PEPTIDE COUPLING REACTIONS WITH PHOSPHONO-PHOSPHINO SUBSTITUTED $\gamma$-THIAPYRONES – FIRST STEP TO UNUSUAL PEPTIDES

Dirk Uwe Hahn and Richard Neidlein*  
Pharmazeutisch-Chemisches Institut, Im Neuenheimer Feld 364, 69120 Heidelberg, Germany

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Abstract – The reactions of phosphono-phosphino substituted $\gamma$-thiapyrones (8/9) with pentafluorphenyldiphenylphosphinate – FDPP – (7) and protected $\alpha$-L-amino acids (10) lead to chiral $\alpha$-peptido substituted phosphono-phosphino $\gamma$-thiapyrones (12/13). Besides $\beta$-peptido- and peptoido substituted phosphono $\gamma$-thiapyrones (16/21) are synthesized in the presence of FDPP as an efficient peptide coupling reagent.

INTRODUCTION

In our previous papers we described the syntheses and reactions of new phosphono-phosphino substituted $\gamma$-thiapyrones$^{1a-c}$ and many different phosphono-phosphino substituted heterocycles were studied by us.$^{1d-g}$ Here, we describe peptide coupling reactions with phosphono-phosphino substituted $\gamma$-thiapyrones. In the last decade, organic chemists have been inspired by the concepts of peptides which structures are referred as unnatural biopolymers or peptido mimetics and which have been developed rapidly in medicinal chemistry.$^{2a,b}$

Phosphonopeptides$^3$ form one of those classes of compounds whose showing interesting relationship between synthetic organic chemistry and biological studies on phosphorus containing compounds. One of the most interested synthetic phosphonopeptides is L-alanyl-L-1-aminoethylphosphonic acid (Alafosfalin) (1) which interferes with bacterial cell wall synthesis with potent antibacterial activity especially against Gram negative bacilli.$^4$ Another interested phosphonopeptide is the phosphorus containing analogue (2) of the amino acid statine which is
a potent binding inhibitor of aspartic peptidase.\textsuperscript{5a} Besides phosphinotricin (3), an inhibitor of glutaminic acid synthetase, and fosfomycin (4) interfere with bacterial cell wall synthesis as an inhibitor of peptidoglycane synthesis.\textsuperscript{5b-d}

The present paper describes the investigations of our studies concerning the preparation of $\alpha$-peptido-, $\beta$-peptido- and peptoido substituted phosphono-phosphino-$\gamma$-thiapyrones as starting compounds of unusual peptides.

**RESULTS AND DISCUSSION**

There are many coupling reagents in peptide synthesis described in the literature in reviews and monographs.\textsuperscript{6,7a-c} We choose pentafluorphenyldiphenylphosphinate (FDPP) (7) as an efficient coupling reagent for peptide synthesis without racemization. Besides there is no problem of insoluble by-product such as (DCU) dicyclohexylurea and FDPP has a high coupling speed.\textsuperscript{8} FDPP is prepared by mixing equimolar amounts of diphenylphosphinic chloride (5) and pentafluorphenol (6) in the presence of imidazole in CH$_2$Cl$_2$ at room temperature.\textsuperscript{8} (Scheme 1).

Scheme 1: Synthesis of FDPP (7)
The phosphono-phosphino substituted γ-thiapyrones (8/9) as amine component, protected α-L-amino acids (10) as carbonyl component, N,N-diisopropylethylamine (Hünig's base) (11) as the tertiary amine and pentafluorphenyldiphenylphosphinate (FDPP) (7) as the coupling reagent in CH₂Cl₂ at room temperature gave the chiral α-L-peptido substituted phosphono-phosphino γ-thiapyrones (12/13) (Scheme 2).

![Image of the reaction scheme](image)

\[ R^1 \text{P} \begin{array}{c} \text{S} \\ \text{H}_2 \text{N} \end{array} \] + \[ \text{R}^4 \text{N}^- \text{H} \text{COOH} \] \[ \xrightarrow{1. (iPr)_2EtN (11)} \] \[ \text{CH}_2\text{Cl}_2, \text{rt, 4-5 h} \] \[ \text{R}^1 \text{P} \begin{array}{c} \text{S} \\ \text{Y} \text{H} \text{NH} \end{array} \text{CO} \]

\[ Y = \text{Fmoc (fluorenyl-9-methoxycarbonyl); Cbz (benzyloxy carbonyl)} \]

<table>
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<th>( R^4 )</th>
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Scheme 2: Syntheses of chiral α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones (12/13)

The UV spectra of the Fmoc- and Cbz-protected α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones (12/13) are different. The Cbz-protected compounds (12.2a, 12.1b, 12.3b, 12.4c and 13.3d) show three characteristic absorption bands between \( \lambda_{\text{max}} = 270-280 \) nm, \( \lambda_{\text{max}} = 310-320 \) nm and \( \lambda_{\text{max}} = 330-334 \) nm (sh). The molecular ions of the compounds (12/13) are measured with FAB–MS spectra. The Fmoc-protecting compounds lead to the base
peak m/z = 178 and the Cbz-protecting compounds to the m/z = 91 which reflects the benzyl fragment. The CO group of the ester-function of the Fmoc-protected compounds is located at 1720–1740 cm⁻¹; the ester-function of the Cbz-protected compounds is given at 1708–1720 cm⁻¹ as a sharp absorption band.

The ¹H NMR spectra of the α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones (12/13) show all characteristic signals in order to describe the structure. The sharp singulet at 5.15 ppm shows the methylene group of the Cbz-protecting group; the five aromatic protons of the benzyl group are given as a singulet at 7.37 ppm. The NH–proton of the protected α-L-amino acid is given as a triplet at 5.35–5.40 ppm with ³JHH = 3.2 Hz; the NH-proton which explains the hydrogen-bonding of the oxygen atom of the P=O bonding in the phosphonate (-phosphinate) group is given at 12.90–13.20 ppm.¹a,b The proton of the chiral carbon atom is registrated at 4.35–4.50 ppm with ³JHH = 3.8 Hz. The phosphinate derivative (13.3d) shows another multiplet at 7.30–7.60 ppm locating the phenylligand of the phosphinate group. The chiral carbon atom of the amino acid is given in the ¹³C NMR spectra at 52.9–56.5 ppm which shows the various groups of the amino acids. The methylene group of the Cbz-protecting group is registrated at 67.4 ppm. The CO groups of the ester function of the protecting groups are given at 155.9–156.8 ppm; the amide function is more downfield shifted at 170–171 ppm. Both ¹H– and ¹³C NMR spectra gave no hints of racemization.

All the compounds (12/13) are obtained in optical pure form as α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones. Optical rotations of the compounds (12/13) are measured between −6 and −20°.

Furthermore we try to couple β-amino acids with phosphono-phosphino substituted γ-thiapyrones in the presence of FDPP. The synthesis of enantiomerically pure β-amino acids has increased in the last decade due to the pharmacological and biological effects shown in the free form and incorporated in peptides.¹⁰a,b An important class of β-amino acid derivatives are the antibiotic β-lactams,¹¹ the anticancer agent paclitaxel (taxol),¹² macrocyclic peptides from marine organisms¹³ and novel emericedins A, B and C which were isolated from the culture broth of Emericella quadrilineata having inhibitory activity of long chain fatty acid oxidation.¹⁴ The β-amino acids (15) were prepared in two steps of commercially available N-Fmoc-L-protected α-amino acids (10) following the Arndt-Eistert pathway with diazo ketone intermediates (14) and Wolff rearrangement (Scheme 3).⁹a–c,¹⁵a,b
Scheme 3: Syntheses of Fmoc-L-protected β-amino acids (15)

The following reaction of the phosphono substituted γ-thiapyrones (8) with Fmoc-β-amino acids (15) in the presence of N,N-diisopropylethylamine (11) and FDPP (7) as the coupling reagent lead to the β-peptido-substituted phosphono-γ-thiapyrones (16) (Scheme 4).

<table>
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<th>R⁵</th>
<th>yield [%]</th>
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</table>

Scheme 4: Syntheses of β-peptido-substituted phosphono-γ-thiapyrones (16)

The reactivity of the β-peptide bond formation is lower than the α-peptide bond formation. The
reaction time is much more higher and the yields of the \( \beta \)-peptido-substituted phosphono-\( \gamma \)-thiapyrones (16) are moderated compared to the \( \alpha \)-peptido-derivatives.

The UV spectra of the \( \beta \)-peptido-substituted phosphono-\( \gamma \)-thiapyrones (16) have no characteristic difference compared to the UV spectra of the \( \alpha \)-peptido-substituted phosphono-phosphino-\( \gamma \)-thiapyrones (12/13). The Fmoc-\( \beta \)-peptido-substituted compounds (16) show two strong absorption bands at 1734 cm\(^{-1}\) and 1700 cm\(^{-1}\) which locate the ester function of the fluorenylmethoxycarbonylligand and the amide function. The molecular ions are observed in the FAB-MS spectra \([C_{14}H_{10}]^+\) and m/z = 154 which is the biphenyl fragment of the Fmoc-protecting group.

The methylene group of the \( \beta \)-amino acid in \( \alpha \)-position of the amide group is located in the \( ^1 \)H NMR spectra at 2.74-2.78 ppm with a \( ^3 \)J\( HH\)-coupling constant of 7.2 Hz. The proton of the chiral carbon atom of the \( \beta \)-amino acid is observed at 4.01 ppm as a triplet with a \( ^3 \)J\( HH\)-coupling constant of 4.6-4.8 Hz. Besides the NH-proton of the Fmoc group is given as a triplet (\( ^3 \)J\( HH \approx 4\) Hz) at 5.30-5.35 ppm. The methylene group in \( \alpha \)-position of the amide group is located at 38.6-42.4 ppm; the chiral carbon atom of the \( \beta \)-amino acid at 49.6-53.1 ppm. The ester function and the CO signal of the amide group are located in the same manner as it is in the compounds (12/13). The signals are measured at 159-160 ppm (ester function) and at 169-170 ppm (CO of the amide group). The \( \beta \)-peptido-substituted phosphono-\( \gamma \)-thiapyrones (16) are isolated after chromatography separation as light red crystals. The melting points are measured between 70-95\(^\circ\)C. The melting points of the \( \beta \)-peptido-substituted phosphono-\( \gamma \)-thiapyrones (16) are much lower compared to the melting points of the \( \alpha \)-peptido compounds (12/13).

Another attractive targets in synthetic, biological and medicinal chemistry are \( N \)-substituted glycines, or "peptoids", which were proposed as new peptidomimetic backbones.\(^{16}\) Peptoids have many advantages e.g. high metabolic stability, high flexibility, the absence of chirality and useful for lead-finding.\(^{17}\) An improved synthesis of peptoids was reported by Liskamp et al.\(^{18}\) In our case we prepared fluorenyl-9-methoxycarbonyloxy-\( N \)-benzylglycine (20) (Scheme 5) starting from ethyl bromoacetate (17) in order to couple the peptoid with phosphono substituted \( \gamma \)-thiapyrones (8). The \( N \)-substituted glycine ethyl ester (18) was saponified using Tesser's base\(^{19}\), yielding the sodium salt (19) which was attached with fluorenyl-9-methoxycarbonylsuccinimid as a protecting group to give the peptoid (20).
Scheme 5: Synthesis of fluorenyl-9-methoxycarbonyloxy-N-benzylglycine (20)

The reaction of phosphono-$\gamma$-thiapyrones (8) with the peptoid (20) and FDPP conditions lead to peptido-substituted phosphono-$\gamma$-thiapyrones (21) (Scheme 6). Even this kind of reaction shows that FDPP is an efficient coupling reagent in order to synthesize $\alpha$-peptido-, $\beta$-peptido- and peptido-substituted phosphono-phosphino-$\gamma$-thiapyrones although the yields of the peptido-substituted $\gamma$-thiapyrones (21) aren’t satisfactory but this could be a novel synthetic route of the first step to unusual peptides and peptoids.

Scheme 6: Syntheses of peptido-substituted phosphono-$\gamma$-thiapyrones (21)

The NMR spectra clearly show the presence of both rotamers and it is in agreement with the literature.\textsuperscript{18} Both protons of the methylene group of the $N$-benzyl-substituted glycine...
(peptoidligand) are located as two different singlets at 3.75 ppm and 4.07 ppm. Besides the protons of the methylene group of the benzylligand are localized as two different doublets at 4.56-4.61 ppm and the NH-signal which is incorporated in the hydrogen bond to the phosphonate group is split into two different singlets at 12.82 ppm and 13.11 ppm. The compounds (21) were isolated as rotamers which could not be separated by chromatography but all NMR data clearly show the presence of both rotamers in solution. Even the presence of the rotamers is dedicated in the $^{13}$C NMR spectra. The carbon atom of the methylene group of the benzylligand is observed at 51.8 ppm and 51.9 ppm. Besides the methylene group of the fluorenylmethoxycarbonyloxyligand at the tertiary nitrogen atom is located at 67.7 ppm and 68.4 ppm; the carbonyl signal of the ester function and the amide function at 157.5 ppm, 157.8 ppm and 166.5 ppm, 166.8 ppm.

The FAB-MS spectra show the molecular ion $m/z = 768$ of 21.3b and $m/z = 812$ of 21.2c. The base peak is given with $m/z = 178$ [C_{14}H_{10}]^+$ and another characteristic fragment is $m/z = 91$ [C_{7}H_{7}]^+. The UV spectra of the peptoid substituted compounds (21) aren’t different compared to the UV spectra of the α-peptido- and β-peptido-substituted compounds (12/13 and 16).

**EXPERIMENTAL**

All reactions were carried out under argon. The solvents were dried or used in absolute quality. Melting points were determined on a Reichert hot stage microscope and are uncorrected. $^1$H- and $^{13}$C NMR spectra were recorded on a Bruker WM-250 ($^1$H NMR: 250.13 MHz, $^{13}$C NMR: 62.89 MHz) and a Bruker WM-360 ($^1$H NMR: 360 MHz, $^{13}$C NMR: 90.56 MHz) spectrometers in CDCl$_3$. All chemical shifts are reported in ppm downfield from tetramethysilane; coupling constants J are given in Hz. $^{31}$P NMR spectra were measured with a Bruker WM-360 ($^{31}$P NMR: 145.79 MHz) spectrometer using H$_3$PO$_4$ (internal standard 85% H$_3$PO$_4$). IR spectra were measured with a Perkin-Elmer IR spectrophotometer 1600 (FT IR) and are given in cm$^{-1}$. FAB-MS spectra were recorded on a Varian MAT 311 A spectrometer (70 eV). Optical rotations were measured with a Polartronic E polarimeter (Schmidt and Haensch, 10 cm cell). All rotations were measured at rt. UV spectra were measured with a Hewlett Packard 8452 A Diode Array spectrometer in acetonitrile. Element analyses were performed on a Hereaus Vario EL CHNS apparatus.

General procedure for the preparation of α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones (12/13)
To a solution of 1 mmol of phosphono-phosphino substituted \( \gamma \)-thiapyrones (8/9) in \( \text{CH}_2\text{Cl}_2 \) (20 mL) were added successively \( N,N \)-diisopropylethylamine (11) (258 mg, 2 mmol), pentafluorophenylphenyldiphenylphosphinate (7) (499 mg, 1.3 mmol) and protected-\( \alpha \)-L-amino acids (10) (1 mmol). The reaction mixture was stirred under argon for 4-5 h at rt and the solution turned deep red. The reaction mixture was washed with saturated \( \text{NaHCO}_3 \) and \( \text{NaCl} \) (40 mL) and extracted with \( \text{CH}_2\text{Cl}_2 \) (40 mL). The organic layer was dried over anhydrous \( \text{MgSO}_4 \) and after evaporation of the solvent the deep red oil was chromatographed on silica gel (ethyl acetate / n-hexane (1:1)) to give the chiral \( \alpha \)-L-peptido-substituted phosphono-phosphino-\( \gamma \)-thiapyrones (12/13) as pink-red crystals in moderate yields (48-61%).

\[
2-(\text{Benzyloxy carbonyl}-\alpha-L-\text{alanyl})\text{amino-5-cyano-6-(4'-chlorophenyl)-4-thioxo-4H-pyran-3-yl-phosphonic acid dimethyl ester (12.2a)}
\]

- 322 mg (56%) of 12.2a were obtained as pink-red crystals after chromatography separation, mp 183-184 °C (ethyl acetate / n-hexane (1:1)). \( ^1\text{H-NMR} \) (360 MHz, \( \text{CDCl}_3 \)) \( \delta \): 2.04 (s, 3H, HCCCH), 3.77, 3.83 (2*dp, \( ^3\text{J}_{\text{HP}} = 12 \text{ Hz} \); 6H, OCH\text{3}), 4.36-4.38 (t, \( ^3\text{J}_{\text{HP}} = 4.4 \text{ Hz} \); 1H, HCCCH), 5.14 (s; 2H, C\text{6H}_5\text{CH}_2CH), 5.36 (t, \( ^3\text{J}_{\text{HP}} = 4.8 \text{ Hz} \); 1H, NHCOOCH\text{2C6H}_3), 7.37 (s, 5H, C\text{6H}_5\text{CH}_2\text{COO}), 7.55-7.57 (d, \( ^3\text{J}_{\text{HP}} = 8.7 \text{ Hz} \); 2H, 3'-H, 5'-H), 8.34-8.37 (d, \( ^3\text{J}_{\text{HP}} = 8.7 \text{ Hz} \); 2H, 2'-H, 6'-H), 13.06 (s, 1H, NHCO). \( ^13\text{C-NMR} \) (90.56 MHz, \( \text{CDCl}_3 \)) \( \delta \): 17.8 (s, HC\text{CH}_3), 52.9 (s, HC\text{CH}_3), 54.1 (dp, \( ^2\text{J}_{\text{CP}} = 6.2 \text{ Hz} \); O\text{CH}_3), 67.4 (s, C\text{6H}_5\text{CH}_2\text{COO}), 102.8 (dp, \( ^1\text{J}_{\text{CP}} = 197 \text{ Hz} \); C-3), 109.8 (dp, \( ^3\text{J}_{\text{CP}} = 10.9 \text{ Hz} \); C-5), 114.1 (s, CN), 126.0 (s, C-1'), 126.8 (s, C-7'), 128.2, 128.3 (2*dp; C-3', C-9', C-11', C-12'), 128.5, 129.7 (2*dp; C-2', C-2', C-3', C-5', C-6'), 135.9 (s, C-10'), 140.6 (s, C-4'), 155.9 (s, C\text{6H}_5\text{CH}_2\text{OCCO}), 158.3 (dp, \( ^2\text{J}_{\text{CP}} = 23.8 \text{ Hz} \); C-2), 158.5 (s, C-6), 170.4 (s, CONH), 194.9 (dp, \( ^2\text{J}_{\text{CP}} = 6.6 \text{ Hz} \); CS). \( ^31\text{P-NMR} \) (145.79 MHz, \( \text{CDCl}_3 \)) \( \delta \): 18.14 (s). IR (KBr): \( \nu \): 3291 cm\(^{-1} \) (m), 3033 (w), 2952 (w), 2873 (w), 2225 (w), 1733 (m), 1708 (s), 1616 (s), 1564 (m), 1520 (m), 1456 (w), 1383 (m), 1354 (m), 1252 (m), 1225 (m), 1092 (m), 1067 (m), 1034 (br s), 883 (m), 823 (m), 742 (m), 697 (m), 573 (m), 488 (w), 430 (w), 409 (w). FAB-MS: \( m/z \) (%): 577 (M\(^++1 \), 20), 576 (14), 371 (37), 308 (12), 307 (56), 155 (28), 154 (100), 136 (94), 107 (38), 91 (58), 77 (50), 41 (46). UV (MeCN): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 272 (4.34), 318 (4.50), 336 (4.46, sh). \( [\alpha]_{D}^{20} \): 0° (c = 0.05, DMF). Anal. Calcd for C\text{23H}_23\text{N}_3\text{O}_7\text{CIPS}: C, 52.12; H, 4.02; N, 7.32; S, 5.56. Found: C, 52.02; H, 3.89; N, 7.21; S, 5.43.

2-(Benzyloxy carbonyl-\( \alpha \)-L-valinyl)amino-5-cyano-6-phenyl-4-thioxo-4H-pyran-3-ylphosphonic
acid diethyl ester (12.1b)

- 346 mg (58%) of 12.1b were obtained as pink-red crystals after chromatography separation, mp 80-81 °C (ethyl acetate / n-hexane (1:1)). 1H-NMR (250.13 MHz, CDCl3): δ = 0.99, 1.09 (2×d, 3JH=6.8 Hz; 6H, CH(CH3)2), 1.35 (dp, 3J=7 Hz; 6H, OCH2CH3), 2.20-2.30 (sept, 3J=6.4 Hz; 1H, CH(CH3)2), 4.14-4.25 (m, 4H, OCH2CH3), 4.52 (t, 3J=4.4 Hz; 1H, HCCCH(CH3)2), 5.13 (s, 2H, COOCH2C6H5), 5.32 (t, 3J=4.9 Hz; 1H, NHCOOCH2C6H5), 7.36 (s, 5H, COOCH2C6H5), 7.56-7.66 (m, 3H, 3'-H, 4'-H, 5'-H), 8.35-8.38 (d, 3J=8.1 Hz; 2H, 2'-H, 6'-H), 13.24 (s, NHCO). 13C-NMR (90.56 MHz, CDCl3): δ= 16.2 (dpq, 3JC=7.1 Hz; OCH3), 19.4 (s, CH(CH3)3), 30.6 (s, CH(CH3)3), 62.3 (s, CH(=NCH2OOCCH2C6H5), 64.2 (dpq, 3JC=6.2 Hz; OCH2CH3), 67.3 (s, NHCOCOOCH2C6H5), 103.6 (dp, 1JC=194 Hz; C-3), 110.1 (dp, 3JC=10.8 Hz; C-5), 114.3 (s, CN), 127.7 (s, C-1), 128.0 (s, C-7'), 128.1, 129.2 (2×d; C-8', C-9', C-11', C-12'), 128.2, 129.3 (2×d; C-2, C-3, C-5, C-6), 133.3 (s, C-10'), 156.3 (s, NHCOOCH2C6H5), 157.8 (dp, 2JC=23.7 Hz; C-2), 159.6 (s, C-6), 169.6 (s, NHCO), 195.1 (dp, 2JC=6.8 Hz; CS). 31P-NMR (145.79 MHz, CDCl3): δ= 15.16 (s). IR (KBr): ν= 3421 cm⁻¹ (w), 3066 (w), 2964 (w), 2923 (w), 2233 (w), 1718 (s), 1653 (s), 1609 (s), 1575 (m), 1540 (m), 1575 (m), 1540 (m), 1504 (m), 1487 (m), 1437 (m), 1365 (m), 1224 (m), 1095 (m), 1027 (br s), 879 (m), 801 (m), 779 (m), 768 (w), 586 (w), 453 (w), 430 (w), 417 (w), 404 (w). MS (70 eV, 162°C): m/z (%)= 597 (M⁺ 2), 507 (4), 506 (6), 445 (21), 444 (31), 385 (4), 384 (8), 357 (6), 356 (8), 179 (5), 178 (5), 108 (45), 107 (34), 105 (24), 92 (9), 91 (100), 83 (23), 79 (46), 77 (33), 60 (52), 51 (15), 44 (40), 43 (6), 41 (7). UV (MeCN): λmax (log ε)= 270 (4.33), 312 (4.36), 330 (4.34, sh). [α]D²⁰=-8.5° (c= 0.05, DMF). Anal. Calcd for C₂₉H₃₂N₃O₇PS: C, 58.27; H, 5.39; N, 7.05; S, 5.50. Exact MS calcd for C₂₉H₃₂N₃O₇PS: 597.1699. Found: 597.1699. Found: 597.1699.

2-(Benzylxoycarbonyl-α-L-methionylamino-5-cyano-6-(4'-fluorophenyl)-4-thioxo-4H-pyran-3-ylphosphonic acid diethyl ester (12.3b)

- 375 mg (58%) of 12.3b were obtained as pink-red crystals after chromatography separation, mp 149 °C (ethyl acetate / n-hexane (1:1)). 1H-NMR (250.13 MHz, CDCl3): δ= 1.24 (dp, 3J=6.2 Hz; 6H, OCH2CH3), 2.27-2.29 (t, 3J=7.3 Hz; 2H, HCCCH₂CH₂SCH3), 2.45 (s, HCCCH₂CH₂SCH3), 2.60-2.63 (t, 3J=9.8 Hz; HCCCH₂CH₂SCH3), 4.05-4.20 (m, 4H, OCH2CH3), 4.48 (t, 3J=4.3 Hz; 1H, HCCCH₂CH₂SCH3), 5.14 (s, COOCH₂C₆H₅), 5.65 (t, 3J=5.1 Hz; 1H, NHCOOCH₂C₆H₅), 7.37-7.41 (m, 5H, COOCH₂C₆H₅), 7.59-7.63 (d, 3J=8.2 Hz; 2H, 3'-H, 5'-
H), 8.24-8.27 (dd, \(^4J_{HF}= 4.8\) Hz; 2H, 2'-H, 6'-H), 13.37 (s, NHCO). \(^{13}\)C-NMR (90.56 MHz, CDCl\(_3\)): \(\delta= 15.4\) (s, SC\(_H\)), 16.2 (dp, \(^3J_{CP}= 6.8\) Hz; OCH\(_2\)CH\(_3\)), 29.8 (s, HC\(_C\)H\(_2\)CH\(_2\)SCH\(_3\)), 30.9 (s, HC\(_C\)H\(_2\)CH\(_2\)SCH\(_3\)), 56.4 (s, HC\(_C\)H\(_2\)CH\(_2\)SCH\(_3\)), 64.4 (dp, \(^2J_{CP}= 6.2\) Hz; OCH\(_2\)CH\(_3\)), 67.4 (s, COOCH\(_2\)C\(_H\))\(_2\)), 104.6 (dp, \(^1J_{CP}= 198\) Hz; C-3), 109.8 (dp, \(^3J_{CP}= 10\) Hz; C-5), 114.3 (s, CN), 116.7 (d, \(^2J_{CF}= 17.3\) Hz; C-3', C-5'), 124.5 (d, \(^4J_{CF}= 3.2\) Hz; C-1'), 128.1 (s, C-7'), 129.4, 130.3 (2*dp, C-8', C-9', C-11', C-12'), 131.6 (d, \(^3J_{CF}= 9.1\) Hz; C-2', C-6'), 135.8 (s, C-10'), 155.8 (s, COOCH\(_2\)C\(_H\))\(_2\)), 157.6 (dp, \(^2J_{CP}= 23.1\) Hz; C-2), 158.5 (s, C-4'), 159.8 (s, C-6), 169.6 (s, NHCO), 194.9 (dp, \(^2J_{CP}= 6.4\) Hz; CS). \(^{31}\)P-NMR (145.79 MHz, CDCl\(_3\)): \(\delta= 15.06\) (s). IR (KBr): \(v= 3318\) cm\(^{-1}\) (m), 3066 (w), 2983 (w), 2922 (w), 2226 (w), 1717 (s), 1683 (m), 1583 (w), 1444 (m), 1503 (m), 1436 (m), 1387 (s), 1355 (m), 1244 (m), 1223 (m), 1169 (m), 1027 (br s), 883 (m), 823 (m), 742 (m), 698 (m), 600 (w), 503 (w), 427 (w), 407 (w). FAB-MS: m/z (%) = 648 (M\(^+\), 30), 647 (10), 383 (64), 381 (24), 154 (30), 136 (29), 91 (100), 77 (20), 51 (16). UV (MeCN): \(\lambda_{\text{max}} \text{(log } c) = 270\) (4.35), 316 (4.51), 340 (4.39, sh). [\(\alpha\)]\(_D^{20}\) = -6.5° (c = 0.05, DMF). Anal. Calcd for C\(_{29}\)H\(_33\)N\(_5\)O\(_7\)F\(_2\)S\(_2\): C, 53.76; H, 4.82; N, 6.51; S, 9.89. Found: C, 53.54; H, 4.87; N, 6.41; S, 10.08.

2-(Fluorenvl-9-methoxycarbonyl-\(\alpha\)-glycyl)amino-5-cyano-6-tert-butyl-4-thioxo-4H-pyranyl-3-yl-phosphonic acid diethyl ester (12.6b)

- 380 mg (61%) of 12.6b were obtained as pink-red crystals after chromatography separation, mp 176 °C (ethyl acetate / n-hexane (1:1)). \(^1\)H-NMR (250.13 MHz, CDCl\(_3\)): \(\delta= 1.27\) (dp, \(^3J_{HF}= 6.7\) Hz; 6H, OCH\(_2\)CH\(_3\)), 1.55 (s, 9H, (CH\(_3\))\(_3\)C), 4.01-4.11 (m, 4H, OCH\(_2\)CH\(_3\)), 4.14 (d, \(^3J_{HF}= 6.4\) Hz; 2H, NHCOCH\(_2\)), 4.25 (t, \(^3J_{HF}= 7.1\) Hz; 1H, COOCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 4.42 (d, \(^3J_{HF}= 4.8\) Hz; 2H, COOCH\(_2\)CH\(_2\)CH\(_2\)), 5.53 (t, \(^3J_{HF}= 3.8\) Hz; 1H, CH\(_2\)NHCOO), 7.25-7.77 (m, 8H, Fluoren-H), 13.3 (s, 1H, NHCOCH\(_2\)). \(^{13}\)C-NMR (62.89 MHz, CDCl\(_3\)): \(\delta= 16.0\) (dp, \(^3J_{CP}= 6.7\) Hz; OCH\(_2\)CH\(_3\)), 28.2 (s, (CH\(_3\))\(_3\)C), 38.4 (s, (CH\(_3\))\(_3\)C), 46.2 (s, COOCH\(_2\)NH), 47.1 (s, C-9a), 64.4 (dp, \(^2J_{CP}= 6.1\) Hz; OCH\(_2\)CH\(_3\)), 67.7 (s, COOCH\(_2\)CH\(_2\)CH\(_2\)), 103.5 (dp, \(^1J_{CP}= 195\) Hz; C-3), 111.8 (dp, \(^3J_{CP}= 12.5\) Hz; C-5), 113.4 (s, CN), 120.0 (s, C-4a, C-5a), 125.1 (s, C-1a, C-8a), 127.0 (s, C-2a, C-7a), 127.8 (s, C-3a, C-6a), 141.3 (s, C-10a, C-11a), 143.7 (s, C-12a, C-13a), 156.5 (s, C-6), 157.6 (dp, \(^2J_{CP}= 23.3\) Hz; C-2), 165.8 (s, NHCOOCH\(_2\)CH\(_2\)), 172.7 (s, NHCOCH\(_2\)), 192.2 (dp, \(^2J_{CP}= 7.2\) Hz; CS). \(^{31}\)P-NMR (145.79 MHz, CDCl\(_3\)): \(\delta= 15.02\) (s). IR (KBr): \(v= 3294\) cm\(^{-1}\) (w), 3033 (w), 2962 (w), 2923 (w), 2233 (w), 1747 (s), 1733 (m), 1710 (s), 1675 (m), 1604 (s), 1545 (m), 1521 (m), 1392 (s), 1375 (s), 1280 (m), 1253 (m), 1231 (m), 1199 (m), 1165 (m), 1030 (br s), 892 (m), 773 (w).
777 (m), 741 (m), 668 (w), 583 (w), 464 (w), 439 (w), 420 (w), 404 (w). MS (70 eV, 190°C): m/z (%) = 623 (M+, 2), 514 (1), 457 (1), 456 (2), 371 (1), 344 (2), 256 (1), 196 (29), 179 (35), 178 (100), 166 (70), 165 (96), 139 (6), 99 (6), 98 (6), 60 (30), 57 (6), 44 (11), 43 (2), 41 (5). UV (MeCN): λmax (log ε) = 250 (4.45), 266 (4.37), 286 (4.12, sh), 300 (4.02), 338 (4.27). Anal. Calcd for C₃₁H₃₄N₃O₇PS: C, 59.68; H, 5.49; N, 6.76; S, 5.13. Found: C, 59.36; H, 5.41; N, 6.52; S, 5.01. Exact MS calcd for C₃₁H₃₄N₃O₇PS: 623.1854. Found: 623.1853.

2-(Fluorenvl-9-methoxvcarbonvl-a-L-try~to~hanvl~amino-5-cvano-6-~henvI-4-thioxo-4H-pvran-3-ylphos~honic acid diisooovl ester (12.1)

- 416 mg (52%) of 12.1c were obtained as pink-red crystals after chromatography separation, mp 118-119 °C (ethyl acetate / n-hexane (1:1)). ¹H-NMR (250.13 MHz, CDCl₃): δ = 1.20, 1.24 (2×d, JHH = 6.2 Hz; 12H, OCH(CH₃)₂), 2.03 (s, 1H, C₆H₅NH), 3.43 (d, JHH = 7.1 Hz; 2H, HCCH₂C₆H₅NH), 4.13-4.19 (d, sept, JHP = 7.4 Hz; 3H, OCH(CH₃)₂), 4.21 (t, JHH = 6.4 Hz; 1H, NHCOOCH₂CHC₁₂H₈), 4.56 (t, JHH = 6.4 Hz; 1H, NHCOOCH₂CHC₁₂H₈), 7.00-7.12 (m, 15H, Aromatic-H), 8.24 (s, 1H, 2a-H, Vinyl H of Trp), 8.36-8.39 (d, JHH = 8 Hz; 2H, 2'-H, 6'-H). ¹³C-NMR (62.89 MHz, CDCl₃): δ = [23.7 (d, JCP = 5 Hz), 23.9 (d, JCP = 4 Hz; OCH(CH₃)₂)], 27.9 (s, HCCH₂C₆H₅NH), 47.1 (s, C-9a), 57.7 (s; HCCCH₂C₆H₅NH), 67.5 (s, COOCH₂CHC₁₂H₈), 73.9 (d, JCP = 7.2 Hz; OCH(CH₃)₂), 104.7 (d, JCP = 194 Hz; C-3), 109.1 (s, C-9'), 110.0 (d, JCP = 10 Hz; C-5), 111.4 (s; C-11'), 114.6 (s, CN), 118.5 (s, C-13'). 119.9 (s, C-4a, C-5a), 122.6 (s, C-12'), 123.3 (s, C-14'), 125.2 (s, C-1a, C-8a), 126.2 (s, C-10'). 126.8 (s, C-1'), 127.1 (s, C-2a, C-7a), 127.7 (s, C-3a, C-6a), 127.9 (s, C-7'), 129.2, 130.4 (2×d, C-2', C-3', C-5', C-6'), 133.8 (s, C-4'), 136.4 (s, C-8'), 141.3 (s, C-10a, C-11a), 143.6 (s, C-12a, C-13a), 156.1 (s, NHCOOCH₂CHC₁₂H₈), 157.5 (d, JCP = 23.8 Hz; C-2), 159.5 (s, C-6), 170.0 (s, NHCO), 192.2 (d, JCP = 6.7 Hz; CS). ⁳¹P-NMR (145.79 MHz, CDCl₃): δ = 11.63 (s). IR (KBr): ν = 3406 cm⁻¹ (w), 3066 (w), 2978 (w), 2933 (w), 2233 (w), 1734 (s), 1718 (s), 1653 (m), 1607 (s), 1575 (s), 1559 (m), 1386 (m), 1355 (s), 1225 (s), 1202 (m), 1100 (m), 1008 (br s), 774 (m), 740 (m), 690 (m), 621 (m), 536 (w), 437 (w), 419 (w), 403 (w). FAB-MS: m/z (%) = 802 (M+, 30), 391 (47), 390 (6), 362 (3), 179 (64), 178 (100), 166 (17), 165 (3), 130 (14), 116 (54), 78 (7), 77 (54), 51 (6). UV (MeCN): λmax (log ε) = 250 (4.58), 290 (4.30), 300 (4.33), 312 (4.28, sh), 338 (4.27, sh). [α]D²₀ = -12° (c = 0.05, DMF). Anal. Calcd for C₄₄H₄₁N₄O₇PS: C, 65.97; H, 5.15; N, 7.02; S, 4.00. Found: C, 65.73; H, 5.02; N, 6.87; S, 3.85.
2-(Benzyloxy carbonyl-\(\alpha\)-L-methionyl)amino-5-cyano-6-p-tolyl-4-thioxo-4\(H\)-pyran-3-ylphosphonic acid diisopropyl ester (12.4c)

-370 mg (55\%) of 12.4c were obtained as pink-red crystals after chromatography separation, mp 105-106 °C (ethyl acetate / n-hexane (1:1)). \(^1\)H-NMR (360 MHz, CDCl\(_3\)): \(\delta = 1.31, 1.35 \ (2\times d, J_{HH} = 6.2 \text{ Hz} \); 12H, OCH(CH\(_3\))\(_2\)), 2.09 (s, 3H, C\(_6\)H\(_4\)CH3), 2.28-2.30 \((t, J_{HH} = 7.2 \text{ Hz} \); 2H, HCC\(_2\)H\(_2\)SCH3), 2.45 (s, 3H, CH\(_2\)CH\(_2\)SCH3), 2.59-2.62 \((t, J_{HH} = 10 \text{ Hz} \); 2H, CH\(_2\)CH\(_2\)SCH3), 4.42 \((t, J_{HH} = 4.2 \text{ Hz} \); 1H, HCC\(_2\)H\(_2\)SCH3), 4.71-4.76 \((d, J_{HP} = 7.4 \text{ Hz} \); 3J\(_{HH} = 6.2 \text{ Hz} \); 2H, OCH(CH\(_3\))\(_2\)), 5.13 \((5, J_{CP} = 194 \text{ Hz} \); 1H, NHCOOCH\(_2\)C\(_6\)H\(_5\)), 5.64 \((t, J_{CP} = 5.2 \text{ Hz} \); 1H, NHCOOCH\(_2\)C\(_6\)H\(_5\)), 7.36-7.39 \((d, J_{CP} = 7.9 \text{ Hz} \); 2H, C-3'\), 7.39 \((s, 5H \); NHCOOCH\(_2\)C\(_6\)H\(_5\)), 8.26-8.29 \((d, J_{CP} = 8.2 \text{ Hz} \); 2H, C-6'), 13.39 \((s, J_{CP} = 4.3 \text{ Hz} \); 1H, NHCO).

\[^{13}\text{C}-\text{NMR}\ (90.56 \text{ MHz, CDCl}_3): \delta = 15.4 \text{ (s, } \text{SCH}_3\), 21.8 \text{ (s, CSH}_4\text{CH}_3\), [23.7 \((d, J_{CP} = 5 \text{ Hz} \); 23.9 \((d, J_{CP} = 4 \text{ Hz} \); OCH(CH\(_3\))\(_2\))] \), 29.9 \text{ (s, HCC\(_2\)H\(_2\)SCH3), 30.9 \text{ (s, HCC\(_2\)H\(_2\)SCH3), 56.3 \text{ (s, HCC\(_2\)H\(_2\)SCH3), 67.4 \text{ (s, NHCOOCH\(_2\)C\(_6\)H\(_5\))}, 73.9 \((d, J_{CP} = 7.2 \text{ Hz} \); OCH(CH\(_3\))\(_2\))], 104.5 \((d, J_{CP} = 194 \text{ Hz} \); C-3), 109.6 \((d, J_{CP} = 9.8 \text{ Hz} \); C-5), 114.7 \text{ (s, CN), 124.9 \text{ (s, C-1), 128.1, 128.5 \text{ (2 s, C-2, C-3, C-5, C-6), 128.8 \text{ (s, C-7'), 129.3, 130.0 \text{ (2 s, C-8', C-9', C-11', C-12'), 135.9 \text{ (s, C-10'), 145.1 \text{ (s, C-4), 155.9 \text{ (s, NHCOOCH\(_2\)C\(_6\)H\(_5\))}, 157.5 \((d, J_{CP} = 23.9 \text{ Hz} \); C-2), 159.7 \text{ (s, C-6), 169.5 \text{ (s, NHCO), 195.1 \((d, J_{CP} = 6.2 \text{ Hz} \); CS). 31P-NMR (145.79 MHz, CDCl\(_3\): \(\delta = 11.73 \text{ (s). IR (KBr): } v = 3280 \text{ cm}^{-1} \text{ (w), 3033 (w), 2983 (w), 2922 (w), 2233 (w), 1734 (s), 1717 (m), 1653 (m), 1602 (s), 1576 (m), 1555 (m), 1521 (m), 1468 (m), 1383 (m), 1349 (m), 1245 (m), 1221 (m), 1195 (m), 1127 (m), 1007 (br s), 823 (m), 777 (m), 705 (m), 608 (m), 491 (w), 433 (w), 418 (w), 402 (w). FAB-MS: m/z (%) = 672 (M\(^+\)+1, 30), 405 (16), 404 (12), 256 (4), 202 (18), 182 (4), 120 (7), 119 (65), 109 (18), 92 (9), 91 (100), 75 (4), 61 (7), 47 (12), 41 (8). UV (MeCN): \(\lambda_{max} \text{ (log } e) = 272 (4.31), 316 (4.52), 342 (4.31, sh). [\alpha]_D^{20} = -7.3^\circ \text{ (c= 0.05, DMF). Anal. Calcd for C\(_{32}\)H\(_{38}\)N\(_3\)O\(_7\)PS\(_2\): C, 57.20; H, 5.70; N, 6.72; S, 9.54. Found: C, 57.31; H, 5.80; N, 6.56; S, 9.41.}

2-(Fluoren-9-methoxy carbonyl-\(\alpha\)-glycyl)amino-5-cyan-6-furyl-4-thioxo-4\(H\)-pyran-3-ylphosphonic acid diisopropyl ester (12.7c)

- 397 mg (60\%) of 12.7c were obtained as pink-red crystals after chromatography separation, mp 136-137 °C (ethyl acetate / n-hexane (1:1)). \(^1\)H-NMR (250.13 MHz, CDCl\(_3\)): \(\delta = 1.27, 1.31 \ (2\times d, J_{HH} = 6.2 \text{ Hz} \); 12H, OCH(CH\(_3\))\(_2\)), 4.12 (d, \(J_{HH} = 7.2 \text{ Hz} \); 2H, COCH\(_2\)NH), 4.24-4.28 \((t, J_{HH} = 3.8 \text{ Hz} \); 1H, NHCOOCH\(_2\)CH\(_2\)C\(_6\)H\(_5\)), 4.41-4.44 \((d, J_{HH} = 7.1 \text{ Hz} \); 2H, NHCOOCH\(_2\)CH\(_2\)C\(_6\)H\(_5\)), 4.64-4.72 \((d, J_{HP} = 7.2 \text{ Hz} \); 3J\(_{HP} = 6.2 \text{ Hz} \); 2H, OCH(CH\(_3\))\(_2\)), 5.37 \((t, J_{HH} = 4.3 \text{ Hz} \); 1H,

NHCOOCH₂CH₃C₂H₆), 6.70 (d, $^3$J_{HH} = 4.8 Hz; 1H, 5'-H), 7.25-7.45 (m, 4H, Aromatic-H), 7.62, 7.78 (2x d, $^3$J_{HH} = 4.8 Hz; 2H, 3'-H, 4'-H), 7.65-7.84 (m, 4H, Aromatic-H), 13.30 (s, 1H, NHCO).

$^{13}$C-NMR (62.89 MHz, CDCl₃): $\delta =$ [23.6 (dpq, $^3$J_{CP} = 5 Hz), 23.9 (dpq, $^3$J_{CP} = 4 Hz; OCH(CH₃)₂)], 46.3 (s, COCH₂NH), 47.2 (s, C-9a), 67.6 (s, COOCH₂CH₃C₂H₆), 74.0 (dpq, $^2$J_{CP} = 7.2 Hz; OCH(CH₃)₂), 104.4 (dp, $^1$J_{CP} = 196 Hz; C-3), 112.2 (dp, $^3$J_{CP} = 13.5 Hz; C-5), 113.1 (s, CN), 113.8 (s, C-3'), 120.0 (s, C-4a, C-5a), 121.8 (s, C-4'), 125.2 (s, C-1a, C-8a), 127.1 (s, C-2a, C-7a), 127.8 (s, C-3a, C-6a), 141.3 (s, C-10a, C-11a), 142.8 (s, C-2'), 143.8 (s, C-12a, C-13a), 148.9 (s, C-5'), 149.0 (s, NHCOOCH₂CH₃C₂H₆), 156.6 (dp, $^2$J_{CP} = 24.1 Hz; C-2), 159.0 (s, C-6), 166.9 (s, NHCO), 194.4 (dp, $^2$J_{CP} = 6.7 Hz; CS). $^{31}$P-NMR (145.79 MHz, CDCl₃): $\delta =$ 11.84 (s). IR (KBr): ν = 3431 cm⁻¹ (w), 3133 (w), 3044 (w), 2980 (w), 2923 (w), 2233 (w), 1733 (s), 1716 (s), 1624 (s), 1559 (m), 1520 (m), 1376 (s), 1242 (m), 1208 (m), 1100 (m), 1006 (br s), 851 (m), 761 (m), 739 (m), 591 (m), 506 (w), 464 (w), 418 (w), 407 (w). FAB-MS: m/z (%) = 662 (M⁺+1, 7), 371 (13), 370 (23), 305 (18), 304 (4), 256 (45), 206 (13), 179 (8), 178 (100), 166 (26), 110 (14), 109 (8), 96 (5), 95 (38), 58 (8), 57 (17), 43 (8), 41 (19). UV (MeCN): $\lambda_{max}$ (log ε) = 266 (4.42), 290 (4.36), 300 (4.31), 312 (4.25, sh), 350 (4.47, sh). Anal. Calcd for C₃₃H₃₇N₃O₈PS: C, 59.89; H, 4.87; N, 6.37; S, 4.84. Found: C, 59.62; H, 4.82; N, 6.38; S, 4.54.

2-(Benzyloxycarbonyl-α-L-alanyl)amino-5-cyano-6-(4'-chlorophenyl)-4-thioxo-4H-pyran-3-ylphenylphosphinic acid ethyl ester (13.3d)

- 295 mg (48%) of 13.3d were obtained as pink-red crystals after chromatography separation, mp 146 °C (ethyl acetate / n-hexane (1:1)). $^1$H-NMR (250.13 MHz, CDCl₃): $\delta =$ 1.41 (t, $^3$J_{HH} = 6.4 Hz; 3H, OCH₂CH₃), 1.62 (s, 3H, HCCH₃), 4.23-4.35 (m, 2H, OCH₂CH₃), 4.74 (t, $^3$J_{HH} = 7.2 Hz; 1H, HCCH₃), 5.13 (s, 2H, NHCOOCH₂C₆H₅), 5.34 (d, $^3$J_{HH} = 6.7 Hz; 1H, NHCOOCH₂C₆H₅), 7.28 (s, 5H, NHCOOCH₂C₆H₅), 7.33-7.43 (m, 5H, 2′a-H, 3′-a, 4′-a, 5′-a, 6′-a), 7.92-7.94 (t, $^2$J_{HH} = 8.8 Hz; 2H, 3′-H, 5′-H), 8.45-8.47 (dd, $^4$J_{HH} = 5.2 Hz; 2H, 2′-H, 6′-H), 13.93 (s, 1H, NHCO). $^{13}$C-NMR (62.89 MHz, CDCl₃): $\delta =$ 16.3 (dp, $^3$J_{CP} = 7.5 Hz; OCH₂CH₃), 18.3 (s, HCCH₃), 53.1 (s, HCCH₃), 62.4 (dp, $^2$J_{CP} = 6.2 Hz; OCH₂CH₃), 67.3 (s, NHCOOCH₂C₆H₅), 104.3 (dp, $^1$J_{CP} = 146 Hz; C-3), 108.5 (dp, $^3$J_{CP} = 10.7 Hz; C-5), 114.2 (s, CN), 116.7 (d, $^2$J_{CP} = 22.1 Hz; C-3', C-5'), 123.9 (s, C-7'), 128.0, 128.3 (2x d, C-2a, C-3a, C-4a, C-5a, C-6a), 128.2, 128.5 (2x d, C-6', C-9', C-10', C-11', C-12'), 129.9 (d, C-1a), 132.0 (d, $^3$J_{CF} = 9.8 Hz; C-2', C-6'), 135.9 (d, $^4$J_{CF} = 3.2 Hz; C-1'), 156.0 (s, NHCOOCH₂C₆H₅), 164.4 (s, C-4'), 167.2 (s, C-6), 169.4 (s, NHCO), 194.4 (dp, $^2$J_{CP} = 7.1 Hz; CS). $^{31}$P-NMR (145.79 MHz, CDCl₃): $\delta =$ 30.35 (s). IR (KBr): ν = 3380 cm⁻¹ (m), 3255 (w), 3035 (w), 2985 (w), 2954 (w), 2234 (w), 1806 (s), 1707 (s), 1616 (s), 1587 (m), 1518
(s), 1455 (m), 1385 (m), 1354 (m), 1253 (s), 1160 (m), 1105 (m), 1065 (s), 1001 (br s), 983 (m), 849 (m), 757 (m), 695 (m), 551 (m), 505 (w), 452 (w), 423 (w), 404 (w). FAB-MS: m/z (%) = 619 (M+), 413 (14), 412 (28), 302 (8), 246 (7), 192 (16), 124 (6), 123 (81), 96 (7), 95 (18), 92 (8), 91 (100), 77 (26), 51 (16). UV (MeCN): \( \lambda \text{max} (\log e) = 278 (4.42), 320 (4.54), 348 (4.13, sh). \) 

\([\alpha]_D^{20} = -16^\circ \) \( (c = 0.05, \text{DMF}) \). Anal. Calcd for C$_{31}$H$_{27}$N$_3$O$_6$FPS: C, 60.08; H, 4.39; N, 6.80; S, 5.17. Found: C, 59.73; H, 4.15; N, 6.48; S, 4.86.

**General procedure for the preparation of chiral \( \beta \)-peptido-substituted phosphono-\( \gamma \)-thiapyrones (16)**

To a solution of 0.5 mmol phosphono substituted \( \gamma \)-thiapyrones (8) in CH$_2$Cl$_2$ (20 mL) were added successively \( N,N \)-diisopropylethylamine (11) (129 mg, 1 mmol), pentafluorphenyldiphenylphosphinate (7) (250 mg, 0.65 mmol) and protected L-amino acids (15) (0.5 mmol). The reaction mixture was stirred under argon for 7-9 h at rt and the solution turned deep red. Until the reaction was completed (TLC monitoring) the reaction mixture was washed with saturated NaHCO$_3$ and NaCl (40 mL) and extracted with CH$_2$Cl$_2$ (40 mL). The organic layer was dried over anhydrous MgSO$_4$ and after evaporation of the solvent the deep red oil was further purified by chromatography on silica gel (ethyl acetate / n-hexane (1:1)) to give light red crystals of \( \beta \)-peptido-substituted phosphono-\( \gamma \)-thiapyrones (16) in moderate yields (39-46%).

2-(Fluorenvl-9-methoxvcarbonyl-\( \beta \)-L-phenylalanvl-amino-5-cyano-6-(4'-fluorophenvl)-4-thioxo-4H-vran-3-vl-hos-thionic acid diethvl ester (16.3b)

- 153 mg (40%) of 16.3b were obtained as light red crystals after chromatography separation, mp 85-86 °C (ethyl acetate / n-hexane (1:1)). $^1$H-NMR (360 MHz, CDCl$_3$): $\delta$ = 1.34 (d, $^3$J$_{HH}$ = 6.2 Hz; 2H, OCH$_2$CH$_3$), 2.75 (t, $^3$J$_{HH}$ = 4.8 Hz; 2H, NHCOCH$_2$), 3.06 (quart, $^3$J$_{HH}$ = 4.7 Hz; 2H, HCCH$_2$C$_6$H$_5$), 4.01 (t, $^3$J$_{HH}$ = 4.6 Hz; 1H, HCCH$_2$C$_6$H$_5$), 4.03-4.21 (m, 4H, OCH$_2$CH$_3$), 4.24 (t, $^3$J$_{HH}$ = 7 Hz; 1H, NHCOOCH$_2$CH$_2$C$_6$H$_5$), 4.42 (d, $^3$J$_{HH}$ = 7.1 Hz; 2H, NHCOOCH$_2$CH$_2$C$_6$H$_5$), 5.31 (t, $^3$J$_{HH}$ = 3.8 Hz; 1H, NHCOOCH$_2$CH$_2$C$_6$H$_5$), 7.18-7.56 (m; 8H, NHCOOCH$_2$CH$_2$C$_6$H$_5$), 7.59-7.62 (t, $^3$J$_{HH}$ = 7.1 Hz; 2H, 3'-H, 5'-H), 8.06-8.09 (dd, $^4$J$_{HF}$ = 4.8 Hz; 2H, 2'-H, 6'-H), 12.81 (s, 1H, NH). $^{13}$C-NMR (90.56 MHz, CDCl$_3$): $\delta$ = 16.2 (d, $^3$J$_{CC}$ = 7 Hz; OCH$_2$CH$_3$), 40.3 (s, HCCH$_2$C$_6$H$_5$), 42.4 (s, NHCOCH$_2$), 47.2 (s, C-9a), 49.6 (s, HCCH$_2$C$_6$H$_5$), 64.5 (d, $^2$J$_{CP}$ = 6.1 Hz; OCH$_2$CH$_3$), 102.7 (d, $^1$J$_{CP}$ = 194 Hz; C-3), 114.3 (s, CN), 116.4 (dd, $^2$J$_{CP}$ = 17.9 Hz; C-3', C-5'), 119.9 (s, C-4a, C-
5a), 124.2 (d, $J_{CF}= 3.1$ Hz; C-1’), 125.0 (s, C-1a, C-8a), 127.6 (s, C-3a, C-4a), 127.9 (s, C-7’), 129.7, 130.3 (2*$d$, C-8’, C-9’, C-11’, C-12’), 131.2 (d, $J_{CF}= 9.1$ Hz; C-2’, C-6’), 132.3 (s, C-10’), 141.3 (s, C-10a, C-11a), 143.7 (s, C-12a, C-13a), 155.7 (s, C-6), 157.6 (d, $J_{CP}= 24.1$ Hz; C-2), 158.4 (s, C-4’), 159.6 (s, NHCOOCH₂CH₂CH₃H₈), 168.1 (s, NHCO), 195.3 (d, $J_{CP}= 6.5$ Hz; CS). $^{31}$P-NMR (145.79 MHz, CDCl₃): $\delta = 13.81$ (s). IR (KBr): $\nu = 3385$ cm⁻¹ (w), 3066 (w), 2966 (w), 2922 (w), 2233 (w), 1734 (s), 1718 (s), 1700 (m), 1623 (s), 1588 (m), 1516 (m), 1437 (m), 1387 (m), 1247 (m), 1167 (m), 1032 (br s), 822 (m), 741 (m), 701 (m), 649 (m), 601 (m), 549 (w), 481 (w), 437 (w), 410 (w). FAB-MS: m/z (%) = 766 (M⁺, 12), 383 (7), 381 (3), 307 (14), 155 (22), 154 (100), 136 (78), 107 (36), 89 (40), 77 (46), 65 (24), 51 (32). UV (MeCN): $\lambda_{\text{max}}$ (log $\epsilon$) = 266 (4.68), 292 (4.34, sh), 300 (4.48), 316 (4.49), 338 (4.40, sh). $[\alpha]_{D}^{20} = -15^\circ$ (c= 0.05, DMF). Anal. Calcd for C₄₁H₃₇N₃O₇F₈PS: C, 64.29; H, 4.86; N, 5.50; S, 4.18. Found: C, 64.08; H, 4.65; N, 5.31; S, 4.02.

2-(Fluorenyl-9-methoxycarbonyl-β-L-phenylalanyl)amino-5-cyan-6-p-tolyl-4-thioxo-4H-pyran-3-vlphosphonic acid diethyl ester (16b)

- 149 mg (39%) of 16b were obtained as light red crystals after chromatography separation, mp 88 °C (ethyl acetate / n-hexane (1:1)). $^1$H-NMR (250.13 MHz, CDCl₃): $\delta = 1.33$ (d, $J_{IH}= 6.1$ Hz; 6H, OCH₂CH₃), 2.42 (s, 3H, CH₃), 2.74 (t, $J_{IH}= 4.8$ Hz; 2H, NHCOCH₃H₂), 3.05 (quart, $J_{IH}= 4.7$ Hz; 2H, HCH₂CH₃), 4.01 (t, $J_{IH}= 4.6$ Hz; 1H, HCH₂CH₃), 4.03-4.18 (m, 4H, OCH₂CH₃), 4.23 (t, $J_{IH}= 7.1$ Hz; 1H, NHCOOCH₂CH₂CH₃), 4.43 (d, $J_{IH}= 7$ Hz; 2H, NHCOOCH₂CH₂CH₃), 5.28 (t, $J_{IH}= 3.8$ Hz; 1H, NHCOOCH₂CH₂CH₃), 7.16-7.58 (m, 13H, NHCOOCH₂CH₂CH₃, HCH₂CH₃, 7.73-7.76 (d, $J_{IH}= 8.1$ Hz; 2H, 3'–H, 5'–H), 8.20-8.23 (d, $J_{IH}= 8.1$ Hz; 2H, 2'–H, 6'–H), 12.77 (s, 1H, NH). $^{13}$C-NMR (90.56 MHz, CDCl₃): $\delta = 16.1$ (d, $J_{CP}= 7$ Hz; OCH₂CH₃), 21.8 (s, CH₃), 40.3 (s, HCH₂CH₃), 42.4 (s, NHCOCH₃), 64.4 (d, $J_{CP}= 6.4$ Hz; OCH₂CH₃), 102.4 (d, $J_{CP}= 196$ Hz; C-3), 114.5 (s, CN), 119.9 (s, C-4a, C-5a), 124.7 (s, C-1’), 124.9 (s, C-1a, C-8a), 126.9 (s, C-1’), 127.4 (s, C-7’), 127.6 (s, C-2a, C-7a), 127.7 (s, C-3a, C-4a), 128.7, 129.2, 130.0 (3*$d$, C-2’, C-3’, C-5’, C-6’, C-8’, C-9’, C-11’, C-12’), 132.3 (s, C-10’), 141.3 (s, C-10a, C-11a), 143.7 (s, C-12a, C-13a), 145.2 (s, C-4’), 155.6 (s, C-6), 157.7 (d, $J_{CP}= 24$ Hz; C-2), 159.7 (s, NHCOOCH₂CH₂CH₃), 168.0 (s, NHCO), 195.2 (d, $J_{CP}= 6.4$ Hz; CS). $^{31}$P-NMR (145.79 MHz, CDCl₃): $\delta = 13.78$ (s). IR (KBr): $\nu = 3391$ cm⁻¹ (w), 3055 (w), 2981 (w), 2924 (w), 2231 (w), 1734 (s), 1718 (m), 1700 (s), 1628 (s), 1558 (m), 1523 (m), 1476 (m), 1422 (m), 1381 (m), 1248 (m),
1171 (m), 1021 (br s), 841 (m), 748 (m), 668 (w), 601 (m), 535 (w), 485 (w), 431 (w), 407 (w).

FAB-MS: m/z (%)= 762 (M+ , 9), 380 (12), 379 (44), 307 (12), 179 (92), 178 (50), 154 (100), 136 (80), 119 (60), 89 (52), 77 (58), 51 (44). UV (MeCN): λmax (log ε)= 266 (4.56), 292 (4.31, sh), 300 (4.42), 316 (4.47), 338 (4.30, sh). [α]D20 = -14° (c= 0.05, DMF). Anal. Calcd for C42H40N3O7PS: C, 66.20; H, 5.29; N, 5.53; S, 4.20. Found: C, 66.07; H, 5.13; N, 5.41; S, 4.02.

2-(Fluorenyl-9-methoxycarbonyl- β-L-alanyl)amino-5-cyano-6-phenyl-4-thioxo-4H-pyran-3-yl-phosphonic acid diisopropyl ester (16.1c)

- 157 mg (45%) of 16.1c were obtained as light red crystals after chromatography separation, mp 73-75 °C (ethyl acetate / n-hexane (1:1)). 1H-NMR (250.13 MHz, CDCl3): δ= 1.28, 1.32 (2*dp, 3JHH= 6.4 Hz; 12H, OCH(CH3)2), 1.63 (s, 3H, HCCCH3), 2.77 (t, 3JHH= 4.8 Hz; 2H, NHCOCH2), 4.72 (t, 3JHH= 7.1 Hz; 1H, HCCCH3), 4.12-4.22 (dpsept, 3JHH= 7.4 Hz, 3HH= 6.2 Hz; 2H, NHCOOCH2C6H5), 4.72 (t, 3JHH= 7.1 Hz; 1H, NHCOOCH2C6H5), 4.36-4.38 (d, JHH2= 4.9 Hz; 2H, NHCOOC6H5), 5.43 (1, 3JHH= 4.1 Hz; 1H, NHCOOCH2C6H5), 7.05-7.70 (m, 13H, NHCOOCH2C6H5), 13.01 (s, 1H, NH). 31P-NMR (145.79 MHz, CDCl3): δ= 13.60 (s). IR (KBr): v= 3350 cm⁻¹ (m), 3251 (w), 3061 (w), 2981 (w), 2963 (w), 2229 (w), 1734 (s), 1717 (m), 1700 (s), 1620 (s), 1581 (m), 1478 (m), 1420 (m), 1381 (m), 1250 (m), 1161 (m), 1009 (br s), 748 (m), 691 (m), 602 (w), 535 (w), 485 (w), 423 (w), 407 (w). FAB-MS: m/z (%)= 699 (M+ , 15), 615 (20), 391 (21), 390 (8), 225 (7), 179 (90), 178 (48), 154 (100), 136 (70), 106 (7), 105 (25), 78 (8), 77 (51), 51 (40). UV (MeCN): λmax (log ε)= 266 (4.51), 292 (4.30, sh), 300 (4.41), 318 (4.41), 338 (4.28, sh). [α]D20 = -27.5° (c= 0.05, DMF). Anal. Calcd for C47H38N3O7PS: C, 63.49; H, 5.47; N, 6.02; S, 4.58. Found: C, 63.19; H, 5.18; N, 5.81; S, 4.31.
- 150 mg (43%) of 16.4c were obtained as light red crystals after chromatography separation, mp 87 °C (ethyl acetate / n-hexane (1:1)). 1H-NMR (360 MHz, CDCl3): δ = 1.33, 1.36 (2*dp, 3JHH = 6.2 Hz; 12H, OCH(CH3)2), 2.45 (s, 3H, C6H4CH3), 2.76 (t, 3JHH = 4.8 Hz; 2H, NHCH2CH2CONH), 3.56 (t, 3JHH = 4.7 Hz; 2H, NHCH2CH2CONH), 4.16 (t, 3JHH = 4.2 Hz; 1H, NHCOOCH2CHC12H8), 4.35-4.38 (d, 3JHH = 3.9 Hz; 2H, NHCOOCH2CHC12H8), 4.68-4.79 (dp, sept, 3JHP = 7.2 Hz, 3JHH = 6.4 Hz; 2H, OCH(CH3)2), 5.29 (t, 3JHH = 3.8 Hz; 1H, NHCOOCH2CHC12H8), 7.27-7.90 (m, 8H, Aromatic-H; 2*d, 2*3JC = 8.1 Hz; 4H, 2'-H, 3'-H, 5'-H, 6'-H), 12.98 (s, 1H, NH). 13C-NMR (90.56 MHz, CDCl3): δ = 21.7 (s, C6H4CH3), [23.7 (dpq, 3JC = 5 Hz), 23.9 (dpq, 3JC = 4 Hz); OCH(CH3)2], 36.1 (s, NHCH2CH2CONH), 38.6 (s, NHCH2CH2CONH), 47.2 (s, C-9a), 67.1 (s, NHCOOCH2CHC12H8), 74.2 (dp, 2JC = 7.2 Hz; OCH(CH3)2), 104.5 (dp, 1JC = 198 Hz; C-3), 110.1 (dp, 3JC = 11.5 Hz; C-5), 114.4 (s, CN), 119.9 (s, C-4a, C-5a), 124.8 (s, C-1a, C-8a), 126.8 (s, C-1'), 127.1 (s, C-2a, C-7a), 127.7 (s, C-3a, C-6a), 129.4, 130.3 (2*d, C-2', C-3', C-5', C-6'), 141.1 (s, C-4'), 156.3 (s, C-6), 157.4 (dp, 2JC = 24.8 Hz; C-2), 158.3 (s, NHCOOCH2CHC12H8), 168.8 (s, NHCO), 194.8 (dp, 2JC = 7.5 Hz; CS). 31P-NMR (145.79 MHz, CDCl3): δ = 13.78 (s). IR (KBr): ν = 3421 cm⁻¹ (m), 3365 (w), 2975 (w), 2973 (w), 2333 (w), 2178 (s), 1700 (s), 1608 (s), 1559 (m), 1457 (m), 1387 (m), 1357 (m), 1226 (m), 1195 (m), 1103 (m), 1009 (br s), 825 (m), 759 (m), 741 (m), 668 (m), 563 (w), 491 (w), 422 (w), 408 (w). FAB-MS: m/z (%) = 700 (M⁺, 14), 407 (7), 324 (5), 323 (34), 179 (100), 178 (56), 154 (68), 136 (54), 119 (70), 89 (42), 77 (50), 51 (38); UV (MeCN): λmax (log ϵ) = 266 (4.44), 290 (4.21, sh), 304 (4.40), 320 (4.48), 348 (4.15, sh). Anal. Calcd for C37H38N307PS: C, 63.49; H, 5.47; N, 6.02; S, 4.58. Found: C, 63.14; H, 5.48; N, 5.67; S, 4.24.

2-(Fluorenyl-9-methoxycarbonyl-β-glycyl)amino-5-cyano-6-(4'-bromophenyl)-4-thioxo-4H-pyran-3-ylphosphonic acid diisopropyl ester (16.5c)

- 175 mg (46%) of 16.5c were obtained as light red crystals after chromatography separation, mp 90–91 °C (ethyl acetate / n-hexane (1:1)). 1H-NMR (360 MHz, CDCl3): δ = 1.33, 1.36 (2*dp, 3JHH = 6.2 Hz; 12H, OCH(CH3)2), 2.77 (t, 3JHH = 4.8 Hz; 2H, NHCH2CH2CONH), 3.56 (t, 3JHH = 4.7 Hz; 2H, NHCH2CH2CONH), 4.17 (t, 3JHH = 4.2 Hz; 1H, NHCOOCH2CHC12H8), 4.70-4.78 (dp, sept, 3JHP = 7.2 Hz, 3JHH = 6.2 Hz; 2H, OCH(CH3)2), 5.30 (t, 3JHH = 3.8 Hz; 1H, NHCOOCH2CHC12H8), 7.26-7.88 (m, 8H, Aromatic-H; 2*d, 2*3JC = 8.4 Hz; 4H, 2'-H, 3'-H, 5'-H, 6'-H), 12.96 (s, 1H, NH). 13C-NMR (90.56 MHz, CDCl3): δ = [23.7 (dpq, 3JC = 5 Hz), 23.9 (dpq, 3JC = 4 Hz); OCH(CH3)2], 36.1 (s, NHCH2CH2CONH), 38.6 (s, NHCH2CH2CONH), 47.2 (s, C-9a), 67.1 (NHCOOCH2CHC12H8), 74.1 (dp, 2JC = 7.1 Hz; OCH(CH3)2), 104.3 (dp, 1JC = 196 Hz; C-3),
110.0 (d, \( ^{3}J_{CP} = 11.1 \) Hz; C-5), 114.2 (s, CN), 119.9 (s, C-4a, C-5a), 124.9 (s, C-1a, C-8a), 126.6 (s, C-1'), 127.0 (s, C-2a, C-7a), 127.6 (s, C-3a, C-6a), 129.7, 130.5 (2*d, C-2', C-3', C-5', C-6'), 140.6 (s, C-4'), 141.2 (s, C-10a, C-11a), 143.7 (s, C-12a, C-13a), 156.2 (s, C-6), 157.2 (d, \( ^{2}J_{CP} = 24.2 \) Hz; C-2), 158.2 (s, NHCOOCH₂CH₂Cl₂H₈), 168.9 (s, NHCO), 194.6 (d, \( ^{2}J_{CP} = 6.4 \) Hz; CS).

\[^{31}P\text{-NMR (145.79 MHz, CDCl}_3\):} \( \delta = 13.81 \) (s).

IR (KBr): \( \nu = 3310 \) cm\(^{-1}\) (m), 3285 (w), 3066 (w), 2979 (w), 2933 (w), 2233 (w), 1717 (s), 1700 (m), 1610 (s), 1587 (m), 1559 (m), 1521 (w), 1490 (w), 1368 (m), 1103 (m), 1008 (br s), 874 (m), 821 (m), 759 (m), 741 (m), 668 (w), 597 (w), 501 (w), 473 (w), 418 (w), 404 (w). FAB-MS: m/z (%) = 766 (M\(^{+}\), 38), 471 (24), 389 (60), 387 (62), 179 (100), 178 (52), 136 (36), 89 (30), 77 (36), 59 (30), 51 (17).

UV (MeCN): \( \lambda_{max} \) (log \( e \)) = 266 (4.50), 290 (4.24, sh), 302 (4.37), 318 (4.46), 346 (4.20, sh). Anal. Calcd for C\(_{35}\)H\(_{35}\)N\(_{3}\)O\(_{2}\)BrPS: C, 56.33; H, 4.61; N, 5.51; S, 4.19. Found: C, 56.18; H, 4.52; N, 5.43; S, 4.01.

**General procedure for the preparation of peptoido-substituted phosphono-γ-thiapyrones (21)**

To a solution of 0.5 mmol of phosphono substituted γ-thiapyrones (8) in CH\(_{2}\)Cl\(_{2}\) (20 mL) were added successively N,N-diisopropylethylamine (11) (129 mg, 1 mmol), pentafluorphenyldiphenylphosphinate (7) (250 mg, 0.65 mmol) and fluorenyl-9-methoxycarbonyloxy-N-benzylglycine (20) (201.5 mg, 0.5 mmol). The reaction mixture was stirred under argon for 7-8 h at rt. Work-up (40 mL NaHCO\(_{3}\) and NaCl, saturated; extraction with 40 mL of CH\(_{2}\)Cl\(_{2}\)) gave a deep red oil which was purified by chromatography on silica gel (ethyl acetate / n-hexane (2:1)). The peptoido-substituted phosphono-γ-thiapyrones (21) were isolated as orange-red crystals in moderate yields (37-41%).

2-(Fluorenyl-9-methoxycarbonyloxy-N-benzylglycyl)amino-5-cyano-6-(4'-fluorophenyl)-4-thioxo-4H-pyran-3-ylphosphonic acid diethyl ester (21.3b)

- 163 mg (41%) of 21.3b were obtained after chromatography separation as orange-red crystals, mp 83-84 °C (ethyl acetate / n-hexane (2:1)). \(^{1}H\text{-NMR (360 MHz, CDCl}_3\):} \( \delta = 1.29 \) (d, \( ^{3}J_{HH} = 7.1 \) Hz; 6H, OCH\(_{2}\)CH\(_{3}\)), 3.75, 4.07 (2*s, 2H, NHCOCH\(_{2}\)), 4.31 (t, \( ^{3}J_{HH} = 7.1 \) Hz; 1H, NHCOOCH\(_{2}\)CH\(_{12}\)H\(_{8}\)), 4.55 (d, \( ^{3}J_{HH} = 4.6 \) Hz; 2H, NHCOOCH\(_{2}\)CH\(_{12}\)H\(_{8}\)), 4.56-4.62 (2*d, m, 4H, NCH\(_{2}\)C\(_{6}\)H\(_{5}\) u. OCH\(_{2}\)CH\(_{3}\)), 7.14-7.67 (m, 13H, Aromatic-H), 7.73-7.75 (d, \( ^{3}J_{HH} = 8.1 \) Hz, 2H, 3'-H, 5'-H), 8.43-8.45 (d, \( ^{3}J_{HH} = 8.1 \) Hz; 2H, 2'-H, 6'-H), 12.82, 13.11 (2*s, 1H, NH). \(^{13}C\text{-NMR (90.56 MHz, CDCl}_3\):}
MHz, CDCl₃): $\delta$ = 16.1 (d, $^3J_{CH}$ = 7.1 Hz; OCH₂CH₃), 47.1 (s, C-9a), 50.9 (s, NHCOCH₂N), 51.8, 51.9 (2×s, NCH₂C₆H₅), 64.3 (d, $^2J_{CH}$ = 6.2 Hz; OCH₂CH₃), 67.7, 68.4 (2×s, NOCOOCH₂CHC₁₂H₈), 103.5 (d, $^1J_{CH}$ = 194 Hz; C-3), 109.6 (d, $^3J_{CH}$ = 10.5 Hz; C-5), 114.4 (s, CN), 116.7 (d, $^3J_{CH}$ = 22 Hz; C-3', C-5'), 120.1 (s, C-4a, C-5a), 124.5 (s, C-1'), 125.0 (s, C-1a, C-8a), 126.3, 126.9 (2×s, C-7'''), 127.0 (s, C-2a, C-7a), 127.7 (s, C-3a, C-6a), 128.1, 128.9 (2×d, C-8'', C-9'', C-11'', C-12''), 130.7 (2×s, C-10''), 132.1 (d, $^4J_{CH}$ = 9.6 Hz; C-2', C-6'), 141.3 (s, C-10a, C-11a), 143.9 (s, C-12a, C-13a), 156.7 (s, C-43), 158.5 (s, C-43), 158.7 (2×s, NOCOOCH₂CHC₁₂H₈), 158.5 (s, C-4''), 166.5, 166.8 (2×s, NHCO), 194.9 (d, $^2J_{CH}$ = 7.2 Hz; CS). $^{31}$P-NMR (145.79 MHz, CDCl₃): $\delta$ = 15.38 (s). IR (KBr): $\nu$ = 3365 cm⁻¹ (m), 3066 (w), 2984 (w), 2928 (w), 2228 (w), 1734 (m), 1700 (s), 1611 (s), 1586 (s), 1540 (m), 1508 (m), 1451 (m), 1387 (m), 1356 (m), 1227 (s), 1126 (m), 1028 (br s), 881 (m), 845 (m), 760 (m), 741 (m), 700 (m), 600 (m), 567 (w), 524 (w), 472 (w), 430 (w), 418 (w), 403 (w), 318 (w), 303 (w), 289 (40), 228 (30), 179 (100), 178 (38), 123 (20), 91 (50), 77 (24), 51 (20). UV (MeCN): $\lambda_{max}$ (log $\varepsilon$) = 266 (4.48), 292 (4.18), 302 (4.30), 316 (4.23), 342 (4.17, sh). Anal. Calcd for C₄₀H₃₅N₃O₈F₂P: C, 62.56; H, 4.59; N, 5.49; S, 4.17. Found: C, 62.52; H, 4.81; N, 5.24; S, 3.90.

2-(Fluoren-9-methoxy carbonyloxy-N-benzylglycyl)amino-5-cyano-6-(4'-chlorophenyl)-4-thioxo-4'H-pyrano-3-ylphosphonic acid diisopropyl ester (21.2c)

- 150 mg (37%) of 21.2c were obtained after chromatography separation as orange-red crystals, mp 170-171 °C (ethanol acetate / n-hexane (2:1)). $^1$H-MR (250.13 MHz, CDCl₃): $\delta$ = 1.26, 1.31 (2×d, $^3J_{HH}$ = 7.8 Hz; 12H, OCH(CH₃)₂), 3.76, 4.08 (2×s, 2H, NHCOCH₂N), 4.31 (t, $^3J_{HH}$ = 7.1 Hz; 1H, NHCOOCH₂CHC₁₂H₈), 4.54 (t, $^3J_{HH}$ = 4.6 Hz; 2H, NHCOOCH₂CHC₁₂H₈), 4.59, 4.62 (2×d, 2H, NCH₂C₆H₅), 4.64-4.70 (d, $^3J_{HH}$ = 7.4 Hz, 1H, Aromatic-H), 7.73-7.75 (d, $^3J_{HH}$ = 8.1 Hz; 2H, 3'-H, 5'-H), 8.33-8.35 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2'-H, 6'-H), 12.99, 13.25 (2×s, 1H, NH). $^{13}$C-NMR (90.56 MHz, CDCl₃): $\delta$ = [23.7 (d, $^3J_{CP}$ = 5 Hz), 23.9 (d, $^3J_{CP}$ = 4 Hz; OCH(CH₃)₂)], 47.2 (s, C-9a), 50.8 (s, NHCOCH₂N), 51.7, 51.9 (2×s, NCH₂C₆H₅), 67.7, 68.3 (2×s, NHCOOCH₂CHC₁₂H₈), 73.9 (d, $^2J_{CP}$ = 6.2 Hz; OCH(CH₃)₂), 104.3 (d, $^1J_{CP}$ = 194 Hz; C-3), 110.0 (d, $^3J_{CP}$ = 11.8 Hz; C-5), 114.3 (s, CN), 120.0 (s, C-4a, C-5a), 125.0 (s, C-1a, C-8a), 126.2, 126.9 (2×s, C-7''''), 127.7 (s, C-2a, C-7a), 127.9 (s, C-3a, C-6a), 128.2, 128.9, 129.4, 129.7 (4×d, C-2', C-3', C-5', C-6', C-8'', C-9'', C-11''), 130.6 (2×s, C-10''), 136.1 (s, C-4'), 141.3 (s, C-10a, C-11a), 143.8 (s, C-12a, C-13a), 156.7 (s, C-6),
156.9 (d, 2JCP= 22.8 Hz; C–2), 157.2, 157.4 (2s, NOCOOCH2CHC12H8), 166.4, 166.8 (2s, NHCOCH2N), 194.6 (d, 2JCP= 7.2 Hz; CS). 31P-NMR (145.79 MHz, CDCl3): δ= 11.95 (s). IR (KBr): ν= 3395 cm⁻¹ (m), 3066 (w), 3033 (w), 2978 (w), 2933 (w), 2233 (w), 1727 (m), 1700 (m), 1610 (s), 1565 (s), 1544 (m), 1472 (m), 1386 (m), 1255 (m), 1227 (m), 1130 (m), 1096 (m), 1014 (br s), 831 (m), 741 (m), 698 (m), 584 (w), 518 (w), 488 (w), 434 (w), 409 (w), 403 (w); FAB-MS: m/z (%)= 812 (M⁺, 26), 445 (58), 443 (57), 179 (100), 178 (82), 136 (24), 89 (18), 77 (24), 51 (20). UV (MeCN): λmax (log ε)= 266 (4.52), 290 (4.20), 302 (4.34), 318 (4.37), 344 (4.26, sh). Anal. Calcd for C₄₂H₃₉N₃O₈CIPS: C, 62.09; H, 4.83; N, 5.19; S, 3.94. Found: C, 61.89; H, 4.78; N, 5.05; S, 3.88.

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REFERENCES


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