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Synthesis of new 2-[2-(dialkyl(diaryl)phosphoryl)-2-methylpropyl]quinoline-4-carboxylic acids

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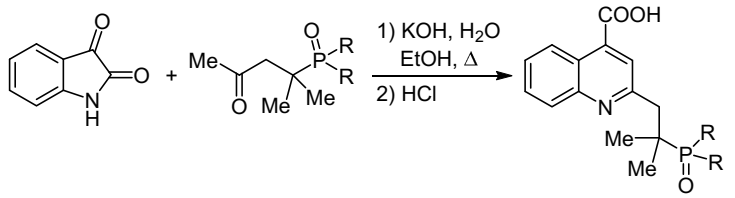


A Pfitzinger reaction of isatin with 2-methyl-(4-oxopent-2-yl)dialkyl(diphenyl)phosphine oxides was used to synthesize new derivatives of 4-quinolinecarboxylic acids, containing a phosphine oxide fragment, and screening for antimicrobial activity was performed.

Keywords: dimephosphone, isatin, 4-phosphoryl ketones, quinoline, quinolinecarboxylic acids, Pfitzinger reaction.

The quinoline nucleus is widely present in pharmacologically active compounds. Quinoline derivatives exhibit various types of biological effects, including antibacterial,[1–4] tuberculostatic,[5–7] antimalarial,[8] and antitumor activity.[9,10] It was also found that quinoline derivatives containing phosphonate or phosphine oxide fragments[11,12] possess anti-inflammatory[13] and antiHIV activity.[14] Besides that, we previously showed that hydrazones of isoniazid and dimephosphone (antacid medication, dimethyl (2-methyl-4-oxopent-2-yl)phosphonate)[15] or its P,C-analogs, dialkyl (2-methyl-4-oxopentyl)phosphine oxides,[16] are significantly less toxic compared to isoniazid, while maintaining its therapeutic effect.[17–19]

We have recently found that phosphine oxides **1**,[16] containing a methyl ketone fragment, are capable of interacting in the Pfitzinger reaction with isatin to yield new phosphorus-containing quinoline-4-carboxylic acids **2**.[20,21]

In this work, we report the synthesis of a range of new 4-quinolinecarboxylic acid derivatives containing a phosphine oxide fragment by using the Pfitzinger reaction – interaction of isatin with 2-methyl(4-oxopent-2-yl)dialkyl-(diphenyl)phosphine oxides (Scheme 1, Table 1). We also performed preliminary biological activity screening for the obtained compounds.

The quinolinecarboxylic acids **2a**–**g** were synthesized by refluxing equimolar amounts of isatin and oxoalkylphosphine oxides **1a**–**g** in aqueous ethanolic medium. The optimum reaction duration according to TLC control was 18–24 h.

Scheme 1

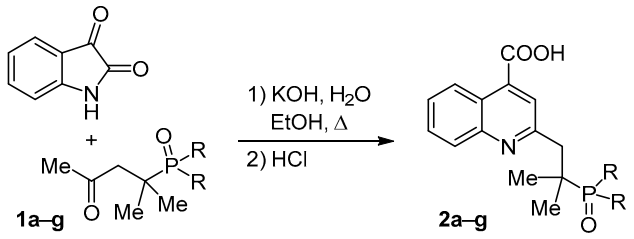
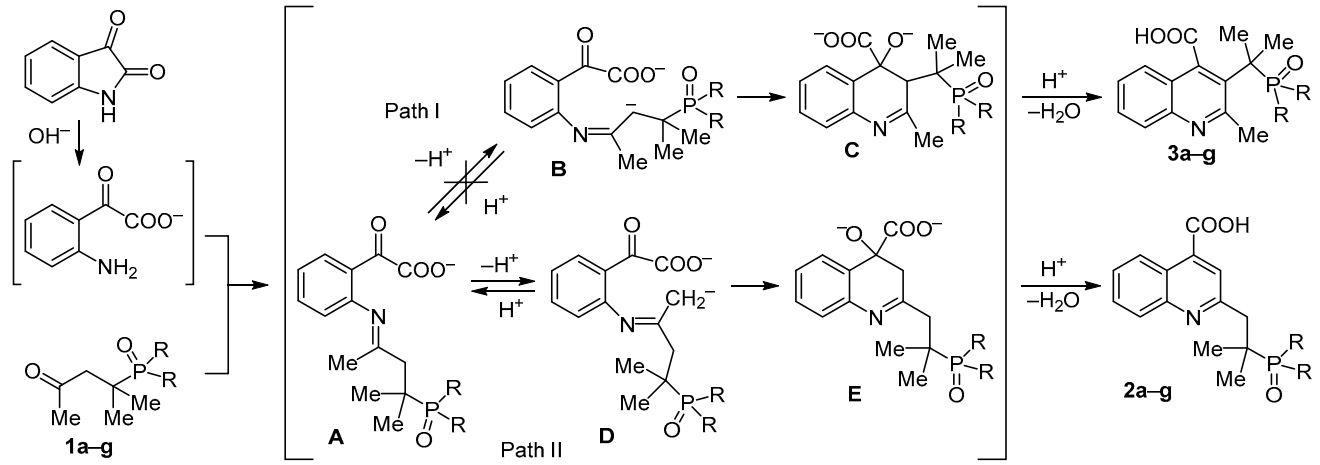


Table 1. The reaction time for obtaining compounds **2a**–**g** and their properties

Compound	R	Reaction time, h	Mp, °C	Yield, %	NMR spectrum $^{31}P-\{^1H\}$, δ_P, ppm
2a	Ph	21	217–219	79	37.2
2b	Me	20	211–212	57	52.8
2c	Et	18	212–214	57	63.5
2d	*n*-Pr	20	180–181	58	61.0
2e	*n*-Bu	22	158–160	47	61.6
2f	*n*-C_5H_{11}	24	127–129	74	61.9
2g	*n*-C_6H_{13}	24	125–127	73	61.6

Scheme 2



There was one signal in $^{31}P–\{^1H\}$ NMR spectra of the mixtures after completion of the reaction, corresponding to the reaction products, compounds **2a**–**g** (Table 1). The use of unsymmetrical ketones in the Pfitzinger reaction may result in a reaction at either the methyl or methylene groups, forming 2- and 3-substituted quinoline-4-carboxylic acids,[22] but in this case the interaction of isatin with phosphoryl ketones **1a**–**g** occurred exclusively at the ketone methyl group to form a single regioisomer.

The high regioselectivity of this reaction was explained by the preference for the smaller or less branched substituent in the Pfitzinger reaction in the case of unsymmetrical dialkyl ketones. According to the proposed mechanism,[23] the initial intermediate should be imine **A** (Scheme 2). The subsequent formation of quinolinecarboxylic acid **3** should have involved the carbanion **B** (and then the structure **C**, route I), the formation of which is difficult due to the steric repulsion of methyl groups at the neighboring carbon atom. The carbanion **B** is additionally destabilized by the electron-donating effect of these methyl groups. Apparently, the slight electron-withdrawing effect of phosphoryl group did not noticeably affect the stability of carbanion. At the same time, the formation of carbanion **D** (and then the intermediate **E**, route II) was not complicated by unfavorable electronic and steric effects from substituents, and the route II was favored.

MALDI mass spectra of quinolinecarboxylic acids **2a**–**g** featured signals of protonated molecular ions $[M+H]^{+\cdot}$. The upfield region of ^1H NMR spectra contained doublets of the methyl groups (1.2–1.3 ppm, $^3J_{PH}$ = 15.3–15.7 Hz). The methylene group protons also gave doublets, albeit at lower field (3.2–3.4 ppm, $^3J_{PH}$ = 7.2–8.0 Hz). The general appearance (multiplicity and chemical shifts) of ^1H NMR signals from alkyl and aryl substituents at the phosphorus atom of compounds **2a**–**g** was similar to the starting phosphine oxides **1** described previously.[16]

The proton signals of quinoline fragment had an appearance characteristic of 2-substituted quinoline-4-carboxylic acids and their derivatives. The most informative upfield ^{13}C NMR signals for compounds **2a**–**g** were those of the methyl groups, observed as quartets (~21 ppm, $^1J_{HC}$ = 127.8 Hz). The signal of quaternary $\underline{C}Me_2$ carbon atom was a doublet coupled to the phosphorus atom at the downfield region (~37 ppm, $^1J_{PC}$ = 63.6–63.7 Hz, for compound **2a** $^1J_{PC}$ = 69.7 Hz). The methylene carbon atom gave a triplet at 42–43 ppm ($^1J_{HC}$ = 127–129 Hz). The general appearance of signals from the phosphorus atom substituents was similar to that in the previously described phosphine oxides **1**.[16] The C-2 carbon atom of the quinoline fragment appeared in $^{13}C–\{^1H\}$ NMR spectrum as a doublet ($^3J_{PC}$ = 13.5–13.7 Hz, for compound **2a** $^3J_{PC}$ = 15.1 Hz). The rest of the carbon signals had appearance characteristic to 2-substituted quinoline-4-carboxylic acids.

An intense stretching vibration band of undissociated carboxyl group was observed in IR spectra of compounds **2a**–**g** at 1680–1700 cm^{-1}. The region of 2250–2700 cm^{-1} lacked any absorption bands, indicating the absence of protonated nitrogen atom in the structure of compounds **2a**–**g**. The aforementioned facts agree with the predominantly neutral molecular form of quinolinecarboxylic acids **2**.

The structure of quinolinecarboxylic acids **2c**,**d** was also confirmed by X-ray structural analysis. The asymmetric part of the unit cell of compound **2c** contained one independent molecule. In the case of compound **2d**, the asymmetric part contained one molecule, as well as solvated molecules of chloroform and water. The phosphorus atom in crystals of both compounds had a destorted tetrahedral configuration. The P(1)–C(10)–C(9)–C(2) fragment also had a nearly s-*trans* conformation (the torsion angle in compound **2c** was –172.4(3)°, while in compound **2d** it was 178.5(2)°). The rest of the molecular geometry (bond lengths, valence angles) was practically equal and close to the standard values within the experimental error.[24]

The crystals also featured OH···O and OH···N hydrogen bonds. In our opinion, the presence of solvated water in crystal of compound **2d** resulted in the formation of both types of hydrogen bonds, while only OH···O bonds were present in crystal of compound **2c**. The solvated water molecule in crystal of compound **2d** formed a bridge between the carbonyl oxygen atom and the nitrogen atom of a neighboring molecule. The hydrogen atom of carboxyl group was linked to the phosphoryl group in both cases. As a result, the crystal structure of compound **2d** contained

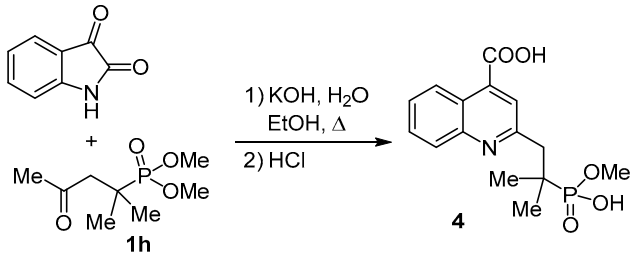
columns of molecules along the *a*0*c* plane, while the crystal structure of compound **2c** had a pleated chain along the 0*b* axis.

The attempt to perform a reaction of isatin with dimethyl 2-methyl-(4-oxopent-2-yl)phosphonate (**1h**) (dimephosphone) showed that a fivefold excess of KOH did not produce the Pfitzinger reaction product, and isatin precipitated after the acidification of reaction mixture. We assumed that dimephosphone was hydrolyzed at one of the phosphate ester bonds under the reaction conditions, and thus the amount of base in the reaction medium was insufficient for this reaction. Indeed, the use of a tenfold excess of KOH resulted in the formation of Pfitzinger reaction product from dimephosphone and isatin, giving quinoline-4-carboxylic acid **4**, in which only one of the methoxy groups at the phosphorus atom was hydrolyzed (Scheme 3).

The molecule of quinolinecarboxylic acid **4** contains a weakly basic quinoline nitrogen atom and a weakly acidic carboxyl group. This compound also contains a phosphonate group with medium strength (pK_a 1–2). At the same time, IR spectrum of derivative **4** lacks absorption bands due to the protonated N^+H nitrogen atom of quinoline ring (2200–2600 cm^{-1}). Thus, we can propose that the quinolinecarboxylic acid **4** exists predominantly in undissociated form.

We performed a preliminary screening of biological activity for quinoline-4-carboxylic acids **2a**–**g**, **4**, which were found to lack *in vitro* bacteriostatic and fungistatic activity over the concentration range of 0.97–500 μg/ml. Nevertheless, the obtained compounds may show other types of biological activity during further testing.

Scheme 3



Experimental

IR spectra were recorded on a Bruker Vector-22 instrument in KBr pellets. ^1H, ^{13}C (^{13}C–{^1H}), and ^{31}P–{^1H} NMR spectra were acquired on a Bruker Avance-400 instrument (400, 100, and 162 MHz, respectively) in DMSO-d_6 (compound **2a**), 1:1 DMSO-d_6–$CDCl_3$ (compound **2c**), D_2O (compounds **2b**, **4**), or $CDCl_3$ (the rest of the compounds). Residual solvent protons were used as internal standard. MALDI mass spectra were recorded on an UltraFlex III TOF/TOF mass spectrometer (Bruker Daltonik GmbH) in linear mode. The laser was Nd: YAG, λ 355 nm. The FlexAnalysis 3.0 software (Bruker Daltonik GmbH) was used for data processing. Positive ions were recorded. Metallic target was used with 2,5-dihydroxybenzoic acid or *p*-nitroaniline matrix. Elemental analysis was performed on a CHN-3 analyzer, the phosphorus content was determined by pyrolysis under oxygen flow. Phosphine oxides **1a**–**g** were obtained according to a previously described method.[16]

The bacteriostatic and fungistatic properties of the obtained compounds were studied by a series of dilutions in liquid growth medium according to published procedures.[25,26] The testing was performed with Gram-positive bacterial cultures: *Staphylococcus aureus ATCC 209p*, *Bacillus cereus ATCC 8035*, as well as with Gram-negative cultures: *Escherichia coli CDC F-50*, *Pseudomonas aeruginosa ATCC 9027*, and fungi: *Aspergillus niger BKMF-1119*, *Trichophyton mentagrophytes var. gypseum 1773*, *Candida albicans 855-653*.

Synthesis of 2-[2-(dialkylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acids 2a–g, 4 (General method).[14,27] A mixture of isatin (1.0 g, 6.8 mmol) and KOH (1.9 g, 33.9 mmol) was dissolved in EtOH (5 ml) and H_2O (10 ml) and stirred for 5 min at 20°C. Then phosphine oxide **1a**–**g** (6.8 mmol) was added, and the obtained mixture was refluxed with stirring for 18–24 h. The reaction progress was controlled by TLC, eluting with CH_2Cl_2 and using the starting phosphine oxide as standard. After cooling, the alcohol was removed under vacuum, the solution was acidified with 10% HCl to pH 5–6. The precipitate that formed was recrystallized from acetone, filtered off, and vacuum-dried (100°C, 10 mmHg).

2-[2-(Diphenylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2a). Yield 2.3 g (79%), white powder, mp 217–219°C. IR spectrum, ν, cm^{-1}: 519, 540, 558, 577, 637, 707, 723, 754, 772, 801, 853, 932, 1000, 1027, 1089, 1115, 1136, 1159, 1188, 1212, 1237, 1264, 1316, 1340, 1370, 1437, 1462, 1592, 1702 (C=O), 2716, 2855, 2926, 2962, 3060, 3365. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (6H, d, $^3J_{PH}$ = 15.7, $C(CH_3)_2$); 3.21 (2H, d, $^3J_{PH}$ = 8.0, CH_2); 7.40–7.56 (7H, m, H-6, H-3,4,5 Ph); 7.64 (1H, t, ^3J = 7.8, H-7); 7.69 (1H, s, H-3); 7.94 (1H, d, ^3J = 8.9, H-8); 7.99 (4H, br. dd, ^3J = 8.4, $^3J_{PH}$ = 8.4, H-2,6 Ph); 8.69 (1H, d, ^3J = 8.4, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.5 (qm (s)*, $^1J_{HC}$ = 129.1, $C(\underline{C}H_3)_2$); 37.8 (dm (d), $^1J_{PC}$ = 69.7, $\underline{C}(CH_3)_2$); 43.2 (br. t (s), $^1J_{HC}$ = 129.3, CH_2); 123.0 (m (s), C-4a); 124.2 (br. d (s), $^1J_{HC}$ = 166.1, C-3); 125.3 (dm (s), $^1J_{HC}$ = 164.9, C-5); 127.3 (br. d (s), $^1J_{HC}$ = 162.9, C-6); 128.5 (dm (d), $^1J_{HC}$ = 161.3, $^3J_{PC}$ = 10.1, C-3,5 Ph); 129.3 (dm (s), $^1J_{HC}$ = 161.6, C-7); 129.6 (br. d (s), $^1J_{HC}$ = 162.7, C-8); 130.8 (br. d (d), $^1J_{PC}$ = 89.3, C-1 Ph); 131.7 (br. d (s), $^1J_{HC}$ = 162.5, C-4 Ph); 132.1 (dm (d), $^1J_{HC}$ = 165.3, $^2J_{PC}$ = 6.2, C-2,6 Ph); 135.7 (br. s (s), C-4); 148.0 (m (s), C-8a); 158.1 (m (d), $^3J_{PC}$ = 15.1, C-2); 167.5 (br. s (s), COOH). ^{31}P–{^1H} NMR spectrum, δ, ppm: 37.2. Mass spectrum, *m*/*z*: 430 $[M+H]^{+\cdot}$. Found, %: C 72.65; H 5.67; N 3.21; P 7.17. $C_{26}H_{24}NO_3P$. Calculated, %: C 72.72; H 5.63; N 3.26; P 7.21.

2-[2-(Dimethylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2b). Yield 1.3 g (63%), yellow powder, mp 211–212°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.02

* Here and below the type of signal in NMR spectrum ^{13}C–{^1H} is given in brackets.

(6H, d, $^3J_{PH}$ = 15.0, C(CH_3)$_2$); 1.39 (6H, d, $^2J_{PH}$ = 12.1, P(CH_3)$_2$); 3.01 (2H, d, $^3J_{PH}$ = 8.5, CH_2); 7.41 (1H, s, H-3); 7.45 (1H, ddd, ^3J = 8.2, ^3J = 6.8, ^4J = 1.3, H-6); 7.62 (1H, ddd, ^3J = 8.4, ^3J = 6.8, ^4J = 1.5, H-7); 7.88 (1H, d, ^3J = 8.3, H-8); 8.66 (1H, d, ^3J = 7.3, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 11.2 (qd (d), $^1J_{HC}$ = 129.7, $^1J_{PC}$ = 65.7, P(CH_3)$_2$); 20.0 (qm (s), $^1J_{HC}$ = 128.5, C($\underline{C}H_3$)$_2$); 35.6 (dm (d), $^1J_{PC}$ = 69.0, $\underline{C}$(CH_3)$_2$); 42.0 (br. t (s), $^1J_{HC}$ = 128.0, CH_2); 120.5 (dt (s), $^1J_{HC}$ = 165.2, $^3J_{HC}$ = 3.8, C-3); 122.9 (m (s), C-4a); 126.0 (dd (s), $^1J_{HC}$ = 164.4, $^3J_{HC}$ = 7.5, C-5); 127.5 (dd (s), $^1J_{HC}$ = 164.2, $^3J_{HC}$ = 8.4, C-6); 127.6 (dd (s), $^1J_{HC}$ = 163.6, $^3J_{HC}$ = 8.4, C-7); 130.9 (dd (s), $^1J_{HC}$ = 163.5, $^3J_{HC}$ = 8.8, C-8); 133.8 (br. s (s), C-4); 146.9 (m (s), C-8a); 157.8 (m (d), $^3J_{PC}$ = 15.3, C-2); 168.2 (d (s), $^3J_{HC}$ = 4.4, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 52.8. Mass spectrum, *m*/*z*: 306 [M+H]$^{+\cdot}$. Found, %: C 62.85; H 6.57; N 4.56; P 10.11. $C_{16}H_{20}NO_3P$. Calculated, %: C 62.94; H 6.60; N 4.59; P 10.14.

2-[2-(Diethylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2c). Yield 1.3 g (57%), yellow powder, mp 212–214°C. IR spectrum, ν, cm^{-1}: 432, 479, 509, 555, 636, 656, 701, 760, 774, 808, 850, 913, 967, 981, 1006, 1036, 1119, 1162, 1189, 1212, 1238, 1265, 1311, 1338, 1356, 1392, 1404, 1422, 1466, 1506, 1557, 1587, 1691 (C=O), 2720, 2885, 2922, 2959, 2976, 3040, 3069, 3368. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (6H, d, $^3J_{PH}$ = 15.4, C(CH_3)$_2$); 1.35 (6H, dt, ^3J= 7.3, $^3J_{PH}$ = 16.0, P($CH_2C\underline{H}_3$)$_2$); 1.77–1.92 (2H, m, part A of ABMX$_3$ system) and 1.94–2.10 (2H, m, part B of ABMX$_3$ system, P($C\underline{H}_2CH_3$)$_2$); 3.43 (2H, d, $^3J_{PH}$ = 7.6, CH_2); 7.61 (1H, ddd, ^3J = 8.3, ^3J = 6.9, ^4J = 1.2, H-6); 7.71 (1H, ddd, ^3J = 8.3, ^3J = 6.9, ^4J = 1.3, H-7); 8.08 (1H, s, H-3); 8.11 (1H, d, ^3J = 8.2, H-8); 8.93 (1H, d, ^3J = 7.8, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 5.2 (qm (d), $^1J_{HC}$ = 128.9, $^2J_{PC}$ = 5.4, P($CH_2\underline{C}H_3$)$_2$); 15.3 (tdm (d), $^1J_{HC}$ = 126.6, $^1J_{PC}$ = 62.6, P($\underline{C}H_2CH_3$)$_2$); 19.7 (qm (s), $^1J_{HC}$ = 128.2, $^3J_{HC}$ = 4.8, C($\underline{C}H_3$)$_2$); 35.4 (dm (d), $^1J_{PC}$ = 64.7, $\underline{C}$(CH_3)$_2$); 41.7 (br. t (s), $^1J_{HC}$ = 129.2, CH_2); 122.3 (m (s), C-4a); 123.2 (dt (s), $^1J_{HC}$ = 166.6, $^3J_{HC}$ = 3.9, C-3); 124. 5 (dd (s), $^1J_{HC}$ = 164.8, $^3J_{HC}$ = 6.9, C-5); 126.1 (dd (s), $^1J_{HC}$ = 161.6, $^3J_{HC}$ = 8.5, C-6); 127.8 (dd (s), $^1J_{HC}$ = 165.5, $^3J_{HC}$ = 7.9, C-7); 128.5 (dd (s), $^1J_{HC}$ = 161.2, $^3J_{HC}$ = 9.3, C-8); 135.0 (br. s (s), C-4); 146.8 (dd (s), $^3J_{HC}$ = 9.4, $^2J_{HC}$ = 6.6, C-8a); 156.5 (m (d), $^3J_{PC}$ = 13.4, C-2); 166.5 (d (s), $^3J_{HC}$ = 5.0, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 63.5. Mass spectrum, *m*/*z*: 334 [M+H]$^{+\cdot}$. Found, %: C 64.65; H 7.29; N 4.17; P 9.21. $C_{18}H_{24}NO_3P$. Calculated, %: C 64.85; H 7.26; N 4.20; P 9.29.

2-[2-(Dipropylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2d). Yield 1.4 g (57%), white powder, mp 180–181°C. IR spectrum, ν, cm^{-1}: 400, 437, 484, 512, 558, 616, 640, 649, 699, 737, 774, 790, 804, 811, 855, 909, 935, 965, 1030, 1046, 1095, 1142, 1168, 1189, 1214, 1243, 1266, 1314, 1341, 1356, 1373, 1395, 1413, 1463, 1507, 1557, 1589, 1703 (C=O), 2874, 2934, 2965, 3071, 3157, 3341, 3580. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (6H, dt, ^3J = 7.1, $^4J_{PH}$ = 1.2, P($CH_2CH_2C\underline{H}_3$)$_2$); 1.25 (6H, d, $^3J_{PH}$ = 15.3, C($C\underline{H}_3$)$_2$); 1.70–2.00 (8H, m, P($C\underline{H}_2C\underline{H}_2Me$)$_2$); 3.40 (2H, d, $^3J_{PH}$ = 7.5, $C\underline{H}_2CMe_2$); 7.59 (1H, ddd, ^3J = 8.3, ^3J = 6.8, ^4J = 1.3, H-6); 7.71 (1H, ddd, ^3J = 8.4, ^3J = 6.8, ^4J = 1.4, H-7); 8.05 (1H, s, H-3); 8.09 (1H, dd, ^3J = 8.2, ^4J = 1.1, H-8); 8.90 (1H, dd, ^3J = 8.6, ^4J = 1.3, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 16.1 (tdm (d), $^1J_{HC}$ = 128.8, $^2J_{PC}$ = 4.5, P($CH_2\underline{C}H_2Me$)$_2$); 16.8 (qdm (d), $^1J_{HC}$ = 125.8, $^3J_{PC}$ = 14.3, P($CH_2CH_2\underline{C}H_3$)$_2$); 21.0 (qm (s), $^1J_{HC}$ = 128.0, C($\underline{C}H_3$)$_2$); 26.4 (tdm (d), $^1J_{HC}$ = 126.5, $^1J_{PC}$ = 61.3, P($\underline{C}H_2CH_2Me$)$_2$); 37.0 (dm (d), $^1J_{PC}$ = 63.7, $\underline{C}$(CH_3)$_2$); 42.6 (br. t (s), $^1J_{HC}$ = 128.8, $\underline{C}H_2CMe_2$); 124.2 (m (s), C-4a); 125.0 (dt (s), $^1J_{HC}$ = 165.5, $^3J_{HC}$ = 3.7, C-3); 126.3 (dd (s), $^1J_{HC}$ = 165.8, $^3J_{HC}$ = 7.2, C-5); 127.5 (dd (s), $^1J_{HC}$ = 161.7, $^3J_{HC}$ = 8.2, C-6); 129.0 (dd (s), $^1J_{HC}$ = 163.3, $^3J_{HC}$ = 6.8, C-7); 129.7 (dd (s), $^1J_{HC}$ = 161.1, $^3J_{HC}$ = 9.2, C-8); 137.2 (br. s (s), C-4); 148.4 (dd (s), $^3J_{HC}$ = 8.2, $^2J_{HC}$ = 7.2, C-8a); 157.6 (m (d), $^3J_{PC}$ = 13.8, C-2); 168.2 (d (s), $^3J_{HC}$ = 5.3, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 61.0. Mass spectrum, *m*/*z*: 361.7 [M+H]$^{+\cdot}$. Found, %: C 66.35; H 7.92; N 3.79; P 8.51. $C_{20}H_{28}NO_3P$. Calculated, %: C 66.47; H 7.81; N 3.88; P 8.57.

2-[2-(Dibutylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2e). Yield 1.25 g (47%), light-yellow powder, mp 158–160°C. IR spectrum, ν, cm^{-1}: 473, 509, 551, 637, 695, 716, 730, 745, 768, 801, 815, 850, 906, 968, 1004, 1027, 1050, 1114, 1164, 1191, 1243, 1259, 1310, 1337, 1369, 1411, 1507, 1556, 1590, 1695 (C=O), 2872, 2932, 2959, 2964, 3038, 3063, 3422. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97 (6H, t, ^3J = 7.3, P((CH_2)$_3$C$\underline{H}_3$)$_2$); 1.29 (6H, d, $^3J_{PH}$ = 15.3, C($C\underline{H}_3$)$_2$); 1.40–1.52 (4H, m, P((CH_2)$_2C\underline{H}_2Me$)$_2$); 1.64–2.07 (8H, m, P(($C\underline{H}_2$)$_2CH_2Me$)$_2$); 3.45 (2H, d, $^3J_{PH}$ = 7.2, $C\underline{H}_2CMe_2$); 7.62 (1H, t, ^3J = 7.6, H-6); 7.74 (1H, t, ^3J = 7.5, H-7); 8.10 (1H, s, H-3); 8.14 (1H, d, ^3J = 7.5, H-8); 8.93 (1H, d, ^3J = 8.4, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.6 (qm (s), $^1J_{HC}$ = 125.1, P((CH_2)$_3\underline{C}H_3$)$_2$); 21.0 (qm (s), $^1J_{HC}$ = 128.0, C($\underline{C}H_3$)$_2$); 23.9 (tdm (d), $^1J_{HC}$ = 125.1, $^1J_{PC}$ = 61.6, P($\underline{C}H_2(CH_2)_2Me$)$_2$); 24.2 (tdm (d), $^1J_{HC}$ = 126.4, $^2J_{PC}$ = 4.6, P($CH_2\underline{C}H_2CH_2Me$)$_2$); 24.5 (tdm (d), $^1J_{HC}$ = 124.7, $^3J_{PC}$ = 13.6, P((CH_2)$_2\underline{C}H_2Me$)$_2$); 37.0 (dm (d), $^1J_{PC}$ = 63.6, $\underline{C}$(CH_3)$_2$); 42.7 (br. t (s), $^1J_{HC}$ = 127.8, $\underline{C}H_2CMe_2$); 124.1 (m (s), C-4a); 125.0 (dt (s), $^1J_{HC}$ = 165.9, $^3J_{HC}$ = 3.7, C-3); 126.3 (dd (s), $^1J_{HC}$ = 166.4, $^3J_{HC}$ = 7.6, C-5); 127.4 (dd (s), $^1J_{HC}$ = 161.9, $^3J_{HC}$ = 8.7, C-6); 128.8 (dm (s), $^1J_{HC}$ = 165.1, C-7); 129.7 (dm (s), $^1J_{HC}$ = 160.6, C-8); 137.3 (br. s (s), C-4); 148.3 (m (s), C-8a); 157.5 (m (d), $^3J_{PC}$ = 13.7, C-2); 168.1 (d (s), $^3J_{HC}$ = 4.9, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 61.6. Mass spectrum, *m*/*z*: 390 [M+H]$^{+\cdot}$. Found, %: C 67.78; H 8.32; N 3.57; P 7.88. $C_{22}H_{32}NO_3P$. Calculated, %: C 67.85; H 8.28; N 3.60; P 7.95.

2-[2-(Dipentylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2f). Yield 2.1 g (74%), light-yellow powder, mp 127–129°C. IR spectrum, ν, cm^{-1}: 440, 512, 548, 638, 689, 728, 765, 801, 820, 1027, 1114, 1165, 1187, 1211, 1245, 1269, 1318, 1340, 1410, 1466, 1507, 1557, 1596, 1695 (C=O), 2872, 2931, 2957, 3431. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (6H, t, ^3J = 7.1, P((CH_2)$_4$C$\underline{H}_3$)$_2$); 1.30 (6H, d, $^3J_{PH}$ = 15.2, C(CH_3)$_2$); 1.34–1.49 (8H, m, P((CH_2)$_2C\underline{H}_2C\underline{H}_2Me$)$_2$); 1.89–2.05 (8H, m, P(($C\underline{H}_2$)$_2$($CH_2$)$_2Me$)$_2$); 3.50 (2H, d, $^3J_{PH}$ = 8.5, $C\underline{H}_2CMe_2$); 7.65 (1H, br. t, ^3J = 7.6, H-6); 7.77 (1H, br. t, ^3J = 7.7,

H-7); 8.14 (1H, s, H-3); 8.24 (1H, br. s, H-8); 8.93 (1H, d, ^3J = 8.4, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.9 (br. qt (s), $^1J_{HC}$ = 124.7, $^2J_{HC}$ = 3.6, P((CH$_2$)$_4$CH$_3$)$_2$); 21.1 (qm (s), $^1J_{HC}$ = 128.2, C(CH$_3$)$_2$); 21.9 (tdm (d), $^1J_{HC}$ = 126.7, $^2J_{PC}$ = 4.6, P(CH$_2$CH$_2$(CH$_2$)$_2$Me)$_2$); 22.1 (tm (s), $^1J_{HC}$ = 126.5, P((CH$_2$)$_3$CH$_2$Me)$_2$); 24.2 (tdm (d), $^1J_{HC}$ = 126.8, $^1J_{PC}$ = 61.2, P(CH$_2$(CH$_2$)$_3$Me)$_2$); 33.6 (tdm (d), $^1J_{HC}$ = 125.6, $^3J_{PC}$ = 13.2, P ((CH$_2$)$_2$CH$_2$CH$_2$Me)$_2$); 37.0 (dm (d), $^1J_{PC}$ = 63.6, CMe$_2$); 42.8 (br. t (s), $^1J_{HC}$ = 127.9, CH$_2$CMe$_2$); 124.1 (m (s), C-4a); 125.0 (dt (s), $^1J_{HC}$ = 165.7, $^3J_{HC}$ = 3.8, C-3); 126.3 (dd (s), $^1J_{HC}$ = 166.3, $^3J_{HC}$ = 7.6, C-5); 127.3 (dd (s), $^1J_{HC}$ = 161.6, $^3J_{HC}$ = 8.6, C-6); 129.0 (dm (s), $^1J_{HC}$ = 161.6, C-7); 129.6 (br. dd (s), $^1J_{HC}$ = 160.4, $^3J_{HC}$ = 8.8, C-8); 137.1 (br. s (s), C-4); 148.4 (m (s), C-8a); 157.6 (m (d), $^3J_{PC}$ = 13.5, C-2); 168.1 (d (s), $^3J_{HC}$ = 5.1, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 61.9. Mass spectrum, *m*/*z*: 418 [M+H]$^{+\cdot}$. Found, %: C 68.98; H 8.75; N 3.31; P 7.40. $C_{24}H_{36}NO_3P$. Calculated, %: C 69.04; H 8.69; N 3.35; P 7.42.

2-[2-(Dihexylphosphoryl)-2-methylpropyl]quinoline-4-carboxylic acid (2g). Yield 2.86 g (94%), white powder, mp 125–127°C. IR spectrum, ν, cm^{-1}: 489, 523, 553, 640, 720, 768, 815, 860, 911, 977, 1008, 1027, 1045, 1139, 1168, 1212, 1244, 1262, 1301, 1326, 1393, 1466, 1558, 1582, 1609, 1709 (COOH), 2731, 2857, 2926, 2955, 3062, 3390. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (6H, t, $^3J_{HH}$ = 7.1, P((CH$_2$)$_5$CH$_3$)$_2$); 1.29 (6H, d, $^3J_{PH}$ = 15.2, C(CH$_3$)$_2$)); 1.32–1.36 (8H, m, P((CH$_2$)$_3$CH$_2$CH$_2$Me)$_2$); 1.39–1.49 (4H, m, P((CH$_2$)$_2$CH$_2$(CH$_2$)$_2$Me)$_2$); 1.63–2.05 (8H, m, P((CH$_2$)$_2$(CH$_2$)$_3$Me)$_2$); 3.47 (2H, d, $^3J_{PH}$ = 6.9, CH$_2$CMe$_2$); 7.63 (1H, ddd, ^3J = 8.2, ^3J = 6.9, ^4J = 1.2, H-6); 7.75 (1H, ddd, ^3J = 8.3, ^3J = 6.9, ^4J = 1.3, H-7); 8.14 (1H, s, H-3); 8.17 (1H, br. s, H-8); 8.93 (1H, dd, ^3J = 8.6, ^4J = 1.4, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.0 (br. q (s), $^1J_{HC}$ = 124.4, P((CH$_2$)$_5$CH$_3$)$_2$); 21.1 (qm (s), $^1J_{HC}$ = 127.8, C(CH$_3$)$_2$); 22.2 (tm (d), $^1J_{HC}$ = 129.3, $^2J_{PC}$ = 4.4, P(CH$_2$CH$_2$(CH$_2$)$_3$Me)$_2$); 22.4 (tm (s), $^1J_{HC}$ = 125.4, P((CH$_2$)$_4$CH$_2$Me)$_2$); 24.3 (tdm (d), $^1J_{HC}$ = 128.9, $^1J_{PC}$ = 61.2, P((CH$_2$(CH$_2$)$_4$Me)$_2$); 31.1 (tm (d), $^1J_{HC}$ = 125.1, $^3J_{PC}$ = 13.2, P((CH$_2$)$_2$CH$_2$(CH$_2$)$_2$Me)$_2$); 31.3 (tm (s), $^1J_{HC}$ = 125.4, P((CH$_2$)$_3$CH$_2$CH$_2$Me)$_2$); 37.0 (dm (d), $^1J_{PC}$ = 63.7, CMe$_2$); 43.0 (br. t (s), $^1J_{HC}$ = 126.5, CH$_2$CMe$_2$); 124.1 (m (s), C-4a); 124.9 (dt (s), $^1J_{HC}$ = 166.1, $^3J_{HC}$ = 3.7, C-3); 126.2 (dd (s), $^1J_{HC}$ = 165.8, $^3J_{HC}$ = 7.1, C-5); 127.2 (dd (s), $^1J_{HC}$ = 161.6, $^3J_{HC}$ = 8.7, C-6); 129.0 (dm (s), $^1J_{HC}$ = 162.3, C-7); 129.5 (br. dd (s), $^1J_{HC}$ = 162.0, $^3J_{HC}$ = 9.5, C-8); 137.0 (br. s (s), C-4); 148.5 (m (s), C-8a); 157.6 (m (d), $^3J_{PC}$ = 13.7, C-2); 168.1 (d (s), $^3J_{HC}$ = 5.0, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 61.6. Mass spectrum, *m*/*z*: 446 [M+H]$^{+\cdot}$. Found, %: C 70.01; H 9.14; N 3.11; P 6.92. $C_{26}H_{40}NO_3P$. Calculated, %: C 70.08; H 9.05; N 3.14; P 6.95.

2-{2-[Hydroxy(methoxy)phosphoryl]-2-methylpropyl}-quinoline-4-carboxylic acid (4). Yield 1.5 g (68%), yellow powder, mp >300°C (decomp.). IR spectrum, ν, cm^{-1}: 450, 462, 473, 501, 516, 528, 561, 596, 636, 647, 670, 710, 748, 767, 782, 822, 864, 872, 898, 959, 1013, 1046 (POC), 1068 (POO$^-$), 1098, 1127, 1142, 1182, 1211, 1296, 1322, 1343, 1360, 1397, 1420, 1441, 1456, 1474, 1505, 1559, 1590, 1688 (C=O), 2845, 2870, 2966, 3008, 3058, 3207, 3382. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.99 (6H, d, $^3J_{PH}$ = 14.1, C(CH$_3$)$_2$); 3.01 (2H, d, $^3J_{PH}$ = 9.2, CH$_2$CMe$_2$); 3.45 (3H, d, $^3J_{PH}$ = 9.2, OCH$_3$); 7.39 (1H, ddd, ^3J = 8.2, ^3J = 6.8, ^4J = 1.3, H-6); 7.44 (1H, s, H-3); 7.56 (1H, ddd, ^3J = 8.3, ^3J = 6.8, ^4J = 1.5, H-7); 7.85 (1H, d, ^3J = 7.9, H-8); 8.66 (1H, dd, ^3J = 8.4, ^4J = 1.3, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.6 (qm (d), $^1J_{HC}$ = 127.6, $^3J_{HC}$ = 4.7, $^2J_{PC}$ = 3.0, C(CH$_3$)$_2$); 35.9 (dm (d), $^1J_{PC}$ = 139.4, CMe$_2$); 44.0 (t (s), $^1J_{HC}$ = 129.6, CH$_2$); 52.0 (qd (d), $^1J_{HC}$ = 146.1, $^2J_{PC}$ = 6.7, OCH$_3$); 120.7 (dt (s), $^1J_{HC}$ = 164.7, $^3J_{HC}$ = 4.3, C-3); 122.6 (m (s), C-4a); 125.7 (dd (s), $^1J_{HC}$ = 162.8, $^3J_{HC}$ = 7.5, C-5); 126.7 (dd (s), $^1J_{HC}$ = 162.7, $^3J_{HC}$ = 8.4, C-6); 127.1 (dd (s), $^1J_{HC}$ = 161.8, $^3J_{HC}$ = 7.2, C-7); 130.0 (dd (s), $^1J_{HC}$ = 161.8, $^3J_{HC}$ = 8.9, C-8); 145.9 (d (s), $^3J_{HC}$ = 3.9, C-4); 146.7 (dd (s), $^3J_{HC}$ = 9.2, $^2J_{HC}$ = 6.9, C-8a); 159.2 (dtd (d), $^3J_{HC}$ = 16.3, $^2J_{HC}$ = 5.9, $^3J_{PC}$ = 3.1, C-2); 175.1 (d (s), $^3J_{HC}$ = 4.5, COOH). ^{31}P–{^{1}H} NMR spectrum, δ, ppm: 26.9. Mass spectrum, *m*/*z*: 323 [M]$^{+\cdot}$. Found, %: C 55.65; H 5.67; N 4.28; P 9.51. $C_{15}H_{18}NO_5P$. Calculated, %: C 55.73; H 5.61; N 4.33; P 9.58.

X-ray structural study of compound 2c. Crystals of compound **2c** ($C_{18}H_{24}NO_3P$, *M* 333.37) suitable for X-ray structural analysis were obtained by slow evaporation of a solution in 1:1 $CHCl_3$–DMSO mixture. Monocrystal X-ray structural investigation of compound **2c** was performed on a Smart Apex II diffractometer with graphite monochromator; MoKα λ=0.71073 Å; ω-scanning. Data acquisition, determination and refinement of unit cell parameters, and processing of diffraction data were performed with the SADABS software.[28] The structure was solved by the direct method and refined by full matrix method of least squares by F^2 with the SHELX 2013 software suite.[29] The structure of compound **2c** was identified as twinned crystal, divided in two domains by the standard procedure of the PLATON software.[30] The graphical representation of molecules in the crystal was obtained with PLATON[30] and ORTEP[31] software. The complete X-ray structural dataset for compound **2c** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1412083).

X-ray structural study of compound 2d. Crystals of compound **2d** ($C_{20}H_{28}NO_3P{\cdot}H_2O{\cdot}CHCl_3$, *M* 498.79) suitable for X-ray structural study were obtained by slow evaporation from $CHCl_3$. Monocrystal X-ray structural study of compound **2d** was performed on a Smart Apex II diffractometer with a graphite monochromator; MoKα λ=0.71073 Å, ω-scanning. Data acquisition, determination and refinement of unit cell parameters, and processing of diffraction data were performed with the SADABS software.[28] The structure was solved by direct method and refined by full matrix method of least squares by F^2 with the SHELX 2013 software suite.[29] One of the propyl groups at the phosphorus atom and the solvated chloroform molecule in crystal **2d** were found to be disordered over two locations, with the relative occupancy of 0.69 and 0.31 for the propyl group, as well as 0.57 and 0.43 for the chloroform molecule. The graphical representation of molecules in the crystal was obtained with PLATON[30] and ORTEP[31] software. The complete X-ray structural dataset for compound **2d** was deposited at the Cambridge

Crystallographic Data Center (deposit CCDC 1412082).

The supplementary information file containing X-ray structural data for compounds **2c**,**d** is available for the authorized users.

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