H, br t, J = 5.0 Hz), δ 6.17 (1H, br s), 4.40 (2H, m), 4.14 (2H, br d, J = 5.0 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.45 (2H, m), 3.25 (2H, br q, J = 7.0 Hz), 3.17 (2H, br q, J = 7.0 Hz), 3.06 (2H, m), 2.78 (6H, s), 1.84 (2H, br quint, J = 7.0 Hz), 1.83 (2H, br sext, J = 7.0 Hz), 1.33 (9H, s) and

0.89 (3H, br t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 173.3 (C), 166.0 (C), 164.2 (C), 161.7 (C), 158.5 (C), 155.9 (C), δ 149.7 (CH), δ 131.5 (C, t, $J_{C\text{-}F}$ = 13.6 Hz), 126.5 (C, d, $J_{C\text{-}F}$ = 5.6 Hz), δ 122.9 (C), δ 122.6 (C), δ 122.2 (C), δ 121.6 (C), 118.3 (CH), 118.2 (CH), δ 117.0 (C), δ 109.3 (C), 106.9 (CH, d, $J_{C\text{-}F}$ = 21.0 Hz), 104.6 (CH), 104.2 (CH), 77.8 (C), 58.8 (CH_2, d, $J_{C\text{-}F}$ = 14.9 Hz), 54.9 (CH_2), 45.0 (CH_2), 42.6 (CH_2), 42.3 (CH_3), 40.7 (CH_2), 36.2 (CH_3), 36.0 (CH_3), 35.6 (CH_2), 28.2 (CH_3), 24.8 (CH_2), 23.4 (CH_2, d, $J_{C\text{-}F}$ = 4.4 Hz) and 10.6 (CH_3); IR (KBr) ν 3637, 3279, 3122, 2976, 2941, 1677, 1653, 1588, 1530 and 1483 cm^{-1}; HRMS (FAB+) calcd. for $C_{39}H_{53}F_2N_7O_{10}$ ([M+H]$^+$): 811.3989, found: 811.4050.

FLQ–di-(*N*-methylpyrrole) conjugate 2a

To a stirred solution **10a** (200 mg, 0.25 mmol) in 5 mL of MeOH was added HCl (4 mol/l, 1,4-dioxane solution, 5 mL) was added the mixture was stirred for 12 h at rt. The mixture was filtered and the residue was washed with MeOH and Et_2O, giving **2a** (110 mg, 56%) as pale yellow powder; mp 190 °C (decomp); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.20 (1H, t, J = 5.0 Hz), 10.04 (1H, s), 9.87 (1H, s), 8.66 (1H, s), 8.15 (1H, t, J = 5.0 Hz), 8.06 (3H, brs), 7.81 (1H, d, $J_{H\text{-}F}$ = 12.0 Hz), 7.18 (2H, s), 6.92 (2H, s), 6.38 (1H, brs), 4.42 (2H, m), 4.15 (2H, d, J = 5.0 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.68 (2H, brs), 3.25 (2H, q, J = 7.0 Hz), 3.11-3.00 (4H, m), 2.75 (3H, s), 2.74 (3H, s), 1.87 (2H, quint, J = 7.0 Hz), 1.80 (2H, sext, J = 7.0 Hz) and 0.90 (3H, t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 173.3 (C), 166.0 (C), 164.2 (C), 161.6 (C), 158.5 (C), 150.0 (CH), 149.6 (C, dd, $J_{C\text{-}F}$ = 8.0 and 240.0 Hz), 139.8 (C, dd, $J_{C\text{-}F}$ = 8.0 and 240.0 Hz), 130.9 (C, t, $J_{C\text{-}F}$ = 14.3 Hz), 126.6 (C, d, $J_{C\text{-}F}$ = 5.6 Hz), 122.9 (C), 122.7 (C), 122.3 (C), 121.7 (C), 118.4 (CH), 118.3(CH), 117.5 (C, d, $J_{C\text{-}F}$ = 6.8 Hz), 109.4 (C), 107.1 (CH, d, $J_{C\text{-}F}$ = 19.8 Hz), 104.6 (CH), 104.0 (CH), 58.9 (CH_2, d, $J_{C\text{-}F}$ =14.9 Hz), 54.6 (CH_2), 42.6 (CH_2), 42.3 (CH_2), 42.1 (CH_3), 39.4 (CH_2), 36.4 (CH_3), 36.2 (CH_3), 35.7 (CH_2) , 24.6 (CH_2), 23.5 (CH_2, d, $J_{C\text{-}F}$ = 3.7 Hz), and 10.7 (CH_3); IR (KBr) ν 3280, 3053, 2968, 2696, 1653, 1640, 1577 and 1542 cm^{-1}; HRMS (FAB+) calcd. for $C_{34}H_{45}F_2N_{10}O_5$ ([M+H]$^+$): 711.3464; found: 711.3567.

FLQ–tri-(*N*-methylpyrrole) conjugate 10b

10b was obtained from **5a** in 61% yield as pale yellow solid by the same procedure employed for the synthesis of **5a**: mp 178 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.18 (1H, br t, J = 5.0 Hz), δ 9.83 (1H, s), δ 9.72 (1H, s), δ 9.71 (1H, s), 8.61 (1H, s), 8.01 (1H, br t, J = 5.0 Hz), 7.77 (1H, d, $J_{H\text{-}F}$ = 12.0 Hz), 7.19 (1H, br s), 7.14 (2H, br s), 7.05 (1H, br s), 6.95 (1H, br s), 6.94 (1H, br s), 6.75 (1H, br s), 6.03 (1H, br s), 4.39 (2H, m), 4.14 (2H, br d, J = 5.0 Hz), 3.86 (6H, br s), 3.83 (3H, br s), 3.47 (2H, m), 3.27 (2H, m), 3.19 (2H, m), 3.04 (2H, m), 2.76 (6H, s), 1.93-1.73 (4H, m), 1.34 (9H, s) and 0.91 (3H, t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 173.2 (C), 165.9 (C), 164.2 (C), 161.7 (C), 158.6 (C), 158.5 (C), 155.9 (C), 149.7 (CH), 149.7 (CF, dd, $J_{C\text{-}F}$ = 7.4 and 241.1 Hz), δ 131.5 (C, t, $J_{C\text{-}F}$ = 14.3 Hz), 126.5 (C, d, J =

4.4 Hz), 122.9 (C), 122.8 (C), 122.6 (C), 122.3 (C), 122.2 (C), 121.6 (C), 118.5 (CH), 118.3 (CH), 118.2 (CH), 116.9 (C), 109.3 (C), 106.8 (CH, d, J = 20.4 Hz), 104.9 (CH), 104.6 (CH), 104.2 (CH), 77.8 (C), 58.8 (CH_2, d, J = 14.9 Hz), 54.9 (CH_2), 45.0 (CH_2), 42.6 (CH_2), 42.3 (CH_3), 40.7 (CH_2), 36.2 (CH_3), 36.1 (CH_3), 36.0 (CH_3), 35.6 (CH_2), 28.2 (CH_3), 24.8 (CH_2), 23.4 (CH_2, d, $J_{C\text{-}F}$ = 3.7 Hz) and 10.5 (CH_3); IR (KBr) ν 3133, 3053, 2973, 2877, 1653, 1602, 1531 and 1479 cm^{-1}; HRMS (FAB+) calcd. for $C_{45}H_{59}F_2N_{12}O_8$ ($[M+H]^+$): 933.4469, found: 933.4558.

FLQ–tri-(*N*-methylpyrrole) conjugate 2b

2b was obtained from **10b** in 64% yield as colorless powder by the procedure employed for the synthesis of **2a**: mp 235 ˚C (decomp); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.31 (1H, t, J = 5.0 Hz), 10.08 (1H, br s), 9.93 (1H, br s), 9.89 (1H, br s), 8.79 (1H, s), 8.10 (1H, t, J = 5.0 Hz), 7.96 (1H, d, $J_{H\text{-}F}$ = 12.0 Hz), 7.36 (1H, s), 7.31 (2H, s), 7.20 (1H, s), 7.09 (1H, s), 7.01 (1H, s), 6.41 (1H, br s), 4.55 (2H, m), 4.30 (2H, d, J = 5.0 Hz), 4.01 (6H, s), 3.97 (3H, s), 3.83 (2H, q, J = 7.0 Hz), 3.47-3.30 (4H, m), 3.19 (2H, t, J = 7.0 Hz), 2.65 (6H, s), 1.97 (2H, quint, J = 7.0 Hz), 1.87 (2H, sext, J = 7.0 Hz) and 1.07 (3H, t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 173.2 (C), 165.9 (C), 164.1 (C), 161.6 (C), 158.6 (C), 158.5 (C), 149.9 (CH), 130.8 (t, J = 14.3 Hz), 126.6 (d, $J_{C\text{-}F}$ = 5.6 Hz), 122.9 (C), 122.8 (C), 122.7 (C), 122.3 (C), 122.2 (C), 121.6 (C), 118.5 (CH), 118.3 (CH), 118.1 (CH), 117.5 (C, d, $J_{C\text{-}F}$ = 6.8 Hz), 109.4 (CH), 107.1 (d, $J_{C\text{-}F}$ = 22.9 Hz), 104.6 (CH), 104.0 (CH), 58.9 (CH_2, d, $J_{C\text{-}F}$ = 14.9 Hz), 54.7 (CH_2), 42.5 (CH_2), 42.3 (CH_2), 42.1 (CH_3), 39.3 (CH_2), 36.2 (CH_3), 36.1 (CH_3), 36.0 (CH_3), 35.7 (CH_2), 24.6 (CH_2), 23.4 (CH_2, d, $J_{C\text{-}F}$ = 3.7 Hz) and 10.5 (CH_3); IR (KBr) ν 3275, 3033, 2969, 2877, 1649, 1602, 1550, 1538 and 1478 cm^{-1}; HRMS (FAB+) calcd. for $C_{40}H_{51}F_2N_{12}O_6$ ($[M+H]^+$): 833.3944, found:833.4037.

REFERENCES

1. B. Armitage, *Chem. Rev.*, 1998, **98**, 1153.
2. K. Toshima, Y. Maeda, H. Ouchi, A. Asai, and S. Matsumura, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2163; K. Toshima, H. Ouchi, Y. Okazaki, T. Kano, M. Moriguchi, A. Asai, and S. Matsumura, *Angew. Chem. Int. Ed.*, 1998, **36**, 2748; I. Saito and K. Nakatani, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 3007; I. Saito and M. Takayama, *J. Am. Chem. Soc.*, 1995, **117**, 5590; I. Saito, M. Takayama, H. Sugiyama, and K. Nakatani, *J. Am. Chem. Soc.*, 1995, **117**, 6406; I. Saito, M. Takayama, and T. Sakurai, *J. Am. Chem. Soc.*, 1994, **116**, 2653.
3. J. M. Domagala, *J. Antimicrob. Chemother.*, 1994, **33**, 685; J. M. Domagdala, L. D. Hann, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez, and M. Solomon, *J. Med. Chem.,* 1986, **29**, 394.
4. E. Fasani, M. Mella, and A. Albini, *Eur. J. Org. Chem.*, 2004, 5075; M. Freccero, M. Fagnoni, and A. Albini, *J. Am. Chem. Soc.*, 2003, **125**, 13182; S. Monti, S. Sortino, E. Fasani, and A. Albini, *Chem.*

Eur. J., 2001, **7**, 2185; G. Condorelli, G. De Guidi, S. Giuffrida, S. Sortino, R. Chillemi, and S. Sciuto, *Photochem. Photobiol.*, 1999, **70**, 280; E. Fasani, F. F. Barberis-Negra, S. Monti, and A. Albini, *J. Org. Chem.*, 1999, **64**, 5388; L. J. Martinez and C. F. Chignell, *Photochem. Photobiol.*, 1997, **65**, 599.

5. L. J. Martinez and C. F. Chignell, *J. Photochem. Photobiol., B: Biol.,* 1998, **45**, 51.
6. I. Suzuki, M. Takahashi, A. Shigenaga, H. Nemoto, and K. Takeda, *Tetrahedron Lett.*, 2006, **47**, 6193; I. Suzuki, S. Uno, Y. Tsuchiya, A. Shigenaga, H. Nemoto, and M. Shibuya, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2959; M. Wakayama, H. Iitsuka, I. Suzuki, and M. Shibuya, *Heterocycles*, 1999, **51**, 325.
7. P. B. Dervan and B. S. Edelson, *Curr. Opin. Struct. Biol.*, 2003, **13**, 284; P. B. Dervan and R. W. Burli, *Curr. Opin. Chem. Biol.*, 1999, **3**, 688; D. E. Wemmer and P. B. Dervan, *Curr. Opin. Chem. Biol.*, 1997, **7**, 355.
8. E. Nishiwaki, H. Lee, T. Matsumoto, K. Toyooka, H. Sakurai, and M. Shibuya, *Tetrahedron Lett.*, 1990, **31**, 1299; E. Nishiwaki, S. Tanaka, H. Lee, and M. Shibuya, *Heterocycles*, 1988, **27**, 1945.
9. T. Ernst and C. Richert, *Synlett*, 2005, 411.
10. A possibility that di- and tri-(*N*-methylpyrrole) moieties acted as photosensitizers cannot be ignored. See references: Y. Sakai, T. Matsumoto, A. Tanaka, and M. Shibuya, *Heterocycles*, 1993, **36**, 565; T. Matsumoto, Y. Utsumi, Y. Sakai, K. Toyooka, and M. Shibuya, *Heterocycles*, 1992, **34**, 1697; T. Matsumoto, Y. Sakai, K. Toyooka, and M. Shibuya, *Heterocycles*, 1992, **33**, 135.