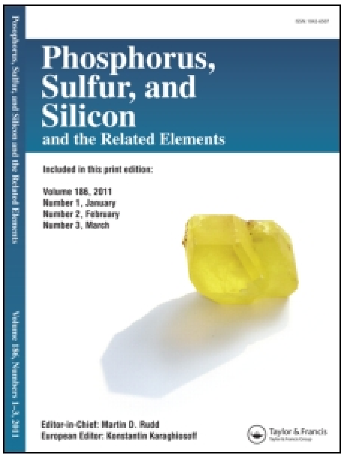

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QUINOLONE ANTIBACTERIAL AGENTS LINKED TO OSTEOTROPIC BISPHOSPHONATE MOIETIES

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QUINOLONE ANTIBACTERIAL AGENTS LINKED TO OSTEOTROPIC BISPHOSPHONATE MOIETIES

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Bisphosphonates are widely used in diagnosis and therapy of different bone diseases. Due to their potential to accumulate in the inorganic bone matrix hydroxylapatite they are useful agents in osteotic vectorization of different types of drugs. We linked bisphosphonate moieties to antibacterial quinolones like norfloxacin to enable a selective targeting of these agents to bone tissue. The quinolones (1,4-dihydro-4-oxo-quinoline-3-carboxylic acids) were modified at position 1 and 7 using alkylbisphosphonates with ethene-, amino- and carboxylic-groups. After coupling with the quinolones, the alkylbisphosphonic esters could smoothly be hydrolyzed via the corresponding silyl esters to obtain the free bisphosphonic acids.

Keywords: bisphosphonates; quinolones; gyrase inhibitors; drug targeting; bone infections

INTRODUCTION

Bisphosphonates, especially *gem*-bisphosphonates, show high affinity towards bone and other calcified tissues[1]. They are used in the therapy of osteoporosis[2,3], tumor-induced hypercalcemia[4,5] and Paget's disease[6,7], due to their influence on bone metabolism and bone-seeking properties[8]. Their great potential to accumulate in the inorganic bone matrix hydroxylapatite makes them useful as carriers for cytotoxic or antibacterial substances, increasing the concentration of the drug in bone tissue. This drug targeting with bisphosphonates can result in an improved therapy of several bone malignancies. Thus, coupling of bisphosphonate moieties to cytotoxic molecules like chlorambucil, methotrexate or plati-

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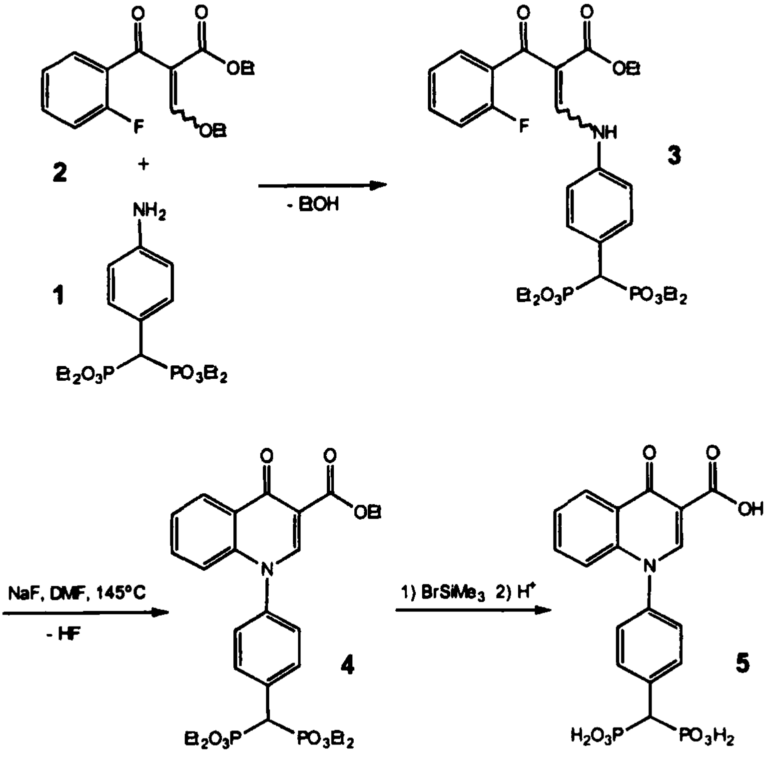
num complexes leads to compounds active against bone tumors[9,10,11]. To our knowledge, no successful attempt has been made to apply this strategy for the design of drugs active against antibacterial bone infections.

Here we report on the synthesis of some model compounds consisting of a bisphosphonate moiety linked to a molecular structure that can be found in gyrase inhibitors of the quinolone type. Quinolones (1,4-dihydro-4-oxo-quinoline-3-carboxylic acids)[12], especially fluoroquinolones like norfloxacin (see **8** in Scheme 2)[13], are widely used antibacterial agents that selectively inhibit bacterial DNA-gyrase relative to mammalian topoisomerase II [14]. Necessary for antibacterial activity of the quinolones is an intact enaminoketocarboxyl system[15,16]. Thus, modifications at position 2 and especially 3 of the quinolone are not suitable. Therefore, we linked the bisphosphonate moieties at position 1 and 7 of the quinolone.

RESULTS AND DISCUSSION

Synthesis of 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids with a bisphosphonate-containing moiety at position 1

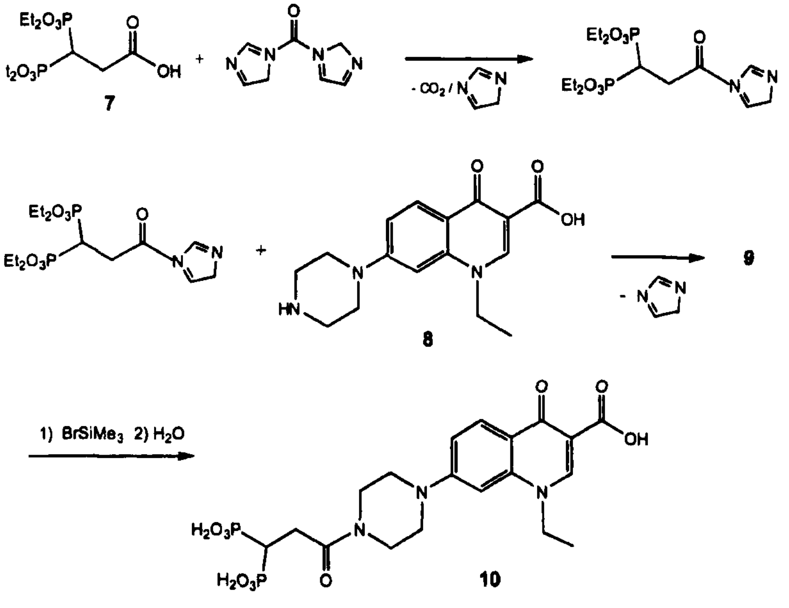
The best way to couple a bisphosphonate-containing moiety with 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids at position 1 is to build up the quinolone according to the malonic ester variant of the cycloaracylation procedure[17] (see Scheme 1). The bisphosphonate moiety was introduced as an aromatic primary amine **1**. The amine was reacted with the enolether **2** to form the enamino keto ester **3**. The enamino keto ester was obtained as a mixture of the Z and E isomer. The subsequent nucleophilic cyclocondensation of **3** led to the 1,4-dihydro-4-oxo-quinoline-3-carboxylic ethyl ester **4**. The free carboxylic acid **5** could be obtained by acidic hydrolysis without hydrolizing the phosphonic ester groups. The phosphonic ester groups could then be hydrolized smoothly by intermediate transformation to the corresponding silyl esters and subsequent addition of water. The crucial step in this synthesis is the cyclisation to the quinolone **4**. The yield of only 10% for the cyclisation of **3** to **4** was obtained if NaF in DMF was used. The use of K_2CO_3 instead or DMSO as solvent could not improve the results. A significantly higher yield of 40% could only be obtained under the same conditions in the case of the corresponding monophosphonate (data not presented). Here we used 4-aminobenzyl-phosphonic ester as primary amine.



SCHEME I

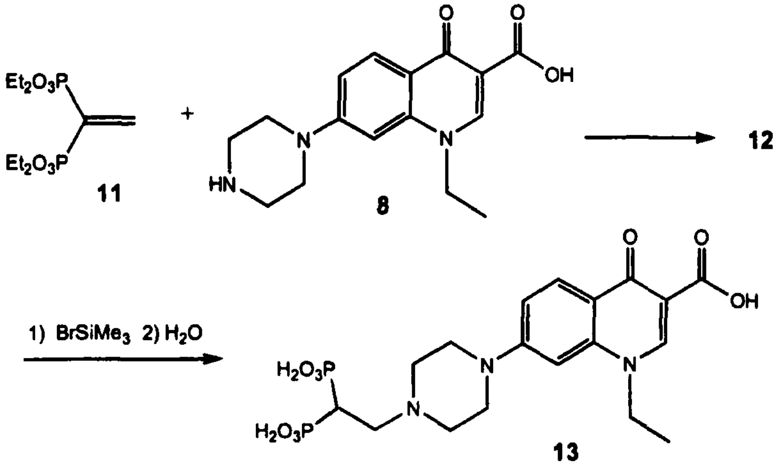
Synthesis of 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids with a bisphosphonate-containing moiety at position 7

Two synthesis pathways have been chosen to couple a bisphosphonate-containing moiety with 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids at position 7. In the first pathway the bisphosphonate contains a carboxyl group that could be linked to the piperazinyl residue of the quinolone via an amide bond (see Scheme 2). The carboxyl group of the bisphoshonate **7** was activated by transformation into the imidazolide, a convenient method for the activation of carboxylic acids first described by Staab et al[18]. The reaction of the intermediate imidazolide with the secundary amino group of the piperazinyl residue of norfloxacin **8** resulted in the quinolone-bisphosphonate **9**. The yield of 30% could not be improved by the use of other carboxylic group activation procedures. The phosphonic ethyl ester groups could be removed smoothly by intermediate transformation to the corresponding silyl esters and subsequent addition of water resulting in the free bisphosphonic acid **10**.



SCHEME 2

The second synthesis pathway, forming a N-alkyl bond, used a Michael-type reaction of the vinylogous electron acceptor-bisphosphonate **11** with the secundary amino group of the piperacinyl residue of norfloxacin **8** (see Scheme 3). The reaction proceeded at room temperature without addition of any acid or base with a yield of 73%. The resulting norfloxacin-coupled bisphosphonic ester **12** could be smoothly hydrolyzed with bromotrimethyl silane / water yielding the free bisphosphonic acid **13**.



SCHEME 3

In conclusion, we were able to link an osteotropic bisphosphonate-moiety to positions 1 and 7 of antibacterial quinolones. This might enable a selective targeting of an antibacterial drug to bone tissue and lead to an improved treatment of bone infections.

EXPERIMENTAL

Norfloxacin was purchased from Sigma. Bromotrimethylsilane was purchased from Aldrich. 4-Aminophenylmethane-bisphosphonic tetraethyl ester **1**[19], 2-(2-fluorobenzoyl)-3-ethoxyacrylic ethyl ester **2**[20], 3,3-bis(diethoxyphosphoryl)propionic acid **7**[21] and ethenylidenebisphosphonic tetraethylester **11**[22] were prepared as described previously. All NMR spectra (^1H, ^{13}C, ^{31}P) were recorded on a Bruker WH 200 MHz spectrometer. Tetramethylsilane, trifluoracetic acid and H_3PO_4 were used as internal standards. NMR spectra coupling constants are listed for H,H and C,P couplings, others are indicated. IR spectra were recorded on a Bruker IFS 66 spectrometer.

Elemental analysis were performed using a Haeraeus C,H,N-Rapid system. P was determined as magnesium pyrophosphate.

3-{4-[Bis(diethoxyphosphoryl)methyl]phenylamino}-2-(fluorobenzoyl)-acrylic ethyl ester, 3

10.0 g (0.026 mol) of 4-aminophenylmethane-bisphosphonic tetraethyl ester **1** in 100 ml of absolute ethanol were added to a solution of 2-(2-fluorobenzoyl)-3-ethoxyacrylic ethyl ester **2** in 15 ml of absolute ethanol, cooled with ice. The mixture was stirred for one hour at room temperature. Then, water was added and the yellow, organic phase was separated. The aqueous phase was extracted twice with methylene chloride and the combined organic phases were dried with sodium sulfate and evaporated to dryness. The resulting oil crystallized slowly. 12.5 g (79%) of the yellow product were obtained as a mixture of Z and E isomer; m.p. 70°C.

NMR (DMSO-d6): ^{1}**H**: $\delta = 0.70$ [t, $^{3}J = 7.0$ Hz, 3 H], 0.82 [t, $^{3}J = 7.0$ Hz, 3 H], 0.93 [t, $^{3}J = 7.0$ Hz, 6 H], 1.07 [t, $^{3}J = 7.0$ Hz, 6 H], 3.81 [m, 4 H], 3.92 [m, 4 H], 4.23 [t, $^{2}J = 24.9$ Hz, 1 H], 4.26 [t, $^{2}J = 24.9$ Hz, 1 H], 7.11 [m, 2 H], 7.33 [m, 6 H], 8.28 [d, $^{3}J = 13.8$ Hz, 1 H], 8.39 [d, $^{3}J = 13.8$ Hz, 1 H], 10.71 [d, $^{3}J = 13.8$ Hz, 1 H], 12.14 [d, $^{3}J = 13.8$ Hz, 1 H]; ^{13}**C**: $\delta = 13.23$, 13.57, 15.85 [d, $^{3}J = 3.1$ Hz], 16.07 [d, $^{3}J = 3.1$ Hz], 42.61, 59.27, 59.39, 62.20 [m], 103.55, 104.09, 114.73, 115.17, 117.60, 118.05, 124.14, 128.25, 128.68, 130.35, 131.50, 137.91, 150.99, 151.80, 155.94, 160.82, 166.01, 167.04, 187.00, 189.99; ^{19}**F**: $\delta = -115.1$, -114.3; ^{31}**P**: $\delta = 20.0$; **IR** (KBr): $\nu = 1698$ [vs, C=O, ester], 1673 [s, C=O, ester], 1626 [vs, C=O], 1606 [s, C=O], 1248 [vs, P=O], 1025 [vs, P-O] cm^{-1}.

$C_{27}H_{36}FNO_9P_2$ (599.53) Calcd.: C 54.09, H 6.05, N 2.34, Found: C 53.71, H 6.19, N: 2.26.

1-{4-[Bis(diethoxyphosphoryl)methyl]phenyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic ethyl ester 4

A mixture of 12.5 g (0.021 mol) of 3 and 0.9 g (0.021 mol) sodium fluoride in 45 ml of dimethyl formamide was stirred at 145°C for two hours. The hot reaction mixture was filtered, poured on ice and extracted several times with diethyl ether. The ether extracts were dried with sodium sulfate and evaporated to dryness. The resulting oil was then chromatographed on silica gel. As second fraction, eluted with acetone, 2.4 g of the educt **3** was recovered. On eluting with acetone / ethanol (1/1), the product **4** could be obtained as the third fraction. The oil could be crystallized by digestion with petroleum ether, yielding 1.2 g (10%) of a white powder after filtration; m.p. 114°C.

NMR (DMSO-d6): ^{1}**H**: $\delta = 1.08$ [t, $^{3}J = 7.0$ Hz, 6 H], 1.23 [t, $^{3}J = 7.0$ Hz, 6 H], 1.25 [t, $^{3}J = 7.1$ Hz, 3 H], 3.96 [m, 4 H], 4.20 [q, $^{3}J = 7.1$ Hz, 2 H], 4.64 [t, $^{2}J_{PH} = 24.7$ Hz, 1 H], 6.86 [d, $^{3}J = 8.3$ Hz, 1 H], 7.48 [m, 1 H], 7.65 [m, 3H], 7.78 [dt, $^{3}J = 8.5$ Hz, $^{4}J_{PH} = 1.8$ Hz, 2 H], 8.28 [dd, $^{3}J = 8.1$ Hz, $^{4}J_{PH} = 1.5$ Hz, 1 H], 8.42 [s, 1 H]; ^{13}**C**: $\delta = 14.22$, 16.02 [m], 42.86, 59.93, 62.45 [m], 107.80, 110.59, 117.55, 125.17, 126.28, 127.48, 132.23, 133.29, 139.33, 140.31, 148.38, 164.21, 172.91; ^{31}**P**: $\delta = 18.4$; **IR** (KBr): $\nu = 1722$ [vs, C=O, acid], 1605, 1647 [vs, C=O], 1255 [s, P=O], 1025 [vs, P-O] cm^{-1}.

$C_{27}H_{35}NO_9P_2$ (579.52) Calcd.: C 55.96, H 6.09, N: 2.42 P: 10.69, Found: C 55.58, H 6.19, N 2.33 P 10.52.

1-[4-(Bisphosphonomethyl)phenyl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid 5

0.5 ml of bromotrimethylsilane (0.004 mol) were added to 0.2 g **4** in 10 ml of absolute chloroform and stirred for four hours at room temperature. Afterwards, 5 ml of methanol were added. After stirring over night, the formed white precipitate, the free phosphonic acid, was filtered and heated to 100°C in a mixture of 0.06 ml of concentrated sulfuric acid, 0.65 ml of acetic acid and 0.50 ml of water. After stirring for half an hour a solution had been formed and 1 ml of water was added. Precipitation occurs on cooling. The precipitate was filtered, washed with water and dried under vacuum. The product was obtained as a trihydrate. $C_{17}H_{15}NO_9P_2 \cdot 3\ H_2O$ (579.52) Calcd.: C 41.39, H 4.29, N: 2.84 P: 12.56, Found: C 41.26, H 4.36, N 2.78, P 12.37.

IR (KBr): $\nu = 1706$ [s, C=O], 1614 [vs, C=O], 1238 [s, P=O], 1008 [s, P-O] cm^{-1}. To improve the solubility of the compound and to obtain NMR spectra, the disodium salt was prepared by titrating a suspension of the bisphosphonic acid in water with 0.1 M NaOH until the solid was totally dissolved. The disodium salt was precipitated by addition of acetone.

NMR (DMSO-d6): ^{1}**H**: $\delta = 3.51$ [t, $^{2}J_{PH} = 22.8$ Hz, 1 H], 7.45 [m, 7 H], 8.24 [d, $^{3}J = 8.0$ Hz, 1 H], 8.64 [s, 1 H]; ^{31}**P**: $\delta = 15.1$; **IR** (KBr): $\nu = 1720$ [vs, C=O], 1614 [vs, C=O], 1236 [s, P=O], 1036, 1022 [s, P-O] cm^{-1}.

7-{4-[3,3-Bis(diethoxyphosphoryl)propyryl]piperacin-1-yl}-1-ethyl-6-fluor-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid 9

0.94 g (0.006 mol) of N,N'-carbonyldiimidazol were added to a solution of 2.0 g (0.006 mol) 3,3-bis(diethoxyphosphoryl)propionic acid **7** in 10 ml of absolute chloroform under generation of CO_2. After stirring for 20 minutes at room temperature, 1.85 g (0.006 mol) of norfloxacin in 170 ml of absolute chloroform were added to the red solution. The mixture was refluxed over night. The reaction mixture was filtered after cooling to room temperature and the filtrate extracted twice with 10% acetic acid and twice with water. The chloroform phase was dried with sodium sulfate and concentrated to about 10 ml and filtered. The filtrate was evaporated and the resulting residual oil dissolved in ethyl acetate. Diethyl ether was added and the precipitate filtered and dried under vacuum to yield 1.1 g (30%) of the solid product. M.p. 182°C.

NMR ($CDCl_3$): **^{1}H**: δ = 1.28 [t, ^{3}J = 7.0 Hz, 12 H], 1.49 [t, ^{3}J = 7.1 Hz, 3 H], 2.86 [dt, $^{3}J_{PH}$ = 15.6 Hz, ^{3}J = 5.7 Hz, 2 H], 3.30 [m, 5 H], 3.76 [m, 4 H], 4.11 [q, ^{3}J = 7.0 Hz, 8 H], 4.27 [q, ^{3}J = 7.1 Hz, 2 H], 6.77 [d, $^{4}J_{FH}$ = 6.8 Hz, 1 H], 7.93 [d, $^{3}J_{FH}$ = 12.8 Hz, 1 H], 8.57 [s, 1 H], 14.8 [s, 1 H]; **^{13}C**: δ = 14.46, 16.36 [d, ^{3}J = 6.3 Hz], 28.88, 31.99 [t, ^{1}J = 134.7 Hz], 42.00, 45.22, 49.70, 62.81 [m], 104.21, 108.36, 112.80 [d, $^{2}J_{FC}$= 23.3 Hz], 120.87 [d, $^{3}J_{FC}$ = 7.6 Hz], 137.04, 145.55 [d, $^{2}J_{FC}$ = 10.6 Hz], 147.19, 153.38, 166.95, 168.24, 176.82; **^{19}F**: δ = −121.0; **^{31}P**: δ = 23.6; **IR** (KBr): ν = 1728 [s, C=O, carboxylic acid], 1655, 1624 [s, C=O], 1238 [s, P=O], 1020 [vs, P-O] cm-1.

$C_{27}H_{41}FN_3O_{10}P_2$ (648.57) Calcd.: C 50.08, H 6.23, N 6.49, P 9.57, Found: C 49.87, H 6.24, N: 6.87, P: 8.72.

7-{4-[3,3-Bis(phosphono)propyryl]piperacin-1-yl}-1-ethyl-6-fluor-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid 10

0.44 ml (0.0034 mol) bromotrimethylsilanee were added to a solution of 0.28 g (0.0004 mol) of **9** in 5 ml of absolute chloroform. After stirring for two hours at room temperature methanol was added to precipitate the free bisphosphonic acid. The precipitate was filtered and recrystallized from methanol / water (10/1). After drying under vacuum 0.2 g (88%) of a light yellow, hygroscopic solid were obtained. m.p. 250°C.

NMR (DMSO-d6): ^{1}**H**: δ = 1.24 [m, 3 H], 2.62 [m, 3 H], 3.15 [m, 4 H], 3.53 [m, 4 H], 4.42 [m, 2 H], 5.71 [broad], 6.98 [d, $^4J_{FH}$ = 7.0 Hz, 1 H], 7.69 [d, $^3J_{FH}$ = 13.2 Hz, 1 H], 8.76 [s, 1 H];^{13}C: δ = 14.35, 28.35, 34.11, 41.42, 44.63, 49.06, 105.90, 111.17 [d, $^2J_{FC}$ = 23.4 Hz], 119.32 [d, $^3J_{FC}$ = 7.8 Hz], 137.12, 145.04 [d, $^2J_{FC}$ = 10.4 Hz], 148.44, 152.14 [d, $^1J_{FC}$ = 249.2 Hz], 166.06, 168.71, 176.06; ^{19}**F**: δ = −119.3; ^{31}**P**: δ = 20.4; **IR** (KBr): ν = 1721 [s, C=O, carboxylic acid], 1628 [vs, C=O], 1244 [vs, P=O], 1017 [vs, P-O] cm^{-1}.

$C_{19}H_{25}FN_3O_{10}P_2$ (536.36) Calcd.: C 42.63, H 4.52, N 7.85, P 11.57, Found: C 42.57, H 4.92, N: 7.88, P: 10.66.

7-{4-[2,2-Bis(diethoxyphosphoryl)ethyl]piperacin-1-yl}-1-ethyl-6-fluor-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid 12

Norfloxacin (1.1 g, 0.0033 mol) was added to 1.0 g (0.0033 mol) of ethylidenebisphosphonic tetraethylester **11** in 100 ml of chloroform. After stirring for one hour at room temperature a solution has formed. The solution was evaporated after stirring over night. The resulting residue was dissolved in ethyl acetate, unreacted norfloxacin was filtered, and the filtrate was slowly evaporated. The crystallized product was filtered and dried under vacuum. Yield: 1.5 g (73%). m.p. 184°C.

NMR (DMSO-d6): ^{1}**H**: δ = 1.29 [t, ^3J = 7.0 Hz, 12 H], 1.51 [t, ^3J = 7.1 Hz, 3 H], 2.68 [m, 4 H], 2.94 [dt, $^3J_{PH}$ = 15.0 Hz, ^3J = 6.6 Hz, 2 H], 3.26 [m, 5 H], 4.13 [m, 8 H], 4.25 [q, ^3J = 7.1 Hz, 2 H], 6.71 [d, $^4J_{FH}$ = 6.9 Hz, 1 H], 7.89 [d, $^3J_{FH}$ = 13.1 Hz, 1 H], 8.59 [s, 1 H], 14.9 [broad]; ^{13}C: δ = 14.42, 16.41 [t, ^3J = 3.3 Hz], 36.19 [t, ^1J = 132.7 Hz], 49.68, 52.37, 62.63, 103.71, 108.23, 112.57 [d, $^2J_{FC}$ = 23.1 Hz], 120.32, 137.04, 145.97 [d, $^2J_{FC}$ = 10.6 Hz], 147.01, 150.94, 167.14, 176.91; ^{19}**F**: δ = −119.4; ^{31}**P**: δ = 22.4; **IR** (KBr): ν = 1727 [s, C=O, carboxylic acid], 1627 [vs, C=O], 1256 [s, P=O], 1024 [vs, P-O] cm^{-1}.

$C_{26}H_{41}N_3FO_9P_2$(620.56) Calcd.: C 50.40, H 6.51, N 6.78, P 10.00, Found: C 50.42, H 6.54, N 6.76, P 9.86.

7-{4-[2,2-Bis(phosphono)ethyl]piperacin-1-yl}-1-ethyl-6-fluor-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid 13

0.31 ml (0.0024 mol) bromotrimethylsilane were added to a solution of 0.15 g (0.0024 mol) of **12** in 5 ml of absolute chloroform. After stirring for

4 hours at room temperature water was added and the mixture evaporated to dryness. The residual oil was digested with diethyl ether until a precipitate formed which was filtered and washed with methanol / water (5/1). The solid product was dried under vacuum. Yield: 1.1 g (92%).

NMR (NaOD): ^{1}**H**: $\delta = 1.49$ [t, $3J = 7.1$ Hz, 3 H], 2.27 [m, 2 H], 2.91 [m, 5 H], 3.34 [m, 4 H], 4.35 [t, $3J = 7.1$ Hz, 2 H], 7.12 [d, $4J_{FH} = 6.8$ Hz, 1 H], 7.92 [d, $3J_{FH} = 7.7$ Hz, 1 H], 8.47 [s, 1 H]; ^{13}C: $\delta = 16.41$, 51.65, 52.44, 54.78, 59.56, 108.35, 114.41, 119.62, 125.32, 139.15, 147.11, 149.63, 174.94, 177.79; ^{19}F: $\delta = -122.2$; ^{31}P: $\delta = 15.2$; **IR** (KBr): $\nu = 1720$ [s, C=O, carboxylic acid], 1639 [vs, C=O], 1264 [vs, P=O], 1016 [vs, P-O] cm-1.

$C_{18}H_{25}N_3FO_9P_2$(508.35) Calcd.: C 42.61, H 4.77, N 8.28, P 12.21, Found: C 42.43, H 5.10, N 8.21, P 11.93.

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