PEPTIDE COUPLING REACTIONS WITH PHOSPHONO-PHOSPHINO SUBSTITUTED γ-THIAPYRONES – FIRST STEP TO UNUSUAL PEPTIDES

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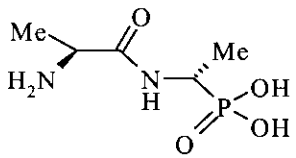
Abstract – The reactions of phosphono-phosphino substituted γ-thiapyrones (**8/9**) with pentafluorphenyldiphenylphosphinate – FDPP – (**7**) and protected α-L-amino acids (**10**) lead to chiral α-peptido substituted phosphono-phosphino γ-thiapyrones (**12/13**). Besides β-peptido- and peptoido substituted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

INTRODUCTION

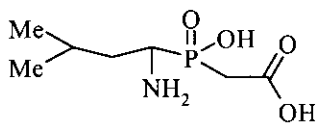
In our previous papers we described the syntheses and reactions of new phosphono-phosphino substituted γ-thiapyrones[1a-c] and many different phosphono-phosphino substituted heterocycles were studied by us.[1d-g] Here, we describe peptide coupling reactions with phosphono-phosphino substituted γ-thiapyrones. 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.[5a] Besides phosphinotricin (**3**), an inhibitor of glutaminic acid synthetase, and fosfomycin (**4**) intereferes with bacterial cell wall synthesis as an inhibitor of peptidoglycane synthesis.[5b-d]



(**1**)



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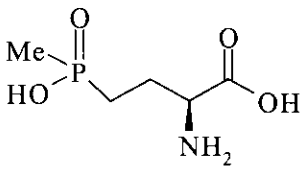

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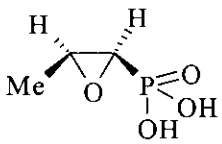
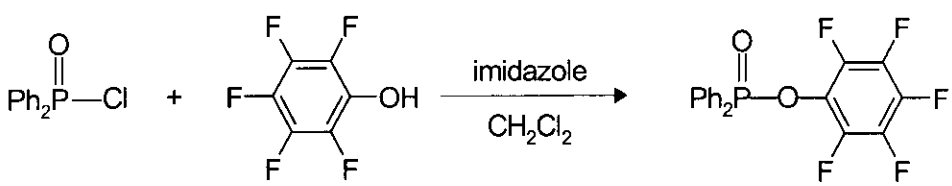


(**4**)

The present paper describes the investigations of our studies concerning the preparation of α-peptido-, β-peptido- and peptoido substituted phosphono-phosphino-γ-thiapyrones as starting compounds of unusual peptides.

RESULTS AND DISCUSSION

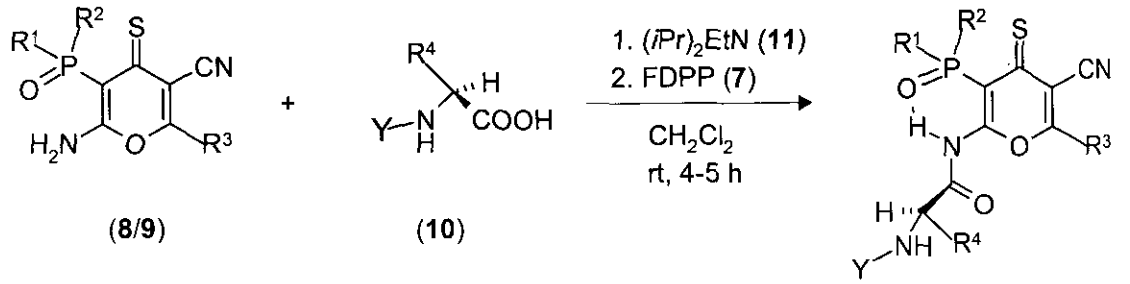
There are many coupling reagents in peptide synthesis described in the literature in reviews and monographs.[6,7a-c] We choose pentafluorphenyldiphenylphosphinate (FDPP) (**7**) as an efficient coupling reagent for peptide synthesis without racemization. Besides there is no problem of insoluble by-product such as (DCU) dicyclohexylurea and FDPP has a high coupling speed.[8] FDPP is prepared by mixing equimolar amounts of diphenylphosphinic chloride (**5**) and pentafluorphenol (**6**) in the presence of imidazole in CH_2Cl_2 at room temperature.[8] (Scheme 1).



(**5**) (**6**) (**7**)

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 CH_2Cl_2 at room temperature gave the chiral α-L-peptido substituted phosphono-phosphino γ-thiapyrones (**12/13**) (Scheme 2).



(**8/9**) (**10**) (**12/13**)

Y= Fmoc (fluorenyl-9-methoxycarbonyl); Cbz (benzyloxycarbonyl)

compound	R^1	R^2	R^3	R^4	Y	yield [%]
12.2a	OMe	OMe	C_6H_4Cl-(*p*)	Ala	Cbz	56
12.1b	OEt	OEt	Ph	Val	Cbz	58
12.3b	OEt	OEt	C_6H_4F-(*p*)	Met	Cbz	58
12.6b	OEt	OEt	*t*Bu	Gly	Fmoc	61
12.1c	O*i*Pr	O*i*Pr	Ph	Trp	Fmoc	52
12.4c	O*i*Pr	O*i*Pr	C_6H_4Me-(*p*)	Met	Cbz	55
12.7c	O*i*Pr	O*i*Pr	C_4H_3O	Gly	Fmoc	60
13.3d	OEt	Ph	C_6H_4F-(*p*)	Ala	Cbz	48

Scheme 2: Syntheses of chiral α-L-peptido–substituted phosphono-phosphino-γ-thiapyrones (**12/13**)

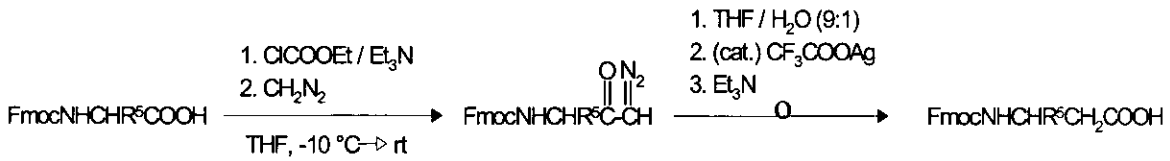
The UV spectra of the Fmoc– and Cbz–protected α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones (**12/13**) are different. The Cbz-protected compounds (**12.2a**, **12.1b**, **12.3b**, **12.4c** and **13.3d**) show three characteristic absorption bands between λ_{max}= 270–280 nm, λ_{max}= 310–320 nm and λ_{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 $^3J_{HH}$= 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 $^3J_{HH}$= 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 ^{13}C 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 ^{13}C 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[9a–c] 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 organisms[13] 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]

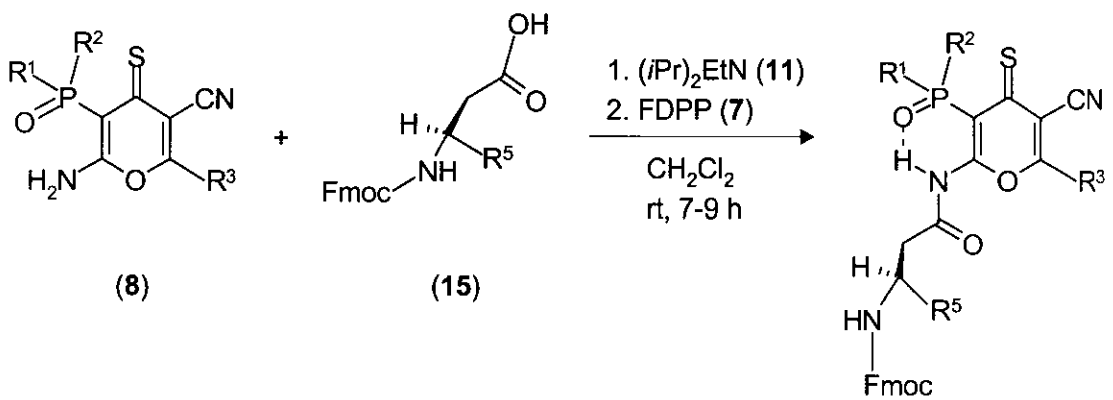


(**10**) (**14**) (**15**)

R^5= H, Me, $PhCH_2$

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).



(**8**) (**15**) (**16**)

compound	R^1=R^2	R^3	R^5	yield [%]
16.3b	OEt	C_6H_4F-(*p*)	Phe	40
16.4b	OEt	C_6H_4Me-(*p*)	Phe	39
16.1c	O*i*Pr	Ph	Ala	45
16.4c	O*i*Pr	C_6H_4Me-(*p*)	Gly	43
16.5c	O*i*Pr	C_6H_4Br-(*p*)	Gly	46

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

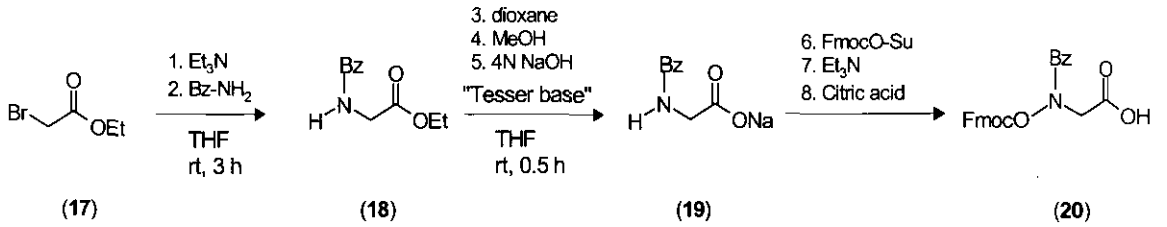
The reactivity of the β-peptide bond formation is lower than the α-peptide bond formation. The

reaction time is much more higher and the yields of the β-peptido-substituted phosphono-γ-thiapyrones (**16**) are moderated compared to the α-peptido-derivatives.

The UV spectra of the β-peptido-substituted phosphono-γ-thiapyrones (**16**) have no characteristic difference compared to the UV spectra of the α-peptido-substituted phosphono-phosphino-γ-thiapyrones (**12/13**). The Fmoc-β-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.

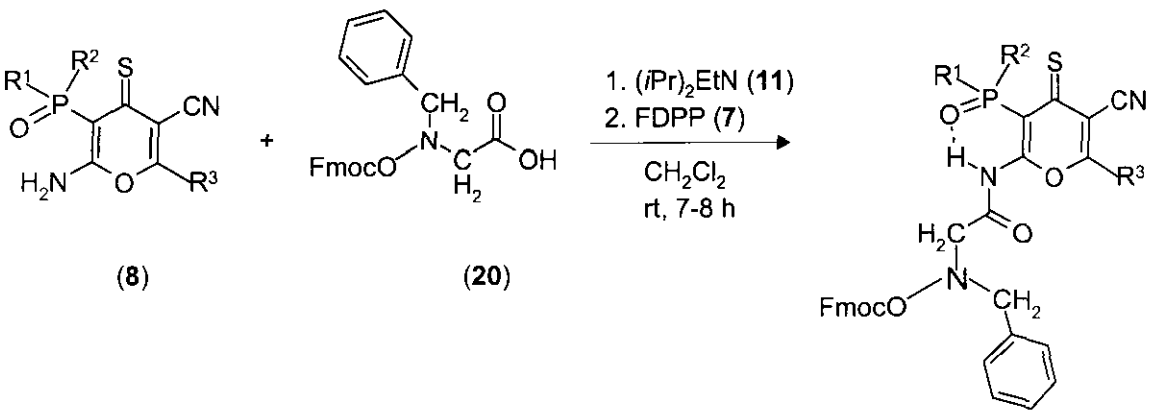
The methylene group of the β-amino acid in α-position of the amide group is located in the ^1H NMR spectra at 2.74-2.78 ppm with a $^3J_{HH}$-coupling constant of 7.2 Hz. The proton of the chiral carbon atom of the β-amino acid is observed at 4.01 ppm as a triplet with a $^3J_{HH}$-coupling constant of 4.6-4.8 Hz. Besides the NH-proton of the Fmoc group is given as a triplet ($^3J_{HH}$~ 4 Hz) at 5.30–5.35 ppm. The methylene group in α-position of the amide group is located at 38.6-42.4 ppm; the chiral carbon atom of the β-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 β-peptido-substituted phosphono-γ-thiapyrones (**16**) are isolated after chromatography separation as light red crystals. The melting points are measured between 70-95°C. The melting points of the β-peptido-substituted phosphono-γ-thiapyrones (**16**) are much lower compared to the melting points of the α-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 γ-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-methoxycarbonyl-succinimid as a protecting group to give the peptoid (**20**).



Scheme 5: Synthesis of fluorenyl-9-methoxycarbonyloxy-*N*-benzylglycine (**20**)

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



compound	R^1=R^2	R^3	yield [%]
21.3b	OEt	C_6H_4F-(*p*)	41
21.2c	O*i*Pr	C_6H_4Cl-(*p*)	37

Scheme 6: Syntheses of peptoido-substituted phosphono-γ-thiapyrones (**21**)

The NMR spectra clearly show the presence of both rotamers and it is in agreement with the literature.[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 dublets at 4.56-4.61 ppm and the NH-signal which is incorporated in the hydrogen bond to the phosphonate group is splitted 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 $[C_7H_7]^+$. The UV spectra of the peptoido 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. ^1H- and ^{13}C NMR spectra were recorded on a Bruker WM-250 (^1H NMR: 250.13 MHz, ^{13}C NMR: 62.89 MHz) and a Bruker WM-360 (^1H NMR: 360 MHz, ^{13}C NMR: 90.56 MHz) spectrometers in $CDCl_3$. All chemical shifts are reported in ppm downfield from tetramethylsilane; 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_3PO_4 (internal standard 85% H_3PO_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 γ-thiapyrones (**8/9**) in CH_2Cl_2 (20 mL) were added successively *N,N*-diisopropylethylamine (**11**) (258 mg, 2 mmol), pentafluorphenyldiphenylphosphinate (**7**) (499 mg, 1.3 mmol) and protected-α-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 $NaHCO_3$ and NaCl (40 mL) and extracted with CH_2Cl_2 (40 mL). The organic layer was dried over anhydrous $MgSO_4$ 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 α-L-peptido-substituted phosphono-phosphino-γ-thiapyrones (**12/13**) as pink-red crystals in moderate yields (48-61%).

2-(Benzyloxycarbonyl-α-L-alanyl)amino-5-cyano-6-(4′-chlorophenyl)-4-thioxo-4*H*-pyran-3-ylphosphonic 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}H-NMR (360 MHz, $CDCl_3$): δ= 2.04 (s, 3H, HCC$\underline{H}_3$), 3.77, 3.83 (2*d_p, $^3J_{HP}$= 12 Hz; 6H, OC$\underline{H}_3$), 4.36-4.38 (t, $^3J_{HH}$= 4.4 Hz; 1H, $\underline{H}$CCH$_3$), 5.14 (s; 2H, $C_6H_5C\underline{H}_2$), 5.36 (t, $^3J_{HH}$= 4.8 Hz; 1H, N$\underline{H}$COOCH$_2$C$_6$H$_5$), 7.37 (s, 5H, $C_6\underline{H}_5CH_2COO$), 7.55-7.57 (d, $^3J_{HH}$= 8.7 Hz; 2H, 3′-H, 5′-H), 8.34-8.37 (d, $^3J_{HH}$= 8.7 Hz; 2H, 2′-H, 6′-H), 13.06 (s, 1H, N$\underline{H}$CO). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 17.8 (s, HC$\underline{C}H_3$), 52.9 (s, H$\underline{C}$CH$_3$), 54.1 (d_p, $^2J_{CP}$= 6.2 Hz; O$\underline{C}H_3$), 67.4 (s, $C_6H_5\underline{C}H_2COO$), 102.8 ($d_p$, $^1J_{CP}$= 197 Hz; C-3), 109.8 (d_p, $^3J_{CP}$= 10.9 Hz; C-5), 114.1 (s, CN), 126.0 (s, C-1′), 126.8 (s, C-7′), 128.2, 128.3 (2*d; *C-8′, C-9′, C-11′, C-12′*), 128.5, 129.7 (*2*d; C-2′, C-3′, C-5′, C-6′*), 135.9 (s, C-10′), 140.6 (s, C-4′), 155.9 (s, C_6H_5CH2O$\underline{C}$O), 158.3 (d_p, $^2J_{CP}$= 23.8 Hz; C-2), 158.5 (s, C-6), 170.4 (s, $\underline{C}$ONH), 194.9 (d_p, $^2J_{CP}$= 6.6 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 18.14 (s). IR (KBr): ν= 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): λ_{max} (log ε)= 272 (4.34), 318 (4.50), 336 (4.46, *sh*). $[\alpha]_D^{20}$= ±0° (c= 0.05, DMF). Anal. Calcd for $C_{25}H_{23}N_3O_7ClPS$: 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-(Benzyloxycarbonyl-α-L-valinyl)amino-5-cyano-6-phenyl-4-thioxo-4*H*-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)). ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ= 0.99, 1.09 (2*d, $^3J_{HH}$= 6.8 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.35 (d_pt, $^3J_{HH}$= 7 Hz; 6H, $OCH_2C\underline{H}_3$), 2.20-2.30 (sept, $^3J_{HH}$= 6.4 Hz; 1H, $C\underline{H}(CH_3)_2$), 4.14-4.25 (m, 4H, $OC\underline{H}_2CH_3$), 4.52 (t, $^3J_{HH}$= 4.4 Hz; 1H, $\underline{H}CCH(CH_3)_2$), 5.13 (s, 2H, $COOC\underline{H}_2C_6H_5$), 5.32 (t, $^3J_{HH}$= 4.9 Hz; 1H, $N\underline{H}COOCH_2C_6H_5$), 7.36 (s, 5H, $COOCH_2C_6\underline{H}_5$), 7.56-7.66 (m, 3H, 3´-H, 4´-H, 5´-H), 8.35-8.38 (d, $^3J_{HH}$= 8.1 Hz; 2H, 2´-H, 6´-H), 13.24 (s, N<u>H</u>CO). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 16.2 (d_pq, $^3J_{CP}$= 7.1 Hz; $OCH_2\underline{C}H_3$), 19.4 (s, $CH(\underline{C}H_3)_2$), 30.6 (s, $C\underline{H}(CH_3)_2$), 62.3 (s, $H\underline{C}NHCOOCH_2C_6H_5$), 64.2 ($d_p$q, $^2J_{CP}$= 6.2 Hz; $O\underline{C}H_2CH_3$), 67.3 (s, $NHCOO\underline{C}H_2C_6H_5$), 103.6 ($d_p$, $^1J_{CP}$= 194 Hz; C-3), 110.1 (d_p, $^3J_{CP}$= 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-4), 135.5 (s, C-10´), 156.3 (s, $NH\underline{C}OOCH_2C_6H_5$), 157.8 ($d_p$, $^2J_{CP}$= 23.7 Hz; C-2), 159.6 (s, C-6), 169.6 (s, NH<u>C</u>O), 195.1 (d_p, $^2J_{CP}$= 6.8 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): 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*), 1387 (*m*), 1356 (*m*), 1224 (*m*), 1095 (*m*), 1027 (br *s*), 879 (*m*), 801 (*m*), 779 (*m*), 668 (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): λ_{max} (log ε)= 270 (4.33), 312 (4.36), 330 (4.34, *sh*). $[\alpha]_D^{20}$= -8.5° (c= 0.05, DMF). Anal. Calcd for $C_{29}H_{32}N_3O_7PS$: C, 58.27; H, 5.39; N, 7.05; S, 5.36. Found: C, 57.89; H, 5.28; N, 7.05; 5.50. Exact MS calcd for $C_{29}H_{32}N_3O_7PS$: 597.1699. Found: 597.1699.

2-(Benzyloxycarbonyl-α-L-methionyl)amino-5-cyano-6-(4´-fluorophenyl)-4-thioxo-4*H*-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)). ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ= 1.24 (d_pt, $^3J_{HH}$= 6.2 Hz; 6H, $OCH_2C\underline{H}_3$), 2.27-2.29 (t, $^3J_{HH}$= 7.3 Hz; 2H, $HCC\underline{H}_2CH_2SCH_3$), 2.45 (s, $HCCH_2CH_2SC\underline{H}_3$), 2.60-2.63 (t, $^3J_{HH}$= 9.8 Hz; $HCCH_2C\underline{H}_2SCH_3$), 4.05-4.20 (m, 4H, $OC\underline{H}_2CH_3$), 4.48 (t, $^3J_{HH}$= 4.3 Hz; 1H, $\underline{H}CCH_2CH_2SCH_3$), 5.14 (s, $COOC\underline{H}_2C_6H_5$), 5.65 (t, $^3J_{HH}$= 5.1 Hz; 1H, $N\underline{H}COOCH_2C_6H_5$), 7.37-7.41 (m, 5H, $COOCH_2C_6\underline{H}_5$), 7.59-7.63 (d, $^3J_{HF}$= 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, $CDCl_3$): δ= 15.4 (s, SCH_3), 16.2 (d_pq, $^3J_{CP}$= 6.8 Hz; OCH_2CH_3), 29.8 (s, $HCCH_2CH_2SCH_3$), 30.9 (s, $HCCH_2CH_2SCH_3$), 56.4 (s, $HCCH_2CH_2SCH_3$), 64.4 (d_pq, $^2J_{CP}$= 6.2 Hz; OCH_2CH_3), 67.4 (s, $COOCH_2C_6H_5$), 104.6 (d_p, $^1J_{CP}$= 198 Hz; C-3), 109.8 (d_p, $^3J_{CP}$= 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*d, 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, $COOCH_2C_6H_5$), 157.6 (d_p, $^2J_{CP}$= 23.1 Hz; C-2), 158.5 (s, C-4′), 159.8 (s, C-6), 169.6 (s, NHCO), 194.9 (d_p, $^2J_{CP}$= 6.4 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 15.06 (s). IR (KBr): ν= 3318 cm^{-1} (*m*), 3066 (*w*), 2983 (*w*), 2922 (*w*), 2226 (*w*), 1717 (*s*), 1683 (*m*), 1616 (*s*), 1586 (*s*), 1544 (*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): λ_{max} (log ε)= 270 (4.35), 316 (4.51), 340 (4.39, *sh*). $[\alpha]_D^{20}$= -6.5° (c= 0.05, DMF). Anal. Calcd for $C_{29}H_{31}N_3O_7FPS_2$: 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-(Fluorenyl-9-methoxycarbonyl-α-glycyl)amino-5-cyano-6-*tert*-butyl-4-thioxo-4*H*-pyran-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, $CDCl_3$): δ= 1.27 (d_pt, $^3J_{HH}$= 6.7 Hz; 6H, OCH_2CH_3), 1.55 (s, 9H, $(CH_3)_3C$), 4.01-4.11 (m, 4H, OCH_2CH_3), 4.14 (d, $^3J_{HH}$= 6.4 Hz; 2H, $NHCOCH_2$), 4.25 (t, $^3J_{HH}$= 7.1 Hz; 1H, $COOCH_2CHC_{12}H_8$), 4.42 (d, $^3J_{HH}$= 4.8 Hz; 2H, $COOCH_2CHC_{12}H_8$), 5.53 (t, $^3J_{HH}$= 3.8 Hz; 1H, CH_2NHCOO), 7.25-7.77 (m, 8H, Fluoren-H), 13.3 (s, 1H, $NHCOCH_2$). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ= 16.0 (d_pt, $^3J_{CP}$= 6.7 Hz; OCH_2CH_3), 28.2 (s, $(CH_3)_3C$), 38.4 (s, $(CH_3)_3C$), 46.2 (s, $COCH_2NH$), 47.1 (s, C-9a), 64.4 (d_pd, $^2J_{CP}$= 6.1 Hz; OCH_2CH_3), 67.7 (s, $COOCH_2CHC_{12}H_8$), 103.5 (d_p, $^1J_{CP}$= 195 Hz; C-3), 111.8 (d_p, $^3J_{CP}$= 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 (d_p, $^2J_{CP}$= 23.3 Hz; C-2), 166.6 (s, $NHCOOCH_2CHC_{12}H_8$), 172.7 (s, $NHCOCH_2$), 192.2 (d_p, $^2J_{CP}$= 7.2 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 15.02 (s). IR (KBr): ν= 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*),

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): λ_{max} (log ε)= 250 (4.45), 266 (4.37), 286 (4.12, *sh*), 300 (4.02), 338 (4.27). Anal. Calcd for $C_{31}H_{34}N_3O_7PS$: 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 $C_{31}H_{34}N_3O_7PS$: 623.1854. Found: 623.1853.

2-(Fluorenyl-9-methoxycarbonyl-α-L-tryptophanyl)amino-5-cyano-6-phenyl-4-thioxo-4*H*-pyran-3-ylphosphonic acid diisopropyl ester (**12.1c**)

- 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)). ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ= 1.20, 1.24 (2*d_p, $^3J_{HH}$= 6.2 Hz; 12H, OCH(C$\underline{H}_3$)$_2$), 2.03 (s, 1H, $C_8H_5N\underline{H}$), 3.43 (d, $^3J_{HH}$= 7.1 Hz; 2H, HCC$\underline{H}_2C_8H_5NH$), 4.13-4.19 ($d_p$sept, $^3J_{HP}$= 7.4 Hz, $^3J_{HH}$= 6.2 Hz; 2H, OC$\underline{H}$(CH$_3$)$_2$), 4.21 (t, $^3J_{HH}$= 6.4 Hz; 1H, NHCOOCH$_2$C$\underline{H}$C$_{12}$H$_8$), 4.35-4.38 (d, $^3J_{HH}$= 4.8 Hz; 2H, COOC$\underline{H}_2$CHC$_{12}$H$_8$), 4.56 (t, $^3J_{HH}$= 6.2 Hz; 1H, $\underline{H}$CCH$_2$C$_8$H$_5$NH), 5.49 (t, $^3J_{HH}$= 3.9 Hz; 1H, N$\underline{H}$COOCH$_2$CHC$_{12}$H$_8$), 7.00-7.12 (m, 15H, Aromatic-H), 8.24 (s, 1H, 2a-H, Vinyl H of Trp), 8.36-8.39 (d, $^3J_{HH}$= 8 Hz; 2H, 2´-H, 6´-H), 13.29 (s, 1H, N$\underline{H}$CO). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ= [23.7 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz; OCH(C$\underline{H}_3$)$_2$)], 27.9 (s, HC$\underline{C}$H$_2$C$_8$H$_5$NH), 47.1 (s, C-9a), 57.7 (s; H$\underline{C}$CH$_2$C$_8$H$_5$NH), 67.5 (s, COO$\underline{C}$H$_2$CHC$_{12}$H$_8$), 73.9 (d_pq, $^2J_{CP}$= 7.2 Hz; O$\underline{C}$H(CH$_3$)$_2$), 104.7 (d_p, $^1J_{CP}$= 194 Hz; C-3), 109.1 (s, C-9´), 110.0 (d_p, $^3J_{CP}$= 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, NH$\underline{C}$OOCH$_2$CHC$_{12}$H$_8$), 157.5 (d_p, $^2J_{CP}$= 23.8 Hz; C-2), 159.5 (s, C-6), 170.0 (s, NH$\underline{C}$O), 192.2 (d_p, $^2J_{CP}$= 6.7 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): 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): λ_{max} (log ε)= 266 (4.58), 290 (4.30), 300 (4.33), 312 (4.28, *sh*), 338 (4.27, *sh*). $[\alpha]_D^{20}$= -12° (c= 0.05, DMF). Anal. Calcd for $C_{44}H_{41}N_4O_7PS$: 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-(Benzyloxycarbonyl-α-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, $CDCl_3$): δ= 1.31, 1.35 (2*d_p, $^3J_{HH}$= 6.2 Hz; 12H, OCH(CH_3)$_2$), 2.09 (s, 3H, $C_6H_4CH_3$), 2.28-2.30 (t, $^3J_{HH}$= 7.2 Hz; 2H, $HCCH_2CH_2SCH_3$), 2.45 (s, 3H, $CH_2CH_2SCH_3$), 2.59-2.62 (t, $^3J_{HH}$= 10 Hz; 2H, $CH_2CH_2SCH_3$), 4.42 (t, $^3J_{HH}$= 4.2 Hz; 1H, $HCCH_2CH_2SCH_3$), 4.71-4.76 ($d_p$sept, 3J_{HP}= 7.4 Hz, $^3J_{HH}$= 6.2 Hz; 2H, OCH(CH_3)$_2$), 5.13 (s, $COOCH_2C_6H_5$), 5.64 (t, $^3J_{HH}$= 5.2 Hz; 1H, $NHCOOCH_2C_6H_5$), 7.36-7.39 (d, $^3J_{HH}$= 7.9 Hz; 2H, 3′-H, 5′-H), 7.39 (s, 5H, $NHCOOCH_2C_6H_5$), 8.26-8.29 (d, $^3J_{HH}$= 8.2 Hz; 2H, 2′-H, 6′-H), 13.39 (s, 1H, NHCO). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 15.4 (s, SCH_3), 21.8 (s, $C_6H_4CH_3$), [23.7 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz; OCH(CH_3)$_2$)], 29.9 (s, $HCCH_2CH_2SCH_3$), 30.9 (s, $HCCH_2CH_2SCH_3$), 56.3 (s, $HCCH_2CH_2SCH_3$), 67.4 (s, $NHCOOCH_2C_6H_5$), 73.9 (d_pq, $^2J_{CP}$= 7.2 Hz; OCH(CH_3)$_2$), 104.5 (d_p, $^1J_{CP}$= 194 Hz; C-3), 109.6 (d_p, $^3J_{CP}$= 9.8 Hz; C-5), 114.7 (s, CN), 124.9 (s, C-1), 128.1, 128.5 (2*d, C-2, C-3, C-5, C-6), 128.8 (s, C-7′), 129.3, 130.0 (2*d, C-8′, C-9′, C-11′, C-12′), 135.9 (s, C-10′), 145.1 (s, C-4), 155.9 (s, $NHCOOCH_2C_6H_5$), 157.5 (d_p, $^2J_{CP}$= 23.9 Hz; C-2), 159.7 (s, C-6), 169.5 (s, NHCO), 195.1 (d_p, $^2J_{CP}$= 6.2 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 11.73 (s). IR (KBr): ν= 3280 cm^{-1} (*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 (8), 91 (100), 75 (4), 61 (7), 47 (12), 41 (8). UV (MeCN): λ_{max} (log ε)= 272 (4.31), 316 (4.52), 342 (4.31, *sh*). $[\alpha]_D^{20}$= -7.3° (c= 0.05, DMF). Anal. Calcd for $C_{32}H_{38}N_3O_7PS_2$: 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-(Fluorenyl-9-methoxycarbonyl-α-glycyl)amino-5-cyan-6-furoyl-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, $CDCl_3$): δ= 1.27, 1.31 (2*d_p, $^3J_{HH}$= 6.2 Hz; 12H, OCH(CH_3)$_2$), 4.12 (d, $^3J_{HH}$= 7.2 Hz; 2H, $COCH_2NH$), 4.24-4.28 (t, $^3J_{HH}$= 3.8 Hz; 1H, $NHCOOCH_2CHC_{12}H_8$), 4.41-4.44 (d, $^3J_{HH}$= 7.1 Hz; 2H, $NHCOOCH_2CHC_{12}H_8$), 4.64-4.72 ($d_p$sept, $^3J_{HP}$= 7.2 Hz, $^3J_{HH}$= 6.2 Hz; 2H, OCH(CH_3)$_2$), 5.37 (t, $^3J_{HH}$= 4.3 Hz; 1H,

NHCOOCH$_2$CHC$_{12}$H$_8$), 6.70 (d, $^3J_{HH}$= 4.8 Hz; 1H, 5′-H), 7.25-7.45 (m, 4H, Aromatic-H), 7.62, 7.78 (2*d, $^3J_{HH}$= 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, $CDCl_3$): δ= [23.6 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz; OCH(CH$_3$)$_2$)], 46.3 (s, COCH$_2$NH), 47.2 (s, C-9a), 67.6 (s, COOCH$_2$CHC$_{12}$H$_8$), 74.0 (d_pq, $^2J_{CP}$= 7.2 Hz; OCH(CH$_3$)$_2$), 104.4 (d_p, $^1J_{CP}$= 196 Hz; C-3), 112.2 (d_p, $^3J_{CP}$= 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, NHCOOCH$_2$CHC$_{12}$H$_8$), 156.6 (d_p, $^2J_{CP}$= 24.1 Hz; C-2), 159.0 (s; C-6), 166.9 (s, NHCO), 194.4 (d_p, $^2J_{CP}$= 6.7 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 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): λ_{max} (log ε)= 266 (4.42), 290 (4.36), 300 (4.31), 312 (4.25, *sh*), 350 (4.47, *sh*). Anal. Calcd for $C_{33}H_{32}N_3O_8PS$: 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-4*H*-pyran-3-yl-phenylphosphinic 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, $CDCl_3$): δ= 1.41 (t_p, $^3J_{HH}$= 6.4 Hz; 3H, OCH$_2$CH$_3$), 1.62 (s, 3H, HCCH$_3$), 4.23-4.35 (m, 2H, OCH$_2$CH$_3$), 4.74 (t, $^3J_{HH}$= 7.2 Hz; 1H, HCCH$_3$), 5.13 (s, 2H, NHCOOCH$_2$C$_6$H$_5$), 5.34 (d, $^3J_{HH}$= 6.7 Hz; 1H, NHCOOCH$_2$C$_6$H$_5$), 7.28 (s, 5H, NHCOOCH$_2$C$_6$H$_5$), 7.33-7.43 (m, 5H, 2′a-H, 3′-a, 4′-a, 5′-a, 6′-a), 7.92-7.94 (t, $^2J_{HF}$= 8.8 Hz; 2H, 3′-H, 5′-H), 8.45-8.47 (dd, $^4J_{HF}$= 5.2 Hz; 2H, 2′-H, 6′-H), 13.93 (s, 1H, NHCO). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ= 16.3 (d_pt, $^3J_{CP}$= 7.5 Hz; OCH$_2$CH$_3$), 18.3 (s, HCCH$_3$), 53.1 (s, HCCH$_3$), 62.4 (d_pd, $^2J_{CP}$= 6.2 Hz; OCH$_2$CH$_3$), 67.3 (s, NHCOOCH$_2$C$_6$H$_5$), 104.3 (d_p, $^1J_{CP}$= 146 Hz; C-3), 108.5 (d_p, $^3J_{CP}$= 10.7 Hz; C-5), 114.2 (s, CN), 116.7 (d, $^2J_{CF}$= 22.1 Hz; C-3′, C-5′), 123.9 (s, C-7′), 128.0, 128.3 (2*d, C-2a, C-3a, C-4a, C-5a, C-6a), 128.2, 128.5 (2*d, C-8′, C-9′, C-10′, C-11′, C-12′), 129.9 (d, C-1a), 132.0 (d, $^3J_{CF}$= 9.8 Hz; C-2′, C-6′), 135.9 (d, $^4J_{CF}$= 3.2 Hz; C-1′), 156.0 (s, NHCOOCH$_2$C$_6$H$_5$), 164.4 (s, C-4′), 167.2 (s, C-6), 169.4 (s, NHCO), 194.4 (d_p, $^2J_{CP}$= 7.1 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 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*), 1437 (*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^+, 22), 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): λ_{max} (log ε)= 278 (4.42), 320 (4.54), 348 (4.13, *sh*). $[\alpha]_D^{20}$= -16° (c= 0.05, DMF). Anal. Calcd for $C_{31}H_{27}N_3O_6FPS$: 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 β-peptido-substituted phosphono-γ-thiapyrones (**16**)

To a solution of 0.5 of mmol phosphono substituted γ-thiapyrones (**8**) in CH_2Cl_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_2Cl_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 β-peptido-substituted phosphono-γ-thiapyrones (**16**) in moderate yields (39-46%).

2-(Fluorenyl-9-methoxycarbonyl-β-L-phenylalanyl)amino-5-cyano-6-(4´-fluorophenyl)-4-thioxo-4*H*-pyran-3-ylphosphonic acid diethyl 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, $CDCl_3$): δ= 1.34 (d_pt, $^3J_{HH}$= 6.2 Hz; 2H, $OCH_2C\underline{H}_3$), 2.75 (t, $^3J_{HH}$= 4.8 Hz; 2H, $NHCOC\underline{H}_2$), 3.06 (quart, $^3J_{HH}$= 4.7 Hz; 2H, $HCC\underline{H}_2C_6H_5$), 4.01 (t, $^3J_{HH}$= 4.6 Hz; 1H, $\underline{H}CCH_2C_6H_5$), 4.03-4.21 (m, 4H, $OC\underline{H}_2CH_3$), 4.24 (t, $^3J_{HH}$= 7 Hz; 1H, $NHCOOCH_2C\underline{H}C_{12}H_8$), 4.42 (d, $^3J_{HH}$= 7.1 Hz; 2H, $NHCOOC\underline{H}_2CHC_{12}H_8$), 5.31 (t, $^3J_{HH}$= 3.8 Hz; 1H, $N\underline{H}COOCH_2CHC_{12}H_8$), 7.18-7.56 (*m*; 8H, $NHCOOCH_2CHC_{12}\underline{H}_8$), 7.59-7.62 (t, $^3J_{HF}$= 7.1 Hz; 2H, 3´-H, 5´-H), 8.06-8.09 (dd, $^4J_{HF}$= 4.8 Hz; 2H, 2´-H, 6´-H), 12.81 (s, 1H, NH). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 16.2 (d_pt, $^3J_{CP}$= 7 Hz; $OCH_2\underline{C}H_3$), 40.3 (s, $HC\underline{C}H_2C_6H_5$), 42.4 (s, $NHCO\underline{C}H_2$), 47.2 (s, C-9a), 49.6 (s, $H\underline{C}CH_2C_6H_5$), 64.5 (d_pd, $^2J_{CP}$= 6.1 Hz; $O\underline{C}H_2CH_3$), 102.7 (d_p, $^1J_{CP}$= 194 Hz; C-3), 114.3 (s, CN), 116.4 (dd, $^2J_{CF}$= 17.9 Hz; C-3´, C-5´), 119.9 (s, C-4a, C-

5a), 124.2 (d, $^4J_{CF}$= 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, $^3J_{CF}$= 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_p, $^2J_{CP}$= 24.1 Hz; C-2), 158.4 (s, C-4′), 159.6 (s, NHCOOCH$_2$CHC$_{12}$H$_8$), 168.1 (s, NHCO), 195.3 (d_p, $^2J_{CP}$= 6.5 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 13.81 (s). IR (KBr): ν= 3385 cm^{-1} (*w*), 3066 (*w*), 2966 (*w*), 2922 (*w*), 2233 (*w*), 1734 (*s*), 1718 (*s*), 1700 (*m*), 1635 (*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): λ_{max} (log ε)= 266 (4.68), 292 (4.34, *sh*), 300 (4.48), 316 (4.49), 338 (4.40, *sh*). $[\alpha]_D^{20}$= -15° (c= 0.05, DMF). Anal. Calcd for $C_{41}H_{37}N_3O_7FPS$: 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-4*H*-pyran-3-ylphosphonic acid diethyl ester (**16.4b**)

- 149 mg (39%) of **16.4b** were obtained as light red crystals after chromatography separation, mp 88 °C (ethyl acetate / *n*-hexane (1:1)). ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ= 1.33 (d_pt, $^3J_{HH}$= 6.1 Hz; 6H, OCH$_2$CH$_3$), 2.42 (s, 3H, C$_6$H$_4$CH$_3$), 2.74 (t, $^3J_{HH}$= 4.8 Hz; 2H, NHCOCH$_2$), 3.05 (quart, $^3J_{HH}$= 4.7 Hz; 2H, HCCH$_2$C$_6$H$_5$), 4.01 (t, $^3J_{HH}$= 4.6 Hz; 1H, HCCH$_2$C$_6$H$_5$), 4.03-4.18 (m, 4H, OCH$_2$CH$_3$), 4.23 (t, $^3J_{HH}$= 7.1 Hz; 1H, NHCOOCH$_2$CHC$_{12}$H$_8$), 4.43 (d, $^3J_{HH}$= 7 Hz; 2H, NHCOOCH$_2$CHC$_{12}$H$_8$), 5.28 (t, $^3J_{HH}$= 3.8 Hz; 1H, NHCOOCH$_2$CHC$_{12}$H$_8$), 7.16-7.58 (m, 13H, NHCOOCH$_2$CHC$_{12}$H$_8$, HCCH$_2$C$_6$H$_5$), 7.73-7.76 (d, $^3J_{HH}$= 8.1 Hz; 2H, 3′-H, 5′-H), 8.20-8.23 (d, $^3J_{HH}$= 8.1 Hz; 2H, 2′-H, 6′-H), 12.77 (s, 1H, NH). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 16.1 (d_pq, $^3J_{CP}$= 7 Hz; OCH$_2$CH$_3$), 21.8 (s, C$_6$H$_4$CH$_3$), 40.3 (s, HCCH$_2$C$_6$H$_5$), 42.4 (s, NHCOCH$_2$), 47.2 (s, C-9a), 49.5 (s, HCCH$_2$C$_6$H$_5$), 64.4 (d_pd, $^2J_{CP}$= 5.9 Hz; OCH$_2$CH$_3$), 102.4 (d_p, $^1J_{CP}$= 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_p, $^2J_{CP}$= 24 Hz; C-2), 159.7 (s, NHCOOCH$_2$CHC$_{12}$H$_8$), 168.0 (s, NHCO), 195.2 (d_p, $^2J_{CP}$= 6.4 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 13.78 (s). IR (KBr): ν= 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): λ_{max} (log ε)= 266 (4.56), 292 (4.31, *sh*), 300 (4.42), 316 (4.47), 338 (4.30, *sh*). $[\alpha]_D^{20}$= -14° (c= 0.05, DMF). Anal. Calcd for $C_{42}H_{40}N_3O_7PS$: 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-4*H*-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)). ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ= 1.28, 1.32 (2*d_p, $^3J_{HH}$= 6.4 Hz; 12H, OCH(C$\underline{H}_3$)$_2$), 1.63 (s, 3H, HCC$\underline{H}_3$), 2.77 (t, $^3J_{HH}$= 4.8 Hz; 2H, NHCOC$\underline{H}_2$), 4.72 (t, $^3J_{HH}$= 7.1 Hz; 1H, $\underline{H}$CCH$_3$), 4.12-4.22 ($d_p$sept, $^3J_{HP}$= 7.4 Hz, $^3J_{HH}$= 6.2 Hz; 2H, OC$\underline{H}$(CH$_3$)$_2$), 4.23 (t, $^3J_{HH}$= 6.2 Hz; 1H, NHCOOCH$_2$C$\underline{H}$C$_{12}$H$_8$), 4.36-4.38 (d, $^3J_{HH}$= 4.9 Hz; 2H, NHCOOC$\underline{H}_2$CHC$_{12}$H$_8$), 5.43 (t, $^3J_{HH}$= 4.1 Hz; 1H, N$\underline{H}$COOCH$_2$CHC$_{12}$H$_8$), 7.05-7.70 (m, 13H, NHCOOCH$_2$CHC$_{12}\underline{H}_8$, 2´-H, 3´-H, 4´-H, 5´-H, 6´), 13.01 (s, 1H, NH). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 18.3 (s, HC$\underline{C}$H$_3$), [23.7 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz; OCH($\underline{C}$H$_3$)$_2$)], 42.4 (s, NHCO$\underline{C}$H$_2$), 47.2 (s, C-9a), 53.1 (s, H$\underline{C}$CH$_3$), 73.8 (d_pq, $^2J_{CP}$= 7.2 Hz; O$\underline{C}$H(CH$_3$)$_2$), 102.7 (d_p, $^1J_{CP}$= 197 Hz; C-3), 114.3 (s, CN), 119.9 (s, C-4a, C-5a), 124.9 (s, C-1a, C-8a), 126.5 (s, C-1´), 127.6 (s, C-2a, C-7a), 127.7 (s, C-3a, C-4a), 128.7, 129.8 (2*d, C-2´, C-3´, C-5´, C-6´), 132.3 (s, C-4´), 141.2 (s, C-10a, C-11a), 143.7 (s, C-12a, C-13a), 155.8 (s, C-6), 157.9 (d_p, $^2J_{CP}$= 24.1 Hz; C-2), 159.6 (s, NH$\underline{C}$OOCH$_2$CHC$_{12}$H$_8$), 168.3 (s, NH$\underline{C}$O), 195.2 (d_p, $^2J_{CP}$= 7.1 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 13.60 (s). IR (KBr): ν= 3350 cm^{-1} (*m*), 3251 (*w*), 3061 (*w*), 3020 (*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): λ_{max} (log ε)= 266 (4.51), 292 (4.30, *sh*), 300 (4.41), 318 (4.41), 338 (4.28, *sh*). $[\alpha]_D^{20}$= –27.5° (c= 0.05, DMF). Anal. Calcd for $C_{37}H_{38}N_3O_7PS$: 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.

2-(Fluorenyl-9-methoxycarbonyl-β-glycyl)amino-5-cyano-6-*p*-tolyl-4-thioxo-4*H*-pyran-3-yl-phosphonic acid diisopropyl ester (**16.4c**)

- 150 mg (43%) of **16.4c** were obtained as light red crystals after chromatography separation, mp 87 °C (ethyl acetate / *n*-hexane (1:1)). ^{1}H-NMR (360 MHz, $CDCl_3$): δ= 1.33, 1.36 (2*d_p, $^3J_{HH}$= 6.2 Hz; 12H, OCH($C\underline{H}_3$)$_2$), 2.45 (s, 3H, $C_6H_4C\underline{H}_3$), 2.76 (t, $^3J_{HH}$= 4.8 Hz; 2H, $NHCH_2C\underline{H}_2CONH$), 3.56 (t, $^3J_{HH}$= 4.7 Hz; 2H, $NHC\underline{H}_2CH_2CONH$), 4.16 (t, $^3J_{HH}$= 4.2 Hz; 1H, $NHCOOCH_2C\underline{H}C_{12}H_8$), 4.35-4.38 (d, $^3J_{HH}$= 3.9 Hz; 2H, $NHCOOC\underline{H}_2CHC_{12}H_8$), 4.68-4.79 ($d_p$sept, $^3J_{HP}$= 7.2 Hz, $^3J_{HH}$= 6.4 Hz; 2H, OC$\underline{H}$(CH_3)$_2$), 5.29 (t, $^3J_{HH}$= 3.8 Hz; 1H, $N\underline{H}COOCH_2CHC_{12}H_8$), 7.27-7.90 (m, 8H, Aromatic-H; 2*d, 2*$^3J_{HH}$= 8.1 Hz; 4H, 2´-H, 3´-H, 5´-H, 6´-H), 12.98 (s, 1H, NH). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= 21.7 (s, $C_6H_4\underline{C}H_3$), [23.7 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz); OCH($\underline{C}H_3$)$_2$)], 36.1 (s, $NHCH_2\underline{C}H_2CONH$), 38.6 (s, $NH\underline{C}H_2CH_2CONH$), 47.2 (s, C-9a), 67.1 (s, $NHCOO\underline{C}H_2CHC_{12}H_8$), 74.2 ($d_p$d, $^2J_{CP}$= 7.2 Hz; O$\underline{C}$H(CH_3)$_2$), 104.5 (d_p, $^1J_{CP}$= 198 Hz; C-3), 110.1 (d_p, $^3J_{CP}$= 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 (d_p, $^2J_{CP}$= 24.8 Hz; C-2), 158.3 (s, $NH\underline{C}OOCH_2CHC_{12}H_8$), 168.8 (s, NH$\underline{C}$O), 194.8 ($d_p$, $^2J_{CP}$= 7.5 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 13.78 (s). IR (KBr): ν= 3421 cm^{-1} (*m*), 3365 (*w*), 3066 (*w*), 2975 (*w*), 2933 (*w*), 2233 (*w*), 1718 (*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): λ_{max} (log ε)= 266 (4.44), 290 (4.21, *sh*), 304 (4.40), 320 (4.48), 348 (4.15, sh). Anal. Calcd for $C_{37}H_{38}N_3O_7PS$: 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-4*H*-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)). ^{1}H-NMR (360 MHz, $CDCl_3$): δ= 1.33, 1.36 (2*d_p, $^3J_{HH}$= 6.2 Hz; 12H, OCH($C\underline{H}_3$)$_2$), 2.77 (t, $^3J_{HH}$= 4.8 Hz; 2H, $NHCH_2C\underline{H}_2CONH$), 3.56 (t, $^3J_{HH}$= 4.7 Hz; 2H, $NHC\underline{H}_2CH_2CONH$), 4.17 (t, $^3J_{HH}$= 4.2 Hz; 1H, $NHCOOCH_2C\underline{H}C_{12}H_8$), 4.70-4.78 ($d_p$sept, $^3J_{HP}$= 7.2 Hz, $^3J_{HH}$= 6.2 Hz; 2H, OC$\underline{H}$(CH_3)$_2$), 5.30 (t, $^3J_{HH}$= 3.8 Hz; 1H, $N\underline{H}COOCH_2CHC_{12}H_8$), 7.26-7.88 (m, 8H, Aromatic-H); 2*d, 2*$^3J_{HH}$= 8.4 Hz; 4H, 2´-H, 3´-H, 5´-H, 6´-H), 12.96 (s, 1H, NH). ^{13}C-NMR (90.56 MHz, $CDCl_3$): δ= [23.7 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz); OCH($\underline{C}H_3$)$_2$)], 36.1 (s, $NHCH_2\underline{C}H_2CONH$), 38.6 (s, $NH\underline{C}H_2CH_2CONH$), 47.2 (s, C-9a), 67.1 ($NHCOO\underline{C}H_2CHC_{12}H_8$), 74.1 ($d_p$d, $^2J_{CP}$= 7.1 Hz; O$\underline{C}$H(CH_3)$_2$), 104.3 (d_p, $^1J_{CP}$= 196 Hz; C-3),

110.0 (d_p, $^3J_{CP}$= 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_p, $^2J_{CP}$= 24.2 Hz; C-2), 158.2 (s, NHCOOCH$_2$CHC$_{12}$H$_8$), 168.9 (s, NHCO), 194.6 (d_p, $^2J_{CP}$= 6.4 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 13.81 (s). IR (KBr): ν= 3310 cm^{-1} (*m*), 3285 (*w*), 3066 (*w*), 2979 (*w*), 2933 (*w*), 2233 (*w*), 1717 (*s*), 1700 (*s*), 1653 (*m*), 1610 (*s*), 1587 (*m*), 1559 (*m*), 1521 (*w*), 1490 (*w*), 1386 (*m*), 1224 (*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): λ_{max} (log ε)= 266 (4.50), 290 (4.24, *sh*), 302 (4.37), 318 (4.46), 346 (4.20, *sh*). Anal. Calcd for $C_{36}H_{35}N_3O_7BrPS$: 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_2Cl_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_2Cl_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-thi-oxo-4*H*-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-NMR (360 MHz, $CDCl_3$): δ= 1.29 (d_pt, $^3J_{HH}$= 7.1 Hz; 6H, OCH$_2$CH$_3$), 3.75, 4.07 (2*s, 2H, NHCOCH$_2$), 4.31 (t, $^3J_{HH}$= 7.1 Hz; 1H, NHCOOCH$_2$CHC$_{12}$H$_8$), 4.55 (d, $^3J_{HH}$= 4.6 Hz; 2H, NHCOOCH$_2$CHC$_{12}$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, $^3J_{HH}$= 8.1 Hz, 2H, 3´-H, 5´-H), 8.43-8.45 (d, $^3J_{HH}$= 8.1 Hz; 2H, 2´-H, 6´-H), 12.82, 13.11 (2*s, 1H, NH). ^{13}C-NMR (90.56

MHz, $CDCl_3$): δ= 16.1 (d_pt, $^3J_{CP}$= 7.1 Hz; $OCH_2\underline{C}H_3$), 47.1 (s, C-9a), 50.9 (s, $NHCO\underline{C}H_2N$), 51.8, 51.9 (2*s, $N\underline{C}H_2C_6H_5$), 64.3 (d_pd, $^2J_{CP}$= 6.2 Hz; $O\underline{C}H_2CH_3$), 67.7, 68.4 (2*s, $NOCOO\underline{C}H_2CHC_{12}H_8$), 103.5 ($d_p$, $^1J_{CP}$= 194 Hz; C-3), 109.6 (d_p, $^3J_{CP}$= 10.5 Hz; C-5), 114.4 (s, CN), 116.7 (d, $^3J_{CF}$= 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, $^4J_{CF}$= 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-6), 157.3 (d_p, $^2J_{CP}$= 22.9 Hz; C-2), 157.5, 157.8 (2*s, $NO\underline{C}OOCH_2CHC_{12}H_8$), 158.5 (s, C-4´), 166.5, 166.8 (2*s, $NH\underline{C}O$), 194.9 (d_p, $^2J_{CP}$= 7.2 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): δ= 15.38 (s). IR (KBr): ν= 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*). FAB-MS: m/z (%): 768 (M^+, 10), 409 (56), 383 (64), 381 (44), 291 (18), 289 (40), 228 (30), 226 (24), 179 (100), 178 (38), 123 (20), 91 (50), 77 (24), 51 (20). UV (MeCN): λ_{max} (log ε)= 266 (4.48), 292 (4.18), 302 (4.30), 316 (4.23), 342 (4.17, *sh*). Anal. Calcd for $C_{40}H_{35}N_3O_8FPS$: 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-(Fluorenyl-9-methoxycarbonyloxy-*N*-benzylglycyl)amino-5-cyano-6-(4´-chlorophenyl)-4-thioxo-4*H*-pyran-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 (ethyl acetate / *n*-hexane (2:1)). ^{1}H-MR (250.13 MHz, $CDCl_3$): δ= 1.26, 1.31 (2*d_p, $^3J_{HH}$= 7.8 Hz; 12H, $OCH(C\underline{H}_3)_2$), 3.76, 4.08 (2*s, 2H, $NHCOC\underline{H}_2N$), 4.31 (t, $^3J_{HH}$= 7.1 Hz; 1H, $NHCOOCH_2C\underline{H}C_{12}H_8$), 4.54 (t, $^3J_{HH}$= 4.6 Hz; 2H, $NHCOOC\underline{H}_2CHC_{12}H_8$), 4.59, 4.62 (2*d, 2H, $N\underline{C}H_2C_6H_5$), 4.64-4.70 ($d_p$sept, $^3J_{HP}$= 7.4 Hz, $^3J_{HH}$= 6.2 Hz; 2H, $OC\underline{H}(CH_3)_2$), 7.14-7.68 (m, 13H, 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, $CDCl_3$): δ= [23.7 (d_pq, $^3J_{CP}$= 5 Hz), 23.9 (d_pq, $^3J_{CP}$= 4 Hz; $OCH(\underline{C}H_3)_2$)], 47.2 (s, C–9a), 50.8 (s, $NHCOC\underline{H}_2N$), 51.7, 51.9 (2*s, $N\underline{C}H_2C_6H_5$), 67.7, 68.3 (2*s, $NHCOOCH_2\underline{C}HC_{12}H_8$), 73.9 ($d_p$d, $^2J_{CP}$= 6.2 Hz; $O\underline{C}H(CH_3)_2$), 104.3 (d_p, $^1J_{CP}$= 194 Hz; C-3), 110.0 (d_p, $^3J_{CP}$= 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´´), 127.1 (s, C-2a, C-7a), 127.9 (s, C-3a, C-6a), 128.2, 128.8, 129.6, 129.7 (4*d, C-2´, C-3´, C-5´, C-6´, C-8´´, C-9´´, C-11´´, C-12´´), 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_p, $^2J_{CP}$= 22.8 Hz; C–2), 157.2, 157.4 (2*s, NOCOOOCH$_2$CHC$_{12}$H$_8$), 166.4, 166.8 (2*s, NHCOCH$_2$N), 194.6 (d_p, $^2J_{CP}$= 7.2 Hz; CS). ^{31}P-NMR (145.79 MHz, $CDCl_3$): 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): λ_{max} (log ε)= 266 (4.52), 290 (4.20), 302 (4.34), 318 (4.37), 344 (4.26, *sh*). Anal. Calcd for $C_{42}H_{39}N_3O_8ClPS$: 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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