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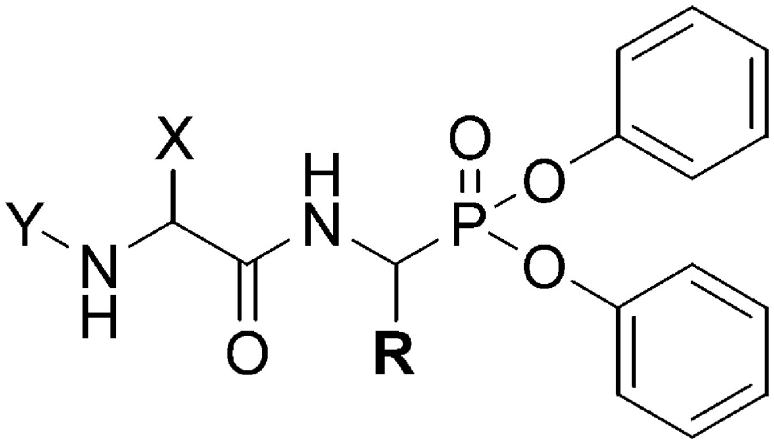

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Rapid Parallel Synthesis of Dipeptide Diphenyl Phosphonate Esters as Inhibitors of Dipeptidyl Peptidases

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In this paper, we present a parallel synthesis of several series of dipeptide diphenyl phosphonates that are known to be irreversible inhibitors of serine proteases. Polymer-assisted solution-phase synthesis (PASP) is used for the rapid and clean coupling between various α-aminoalkyl diphenyl phosphonate ester building blocks and commercially available or easily accessible amino acids. These compounds were used for the rapid profiling of dipeptidyl peptidase II (DPP II) and the closely related dipeptidyl peptidase IV (DPP IV). A highly selective DPP II inhibitor was identified, *N*-cyclopentylglycyl-NHCH(C_6H_5)PO($OPh)_2$ (**9.35**), that will be useful to discriminate between DPP II and DPP IV in biological systems in order to further elucidate the biological function of DPP II.

Introduction

Serine proteases are a well-known group of enzymes that are involved in a variety of physiological and pathological processes. Development of specific inhibitors of this class of enzymes is a valuable tool for understanding the contribution of individual enzymes to homeostasis and pathophysiology and for the rational design of therapeutic drugs. A variety of phophorus-containing compounds have been reported to be inhibitors of proteases with a serine-type mechanism. Diisopropyl phosphofluoridate (DFP) belongs to the class of fluorophosphates and is still one of the most widely used broad-spectrum inhibitors of these enzymes;[1] however, it has an extreme toxicity and low stability and is unable to discriminate between different subclasses of serine proteases in biological studies.

An important progress to enhance the selectivity was the development of peptidyl phosphonates in which the scissile peptide bond of a peptide substrate is replaced by a diphenyl phosphonate residue. A variety of peptidyl diphenylphosphonate esters based on sequences of known substrates for various serine proteases were reported to be excellent irreversible inhibitors. The proposed mechanism of inhibition involves a nucleophilic substitution at the phosphorus atom by the active-site serine to form a phosphonylated enzyme through a pentavalent intermediate[2] and is accompanied by the loss of one phenoxy group (Figure 1). The resulting enzyme−inhibitor complex may undergo slow aging to form a serine phosphonomonoester upon loss of the second phenoxy group.[3] The irreversible character of these types of inhibitors and their discriminatory capabilities make them useful in establishing the biological function of a specific serine protease.

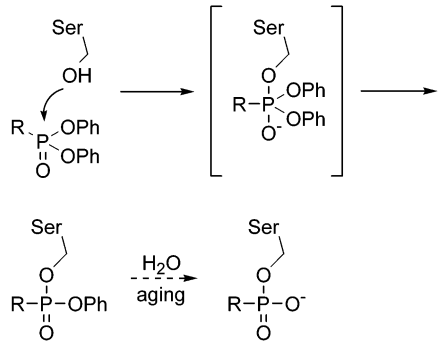

Figure 1. Proposed mechanism for the inhibition of serine proteases by diphenyl phosphonates.

Oleksyszyn and Powers prepared a series of α-aminoalkyl diphenyl phosphonate ester analogues of aromatic (Phe) and aliphatic (Val, Leu, Nva, Met) amino acids as inhibitors of elastases and various chymotrypsin enzymes.[2,4] Diphenyl phosphonate esters of basic amino acids, such as lysine, homolysine, ornithine, and arginine, have been incorporated into peptide sequences selective for trypsine-like serine proteases, including thrombine.[5,6] Oleksyszyn et al. described a series of diphenyl phosphonate esters containing 4-amidinophenyl groups at the P_1 site as irreversible inhibitors of thrombin[7] and related enzymes, including granzyme A and K.[8] In addition, acidic amino acid (Asp, Glu) analogues have been reported as inhibitors of *Staphylococcus aureus V8* protease and granzyme B.[9]

We are particularly interested in dipeptidyl peptidases from the serine protease family. A series of dipeptides that contained phosphonate analogues of proline and homoproline have been described to irreversibly inhibit dipeptidyl peptidase IV (DPP IV).[10−13]Although the rates of inhibition of DPP IV by these compounds were moderate, the inhibitors were shown to be quite specific for DPP IV and gave no

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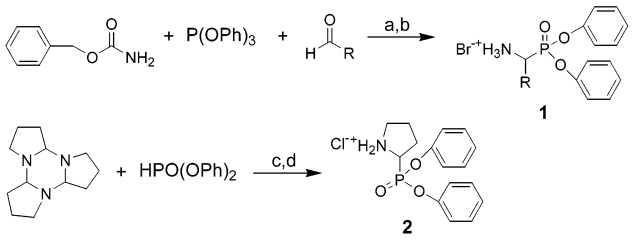
Scheme 1. Synthesis of α-Aminoalkylphosphonate (1) and 2-Pyrrolidylphosphonate (2) Building Blocks[a]



[a] Reagents: (a) AcOH, 2h, 80 °C; (b) HBr/AcOH, 3 h, rt; (c) 85 °C under N_2, 2h; (d) HCl gas/Et_2O. (R: see Table 1).

inhibition of trypsine; elastases, such as human leukocyte elastase (HLE) and porcine pancreatic elastase (PPE); acetylcholinesterase; papain; and cathepsin B. Some compounds slowly inhibited chymotrypsin.

Dipeptidyl peptidase II (DPP II), recently reported to be identical to quiescent cell proline dipeptidase (QPP),[14,15] is a very closely related enzyme. To further investigate the DPP II function, it is necessary to develop highly specific and potent inhibitors that are able to differentiate between DPP II and DPP IV in biological systems. To date, no specific and potent phosphorus-based inhibitor has been reported.

A parallel synthesis of dipeptide diphenyl phosphonates would be a valuable tool for the rapid profiling of serine proteases, in particular, dipeptidyl peptidases. In this paper, we present a polymer-assisted solution-phase synthesis (PASP) for the rapid and clean coupling between various α-aminoalkyl diphenyl phosphonate ester building blocks and commercially available or easily accessible amino acids. All compounds were biochemically evaluated for their DPP II and DPP IV inhibitory activity.

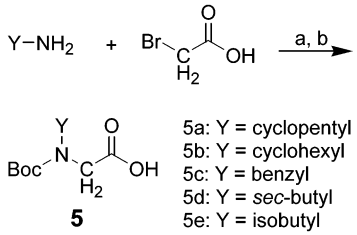
Results and Discussion

Synthesis. About 50 dipeptide diphenyl phosphonates were synthesized using a polymer-assisted solution phase protocol[16] by coupling diphenyl α-aminoalkyl phosphonates (**1** and **2**) with amino acids (**4** and **5**). Building blocks **1** were obtained as a mixture of enantiomers using an amidoalkylation reaction, starting from triphenyl phosphite, benzylcarbamate, and the corresponding aldehyde, as described by Oleksyszyn et al.[17] Diphenyl pyrrolidine-2-phosphonate hydrochloride (**2**) cannot be obtained using the previous synthesis and was prepared from 1-pyrroline trimer and diphenyl phosphite to yield the phosphonate building block **2** in an enantiomeric mixture (Scheme 1).[11,18]

The N-terminal building blocks (**4**) are commercially available *N-tert*-butyloxycarbonyl (Boc)-protected amino acids with acid-labile side chain protection. To increase the diversity, a set of Boc-protected N-substituted glycines **(5)** were prepared by reaction of bromoacetic acid and an amine, followed by Boc-protection of the α-amino function (Scheme 2).[19]

Building blocks (**4**) or (**5**) reacted with hydroxybenzotriazole (HOBt) and a polymer-bound carbodiimide to afford the activated esters (**6**) (Scheme 3). A limiting amount of building blocks (**1**) or (**2**) was then added, and after reaction overnight, addition of polymer-bound polyamine captured the excess of activated ester (**6**) and HOBt. Filtration and

Scheme 2. Synthesis of *N*-Substituted Glycines[a]



[a] Reagents: (a) Et_2O, overnight, rt; (b) Boc_2O, TEA, dioxane, H_2O, 5 h, rt.

Table 1. Synthesized Dipeptide Diphenyl Phosphonate Analogues of Proline

8 or **10**	Y	Xaa[a]	purity[b] **(8)** %	purity[c] **(10)** %	yield[d] **(10)** %
.1	H	Ala	58	96	36
.2	H	Asn	87	99	59
.3	H	Asp	66	98	48
.4	H	Gly	64	94	61
.5	H	His	31	100[e]	7[e]
.6	H	Lys	66	100[e]	51[e]
.7	H	Phe	83	95	58
.8	H	Ser	68	84	60
.9	H	ThiaPro	75	95	41
.10	H	Val	69	90	41

[a] Side chain protection for the synthesis of **8** is as follows: Asn(Trt), Asp(O*t*Bu), His(Boc), Lys(Boc), Ser(*t*Bu). [b] The HPLC purity of **8** at 214 nm before purification by preparative TLC. [c] The HPLC purity of **10** at 214 nm. [d] This is the total yield of both coupling and deprotection; in some cases,[e] after purification by preparative reversed-phase HPLC. [e] These compounds were purified by preparative reversed-phase HPLC after deprotection.

evaporation afforded the protected dipeptide diphenyl α-aminoalkyl phosphonates (**7**) and dipeptide diphenyl proline phosphonates (**8**). Purity of crude **7** and **8** (Tables 1 and 2) ranged from 50 to 98% at 214 nm and was usually above 80%. Impurities were mostly due to the presence of unscavenged HOBt and phenol that can be explained by the low stability of the phosphonates. Only BocHis(Boc)OH as N-terminal building block and diphenyl phosphonate building blocks carrying cyano-substituted phenyl side chains gave lower purities. An intermediate purification of the protected dipeptides by preparative TLC was carried out in order to ensure the 90−95% purity needed for biological evaluation of the final compounds. Deprotection using 50% trifluoroacetic acid (TFA) in dichloromethane yielded the target compounds **9** and **10** in good purity. Only a few compounds needed a final purification after deprotection by preparative HPLC (Tables 1 and 2).

Biochemical Evaluation. Initially, dipeptide diphenyl phosphonates analogues of proline and alanine were evaluated because of the reported substrate specificity of DPP II and DPP IV for peptides containing proline or alanine at the penultimate position.

Dipeptide Phosphonate Analogues of Proline (10, Table 3). These compounds have a DPP IV inhibitory activity as expected,[10] comparable to previous results.[20] However, these compounds are not very promising as DPP II inhibitors: Gly-Pro^P(OPh)$_2$ (**10.4**) and His-Pro^P(OP)$_2$ (**10.5**) are the most active DPP II inhibitors, but with low selectivity with respect to DPP IV.

Table 2. Synthesized Dipeptide α-Aminoalkyl Diphenyl Phosphonates

7 or **9**	Y	R	Xaa[a]	purity[b] **(7)** %	purity[c] **(9)** %	yield[d] **(9)** %
.1	H	CH_3	Ala	76	91	51
.2			Asn	80	77	23
.3			Asp	53	91	32
.4			Cha[e]			
.5			Ach[f]	89	99	82
.6			Acp[g]	76	100	66
.7			Gly	78	94	60
.8			His	30	100[h]	27[h]
.9			Ile	85	97	21
.10			Leu	80	99	77
.11			Lys[i]			
.12			Phe	89	97	13
.13			Pro	90	95	55
.14			Ser	56	83	18
.15			Tyr	90	95	65
.16			Val	94	95	13
.17	H	CH_2CH_3	Cha	91	100	58
.18			Ile	97	98	59
.19	H	$CH_2CH_2CH_3$	Cha	98	85	52
.20			Ile	93	100	6
.21			Lys	97	90	56
.22	H	$CH(CH_3)_2$	Ile	83	85	39
.23	H	$CH(CH_3)CH_2CH_3$	Ile	84	100	36
.24	H	$CH_2CH(CH_3)_2$	Ile	77	94	59
.25	H	$CH(CH_2CH_3)_2$	Ile	87	89	60
.26	H	C_6H_{11}	Cha	98	100	73
.27			Dab	72	95	54
.28			His	72	99	58
.29			Ile	92	90	35
.30		C_6H_5	Ile	92	99	51
.31	H	$CH_2C_5H_6$	Ile	69	100	42
.32	H	C_6H_4(4-CN)	Ile	48	96	28
.33	H	C_6H_4(3-CN)	Ile	43	74	14
.34	C_5H_9	C_6H_{11}	Gly	96	96	51
.35		C_6H_5	Gly	93	98	55
.36	C_6H_{11}	C_6H_{11}	Gly	97	99	54
.37	$CH_2C_5H_6$	C_6H_{11}	Gly	92	98	63
.38	$CH(CH_3)CH_2CH_3$	C_6H_{11}	Gly	97	98	57
.39	$CH_2CH(CH_3)_2$	C_6H_{11}	Gly	96	97	53

[a] Side chain protection for the synthesis of **7** was as follows: Asn(Trt), Asp(O*t*Bu), His(Boc), Lys(Boc), Ser(*t*Bu), Tyr(*t*Bu). [b] HPLC purity of **7** at 214 nm before purification by preparative TLC. [c] HPLC purity of **9** at 214 nm; in one case,[h] after purifacation by preparative reversed-phase HPLC. [d] Total yield of both coupling and deprotection. [e] Cyclohexylalanine. This compound was not synthesized using the PASP protocol. [f] 1-Amino-1-cyclohexanecarboxylic acid. [g] 1-Amino-1-cyclopentanecarboxylic acid. [h] This compound was purified by preparative reversed-phase HPLC after final deprotection. [i] This compound was not synthesized using the PASP protocol.

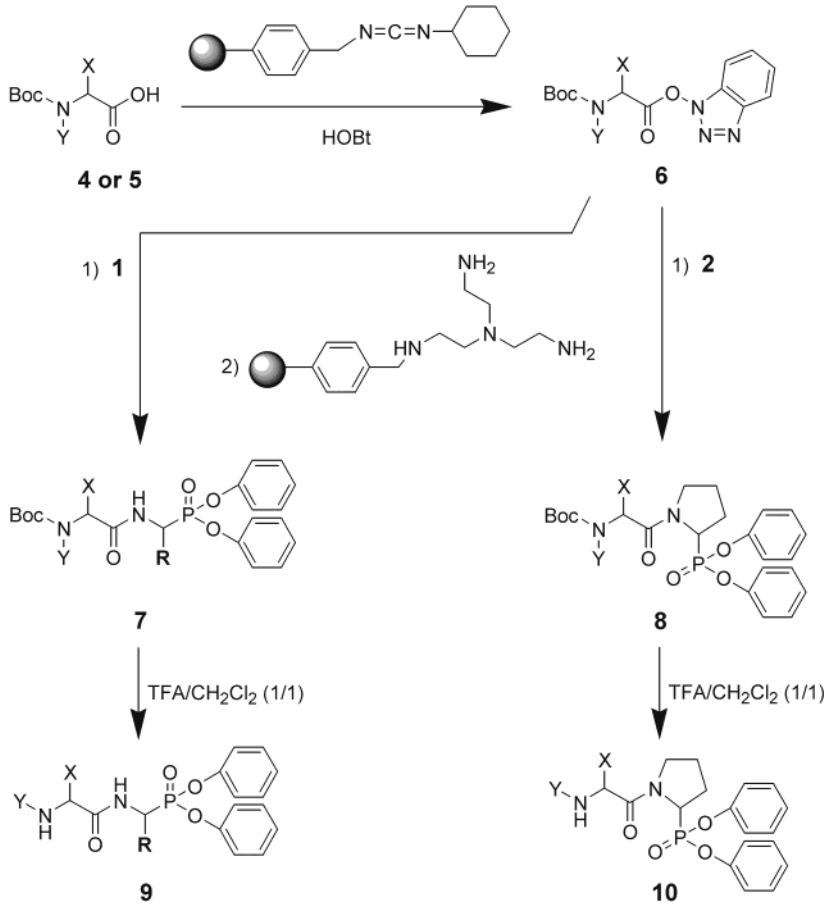
Dipeptide Phosphonate Analogues of Alanine (9.1−9.16, Table 4, Figure 2). These compounds afforded only minimal inhibition of DPP II as well as of DPP IV. Data obtained for DPP IV inhibition were comparable to previous results.[20] Only Cha-Ala^P$(OPh)_2$ (**9.4**) and Ile-Ala^P$(OPh)_2$ (**9.9**) exhibited a moderate IC_{50} value for DPP II, respectively 47 and 116 μM, combined with a promising selectivity with respect to DPP IV (Figure 2). Therefore, Cha and Ile were retained for further investigation with other diphenyl α-aminoalkyl phosphonates.

Variation of the Diphenyl α-aminoethyl Phosphonate Side Chain (Table 4, Figure 2). Elongation or branching of the diphenyl α-aminoalkyl phosphonate side chain (**9.17−9.25**) in general did not improve the DPP II inhibition. However, Cha-$NHCH(CH_2CH_3)PO(OPh)_2$ (**9.17**) with an ethyl side chain had an IC_{50} value in the same range as compound **9.4** bearing a methyl side chain (Figure 2). Further elongation did not favor the DPP II inhibition.

Interestingly however, introduction of a cyclohexyl side chain in the phosphonate building block increased DPP II inhibition. This increase, however, was observed only with Cha (**9.26**) and not with Ile (**9.29**) as N-terminal building block (Figure 2). Compound Cha-$NHCH(C_6H_{11})PO(OPh)_2$ (**9.26**) exhibited an IC_{50} value of 30 μM and gave practically no DPP IV inhibition. In addition, aromatic side chains were introduced (**9.30−9.33**): Ile-$NHCH(C_6H_5)PO(OPh)_2$ (**9.30**) containing a phenyl side chain was 8 times more active than **9.29** with a cyclohexyl side chain and had an IC_{50} value of 18 μM for DPP II; however, introduction of benzyl- (**9.31**) or cyano-substituted phenyl side chains (**9.32**, **9.33**) decreased activity.

N-Terminal Building Block Variation (Table 4, Figure 2). Recently, our laboratory identified 2,4-diaminobutyric acid (Dab) and histidine (His) as very interesting N-terminal building blocks in a series of dipeptide piperidides leading to highly active and selective, reversible DPP II-inhibitors.[21] Therefore, the potential of these amino acids as N-terminal building blocks in the series of diphenyl phosphonates was studied. Both were combined with a cyclohexyl side chain containing phosphonate, leading to compounds **9.27** and **9.28**

Scheme 3. Parallel Synthesis of Dipeptide Diphenyl α-Aminoalkylphosphonates (9) and Diphenyl Phosphonate Analogues of Proline (10) Using Polymer-Bound Reagents[a]



[a] X represents the side chain of the amino acid Xaa in Tables 1 and 2.

Table 3. Inhibitory Activities and Selectivity Index for Diphenyl Phosphonate Analogues of Proline (**10**)[a]

	IC_{50} (μM)		
10	DPP IV inhibition	DPP II inhibition	SI[b]
.1	>1000	>1000	1
.2	*c*	>125	
.3	>1000	no inhibition	
.4	16 ± 1.6	79 ± 48	0.2
.5	326 ± 40	60 ± 7.5	5.4
.6	117 ± 21	>1000	<0.12
.7	142 ± 16	>1000	<0.14
.8	503 ± 55	>1000	<0.5
.9	>1000	no inhibition	
.10	89 ± 6	no inhibition	

[a] In a standard assay, the highest concentration of test compound was 1000 μM. Because of solubility problems, the highest concentration measured was sometimes limited to 125 μM. In case of enzyme activity >50% in the presence of the highest concentration tested, the IC_{50} value is reported as >125. [b] SI = selectivity index = IC_{50} value for DPP IV divided by IC_{50} value for DPP II. [c] No data due to solubility problems.

(Figure 2). Results of biochemical evaluation again show the interesting characteristics of Dab (IC_{50} value of **9.27** = 21 μM) as N-terminal building block; His (**9.28**), however, gave only moderate DPP II inhibition.

A series of N-substituted glycine amino acids (**5**) were synthesized containing hydrophobic side chains (cyclopentyl, cyclohexyl, benzyl, ...) to mimic cyclohexylalanine. Compound **9.34** with *N*-cyclopentylglycine gave an almost 4-fold increase of the DPP II inhibition (IC_{50} value = 8 μM) compared to Cha-NHCH(C_6H_{11})PO($OPh)_2$ (**9.26**) (Figure 2). *N*-Cyclohexylglycine (**9.36**) and other N-substituted glycines (**9.37** to **9.39**) were less active as N-terminal building blocks.

Finally, combination of *N*-cyclopentylglycine and a phosphonate building block containing the phenyl side chain yielded the most active compound (**9.35**) synthesized, with an IC_{50} value for DPP II of 3.8 μM and with high selectivity with respect to DPP IV (SI much higher than 33). After initial screening of a series of potential inhibitors, followed by an extensive investigation of the structure−activity relationship, we were able to identify *N*-cyclopentylglycyl-NHCH(C_6H_5)-$PO(OPh)_2$ (**9.35**) as a potent and selective DPP II inhibitor in a limited time period.

Conclusions

With parallel synthesis, we were able to investigate in a short time the structure−activity of these dipeptide diphenyl phosphonates as inhibitors of DPP II. In a three-step synthesis, we prepared a large number of potential DPP II inhibitors without difficult purification steps. The importance of both the N-terminal and diphenyl α-aminoalkyl phosphonate building blocks could be evaluated. Cyclohexylalanine (Cha) and, more importantly, *N*-cyclopentylglycine were selected as the most promising N-terminal building blocks with respect to DPP II inhibition and selectivity. In evaluating the phosphonate building blocks, the phenyl side chain was

Table 4. Inhibitory Activities and Selectivity Index for the α-aminoalkyl Diphenyl Phosphonates Compounds (**9**)[a]

	IC_{50} (μM)				IC_{50} (μM)		
9	DPP IV inhibition	DPP II inhibition	SI[ab]	**9**	DPP IV inhibition	DPP II inhibition	SI[b]
.1	>500	<1000	>0.1	.21	>1000	>1000	1
.2	*c*	286 ± 27		.22	>1000	±1000	>5
.3	>500	no inhibition		.23	>1000	414	>12.1
.4	>500	47 ± 8	>10.6	.24	>1000	286	>17.5
.5	>1000	>1000	1	.25	>1000	>1000	5
.6	>500	>500	1	.26	>250[d]	30 ± 2	>8.5
.7	>500	>1000	>0.5	.27	1000	21 ± 1	47.6
.8	>500[d]	>500	>1	.28	>1000[d]	241 ± 30	>4.2
.9	>500	116 ± 10	>4.3	.29	>1000	148	>34
.10	>1000	>500	2	.30	>250[d]	18 ± 1	>13.7
.11	>500	>1000	>0.5	.31	>125[d]	288 ± 28	>0.4
.12	>500	<1000	>0.5	.32	>250	150 ± 30	>1.7
.13	>500	<1000	>0.1	.33	>125[d]	509 ± 22	>0.3
.14	>500	>1000	>0.5	.34	>125[d]	8.0 ± 0.5	>17
.15	>500	>500	1	.35	>125[d]	3.8 ± 0.1	>33.2
.16	>500	<1000	>0.5	.36	>125[d]	67 ± 10	>1.9
.17	>1000	62 ± 12	>16.1	.37	>125	43 ± 7	>2.9
.18	>1000	±1000	>5	.38	>1000	109 ± 7	>9.2
.19	>250[d]	500 ± 100	>0.5	.39	>125[d]	158 ± 18	>0.8
.20	>1000	±1000	>5				

[a] In a standard assay, the highest concentration of test compound was 1000 μM. Because of solubility problems, the highest concentration measured was sometimes limited to 125, 250, or 500 μM. In the case of enzyme activity >50% in the presence of the highest concentration tested, the IC_{50} value is reported as >125, >250, or >500 μM, respectively. [b] SI = selectivity index = IC_{50} value for DPP IV divided by IC_{50} value for DPP II. [c] No data due to solubility problems. [d] Enzyme activity at the highest concentration was more than 80%.

discovered to give interesting results. *N*-Cyclopentylglycyl-$NHCO(C_6H_5)PO(OPh)_2$ (**9.35**) will be used as an active and selective inhibitor in biological studies to further elucidate the DPP II function.

Experimental Section

Materials. Parallel synthesis was performed using the Quest 210 Organic Synthesizer (Argonaut Technologies). Boc-protected amino acids, *N*-cyclohexycarbodiimide, *N*′-methylpolystyrene resin (PS-carbodiimide) and tris-(2-aminoethyl)-amine polystyrene resin were purchased from Novabiochem. Other reagents were obtained from Sigma-Aldrich or Acros.

Analysis. Characterization of all compounds was done with ^{1}H NMR, mass spectrometry, and analytical reversed-phase HPLC. ^{1}H NMR results were recorded on a Bruker Avance DRX-400 spectrometer (400 MHz). Fast atom bombardment (FAB^+) mass spectra were obtained on a VG 70-SEQ hybrid mass spectrometer (Micromass, Manchester, U.K.), equipped with a cesium ion gun. Electrospray (ES^+) mass spectra were acquired on a Autospec-ao-TOF mass spectrometer (Micromass, Manchester, U.K.) or a tripple quadrople mass spectrometer (Quattro II, Micromass, Manchester, U.K.) or a Bruker Esquire 3000 plus. Analytical HPLC was run on a Gilson instrument (Viliers-le-bel, France) equipped with an Ultrasphere ODS column (4.6 × 250 mm, 5 μm, Beckman, Fullerton, CA). Preparative TLC was performed on Silicagel $60PF_{254}$ containing gypsum.

Biochemical Evaluation. DPP IV was purified from human seminal plasma as described previously.[22] DPP II was isolated from the same source using techniques described previously for purification of the enzyme from porcine seminal plasma,[23] supplemented with adenosine deaminase affinity chromatography to eliminate contaminating DPP IV.[22] Enzyme activity was measured kinetically with the chromogenic substrates Gly-Pro-*p*-nitroanilide at pH 8.3 and Lys-Ala-*p*-nitroanilide at pH 5.5 for DPP IV and DPP II, respectively. Test compounds were dissolved and diluted in DMSO (final concentration DMSO during assay, 5% v/v). The highest concentration of compounds tested was 1 mM. IC_{50} value was defined as the inhibitor concentration that caused a 50% decrease of the activity under assay conditions.

Synthesis. Diphenyl α-aminoalkyl phosphonate hydrobromide[17] (**1**) and diphenyl pyrrolidine-2-phosphonate hydrochloride[10] (**2**) were synthesized as described earlier.

Coupling of the Building Blocks Using Polymer-Assisted Solution-Phase Synthesis[16]. Protected amino acids (**4** or **5**) (0.375 mmol), HOBt (0.425 mmol), and PS−carbodiimide (0.75 mmol) were added to a dry reaction vessel. Dichloromethane (4 mL) was added, and the mixture was stirred for 10 min prior to the addition of the phosphonate building block (**1** or **2**) (0.25 mmol), dissolved in 1 mL of dichloromethane. Diphenyl α-aminoalkyl phosphonate hydrobromide (**1**) was prior to its use converted to the free-base form by basic extraction. Diphenyl pyrrolidine-2-phosphonate hydrochloride (**2**) was used as such: coupling was mediated by adding an equivalent amount of triethylamine to the reation mixture. After stirring at room temperature overnight, the polymer-bound polyamine (1.5 mmol) was added, and stirring was continued for 5 h. The reaction mixture was filtered, and the amide product (**7** or **8**) was collected in the filtrate. The resins are washed two times with 4 mL of dichloromethane, and the combined fractions were evaporated under reduced pressure. The purity of the compounds (**7** or **8**) was checked by TLC and reverse-phase HPLC. Compounds were purified by preparative TLC using a mixture of EtOAc and hexane (usually 40/60) as eluent. Deprotection was done by dissolving **7** or **8** in 4 mL of a TFA/dichloromethane (1:1) mixture. The solution was stirred for 3 h, and the volatile part was removed under

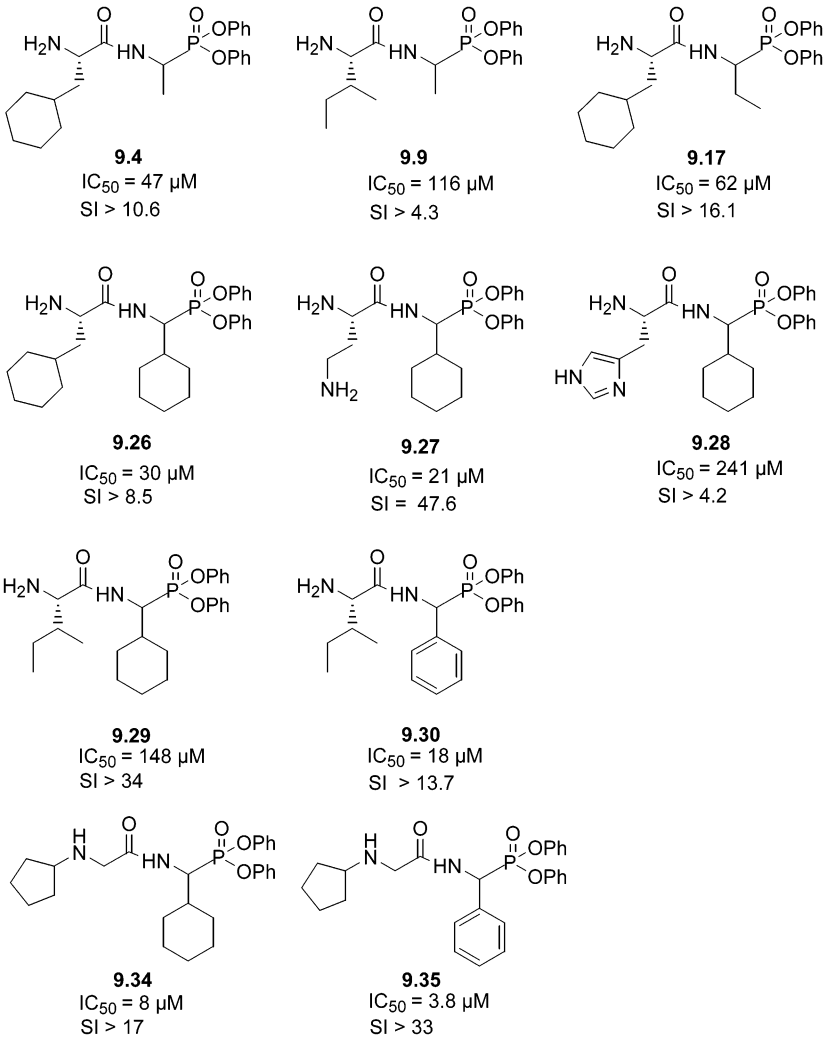


Figure 2. IC_{50} values for DPP II inhibition of the most potent inhibitors.

reduced pressure. After coevaporating several times with ether, the residues were lyophilised from *tert*-butyl alcohol/water (4:1) to yield compounds **9** or **10**. All compounds were evaluated and analyzed as a mixture of diastereomers of the diphenyl phosphonate esters.

Diphenyl1(*R,S*)-[(L-Alanyl)amino]ethylphosphonateTrifluoroacetate (9.1). ^{1}H NMR (D_2O, 400 MHz) δ 1.58 (d, J = 7.2 Hz, 1.5H, CH_3), 1.60 (d, J = 7.2 Hz, 1.5H, CH_3), 1.71, (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, 1.5H, CH_3) 1.72 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, 1.5H, CH_3), 4.14−4.23 (m, 1H, α-CH), 4.95−5.02 (m, 1H, α-CH), 7.18−7.24 (m, 4H, *o*-H_{arom}), 7.35−7.38 (m, 2H, *p*-H_{arom}), 7.45−7.56 (m, 4H, *m*-H_{arom}); MS (ES^+) *m/z* 349 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Asparaginyl)amino]ethylphosphonate Trifluoroacetate (9.2). ^{1}H NMR (D_2O, 400 MHz) δ 1.73 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, 3H, CH_3), 2.94−2.97 (m, 1H, CH_2), 3.06−3.16 (t, 1H, CH_2), 4.41 (t, 0.5H, α-CH), 4.47 (t, 0.5H, α-CH), 4.92−5.04 (m, 1H, α-CH), 7.17−7.28 (m, 4H, *o*-H_{arom}), 7.35−7.42(m, 2H, *p*-H_{arom}), 7.46−7.54 (m, 4H, *m*-H_{arom}(m, 1H, α-CH),); MS (ES^+) *m/z* 392 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Aspartyl)amino]ethylphosphonate Trifluoroacetate (9.3). ^{1}H NMR (D_2O, 400 MHz) δ 1.70 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.8 Hz, 1.5H, CH_3), 1.69 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.8 Hz, 1.5H, CH_3), 3.05 (d, 1H, CH_2), 3.13−3.19 (m, 1H, CH_2), 4.42 (t, 0.5H, α-CH), 4.48 (t, 0.5H, α-CH), 4.73−5.02 (m, 1H, α-CH), 7.14−7.25 (m, 4H, *o*-H_{arom}), 7.31−7.38 (m, 2H, *p*-H_{arom}), 7.43−7.58 (m, 4 H, *m*-H_{arom}); MS (ES^+) *m/z* 393 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(*S*-Cyclohexylalanyl)amino]ethylphosphonate Trifluoroacetate (9.4). ^{1}H NMR (D_2O, 400 MHz) δ 0.99−1.72 (m, 13H, CH_2, CH), 1.54 (dd, 3H, CH_3), 3.85 (t, 1H, α-CH), 4.74−4.83 (m, 1H, α-CH), 7.01−7.04 (m, 2H, H_{arom}), 7.11−7.16 (m, 4H, H_{arom}), 7.23−7.32 (m, 4H, H_{arom}); MS (ES^+) *m/z* 431 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(*S*-1-Amino-1-cyclohexylcarbonyl)-amino]ethylphosphonate Trifluoroacetate (9.5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30−1.61 (m, 9H, CH_3, CH_2), 1.69−2.99 (m, 4H, CH_2), 4.85−4.93 (m, 1H, α-CH), 7.07−7.20 (m, 6H, H_{arom}), 7.26−7.32 (m, 4H, H_{arom}); MS (ES^+) *m/z* 403 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(*S*-1-Amino-1-cyclopentylcarbonyl)-amino]ethylphosphonate Trifluoroacetate (9.6). ^{1}H NMR (D_2O, 400 MHz) δ 1.69 (dd, 3H, CH_3), 1.91−2.21 (m, 7H, CH_2), 2.32−21.37 (m, 1H, CH_2), 4.94−5.00 (m, H, α-CH), 7.13−7.19 (m, 4H, H_{arom}), 7.29−7.34 (m, 2H, H_{arom}), 7.40−7.46 (m, 4H, H_{arom}); MS (ES^+) *m/z* 389 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(Glycyl)amino]ethylphosphonate Trifluoroacetate (9.7). ^{1}H NMR (D_2O, 400 MHz) δ 1.69 (dd, 3H, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, CH_3), 3.82−4.00 (m, 2H,

CH_2), 4.94−5.01 (m, 1H, α-CH), 7.20 (d, 4H, *o*-H_{arom}), 7.33−7.37 (m, 2H, *p*-H_{arom}), 7.40−7.49 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 335 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Histidyl)amino]ethylphosphonate Trifluoroacetate (9.8). ^1H NMR (D_2O, 400 MHz) δ 1.51 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.8 Hz, 1.5 H, CH_3), 1.62 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.8 Hz, 1.5H, CH_3), 3.30−3.44 (m, 2H, CH_2), 4.29 (t, 0.5H, α-CH), 4.36 (t, 0.5H, α-CH), 7.00−7.16 (m, 5H, *o*-H_{arom}, 4-H_{arom}), 7.25−7.36 (m, 2H, *p*-H_{arom}), 7.37−7.47 (m, 4H, *m*-H_{arom}), 8.38 (s, 0.5H, 2-H_{arom}), 8.71 (s, 0.5H, 2-H_{arom}); MS (ES^+) *m*/*z* 415 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]ethylphosphonate Trifluoroacetate (9.9). ^1H NMR (D_2O, 400 MHz) δ 0.90 (t, *J* = 7.2 Hz, 1.5H, δ-CH_3), 1.00 (t, *J* = 7.2 Hz, 1.5H, δ-CH_3), 1.06 (d, *J* = 7.2 Hz, 1.5H, γ-CH_3), 1.12 (d, *J* = 7.2 Hz, 1.5H, γ-CH_3), 1.23−1.36 (m, 1H, CH_2), 1.53−1.65 (m, 1H, CH_2), 1.72 (dd, 3H, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, CH_3), 2.00−2.54 (m, 1H, β-CH), 3.96 (d, *J* = 5.8 Hz, 0.5H, α-CH), 4.03 (d, *J* = 4.9 Hz, 0.5H, α-CH), 4.79−5.05 (m, 1H, α-CH), 7.12−7.28 (m, 4H, H_{arom}), 7.30−7.40 (m, 2H, H_{arom}), 7.41−7.52 (m, 4H, H_{arom}); MS (ES^+) *m*/*z* 391 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Leucyl)amino]ethylphosphonate Trifluoroacetate (9.10). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.71−0.89 (m, 6H, CH_3), 1.44−1.62 (m, 6H, CH, CH_2, CH_3), 4.05−4.21 (m, 1H, α-CH), 4.70−4.81 (m, 1H, α-CH), 7.01−7.16 (m, 6H, H_{arom}), 7.25−7.27 (m, 4H, H_{arom}); MS (ES^+) *m*/*z* 391 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Lysyl)amino]ethylphosphonate Trifluoroacetate (9.11). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36−1.46 (m, 1H, CH_2), 1.49−1.62 (m, 2H, CH_2), 1.68 (dd, 3H, CH_3), 1.74−1.84 (1, 1H, CH_2), 1.99−2.08 (m, 1H, CH_2), 2.68 (t, 1H, ϵ-CH_2), 3.06 (t, 1H, ϵ-CH_2), 4.10−4.15 (m, 1H, α-CH), 4.84−5.00 (m, 1H, α-CH), 7.09−7.21 (m, 4H, *o*-H_{arom}), 7.24−7.33 (m, 2H, *m*-H_{arom}), 7.36−7.46 (m, 4H, *p*-H_{arom}); MS (ES^+) *m*/*z* 406 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Phenylalanyl)amino]ethylphosphonate Trifluoroacetate (9.12). ^1H NMR (D_2O, 400 MHz) δ 1.44 and 1.69 (dd, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, 3H, CH_3), 3.17−3.20 (m, 2H, CH_2), 4.30−4.42 (m, 1H, α-CH), 4.89−4.99 (m, 1H, α-CH), 7.10−7.23 (m, 5H, H_{arom}), 7.29−7.42 (m, 5H, H_{arom}), 7.45−7.54 (m, 5H, H_{arom}); MS (ES^+) *m*/*z* 425 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Prolyl)amino]ethylphosphonate Trifluoroacetate (9.13). ^1H NMR (D_2O, 400 MHz) δ 1.71 (dd, J_{HH} = 7.6 Hz, J_{PH} = 18.8 Hz, 3H, CH_3), 1.92−2.02 (m, 1H, β-CH_2), 2.05−2.19 (m, 2H, γ-CH_2), 2.44−2.57 (m, 1H, β-CH_2), 3.44−3.57 (m, 2H, δ-CH_2), 4.38 (t, 0.5H, α-CH), 4.50 (t, 0.5H, α-CH), 4.79−5.01 (m, 1H, α-CH), 7.17−7.25 (m, 4H, *o*-H_{arom}), 7.34−7.39 (m, 2H, *p*-H_{arom}), 7.45−7.51 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 375 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Seryl)amino]ethylphosphonate Trifluoroacetate (9.14). ^1H NMR (D_2O, 400 MHz) δ 1.72 + 1.73 (dd, 3H, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, CH_3), 3.87−4.12 (m, 2H, CH_2), 4.22−4.26 (m, 1H, α-CH), 4.97−5.02 (m, 1H, α-CH), 7.21−7.25 (m, 4H, *o*-H_{arom}), 7.36−7.40 (m, 2H, *p*-H_{arom}), 7.47−7.52 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 365 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Tyrosyl)amino]ethylphosphonate Trifluoroacetate (9.15). ^1H NMR (D_2O, 400 MHz) δ 1.41 (dd, J_{HH} = 7.6 Hz, J_{PH} = 18.4 Hz, 1.5H, CH_3), 1.65 (dd, J_{HH} = 7.6 Hz, J_{PH} = 18.4 Hz, 1.5H, CH_3), 3.13−3.18 (m, 1H, CH_2), 3.26−3.31 (m, 1H, CH_2), 4.24 (t, 0.5H, α-CH), 4.33 (t, 0.5H, α-CH), 4.90−4.95 (m, 1H, α-CH), 6.72 (d, 1H, 3,5-H_{arom}), 6.97 (d, 1H, 3,5-H_{arom}), 7.06 (d, 1H, 2,6-H_{arom}), 7.14−7.18 (m, 4H, *o*-H_{arom}), 7.24 (d, 1H, 2,6-H_{arom}), 7.33−7.39 (m, 2H, *p*-H_{arom}), 7.43−7.52 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 441 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Valyl)amino]ethylphosphonate Trifluoroacetate (9.16). ^1H NMR (D_2O, 400 MHz) δ 1.08−1.16 (m, 6H, CH_3), 1.73 + 1.74 (dd, 3H, J_{HH} = 7.2 Hz, J_{PH} = 18.4 Hz, CH_3), 2.25−2.40 (m, 1H, β-CH), 3.92 (d, *J* = 6 Hz, 0.5H, α-CH), 3.96 (d, *J* = 6 Hz, 0.5H, α-CH), 4.93−5.08 (m, 1H, α-CH), 7.15−7.27 (m, 4H, *o*-H_{arom}), 7.35−7.40 (m, 2H, *p*-H_{arom}), 7.44−7.53 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 377 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(*S*-Cyclohexylalanyl)amino]propylphosphonate Trifluoroacetate (9.17). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.68−1.15 (m, 8H, CH_3, CH_2), 1.27−1.74 (m, 8H, CH_2, CH), 1.81−1.98 (m, 1H, β-CH_2), 2.02−2.13 (m, 1H, β-CH_2), 4.20−4.32 (m, 1H, α-CH), 4.53−4.66 (m, 1H, α-CH), 7.05−7.33 (m, 10H, H_{arom}); MS (FAB^+) *m*/*z* 445 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]propylphosphonate Trifluoroacetate (9.18). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75−1.06 (m, 9H, CH_3), 1.11−1.57 (m, 2H, γ-CH_2), 1.81−2.15 (m, 3H, β-CH, β-CH_2), 4.15−4.24 (m, 1H, α-CH), 4.57−4.67 (m, 1H, α-CH), 7.05−7.33 (m, 10H, H_{arom}); MS (FAB^+) *m*/*z* 405 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(*S*-Cyclohexylalanyl)amino]butylphosphonate Trifluoroacetate (9.19). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.71−1.43 (m, 11H, CH_3, CH_2), 1.49−2.03 (m, 9H, β-CH_2, β-CH, CH_2), 4.18 (t, 0.5H, α-CH), 4.27 (t, 0.5H, α-CH), 4.68−4.79 (m, 1H, α-CH), 7.06−7.31 (m, 10H, H_{arom}); MS (FAB^+) *m*/*z* 459 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]butylphosphonate Trifluoroacetate (9.20).. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.70−0.96 (m, 9H, CH_3), 1.04−1.17 (m, 1H, CH_2), 1.30−1.57 (m, 3H, CH_2), 1.81−2.00 (m, 3H, CH, β-CH_2), 4.12−4.20 (m, 1H, α-CH), 4.66−4.78 (m, 1H, α-CH) 7.04−7.30 (m, 10H, H_{arom}); MS (FAB^+) *m*/*z* 419 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Lysyl)amino]butylphosphonate Trifluoroacetate (9.21). ^1H NMR (D_2O, 400 MHz) δ 0.90−0.94 (t, 3H, CH_3), 1.33−1.56 (m, 5H, CH_2), 1.68−1.72 (m, 1H, CH_2), 1.82−1.88 (m, 1H, CH_2), 1.93−2.07 (m, 2H, CH_2), 2.54−2.58 (t, 1H, ϵ-CH_2), 2.95−2.98 (t, 1H, ϵ-CH_2), 4.05−4.07 (m, 1H, α-CH), 4.74−4.82 (m, 1H, α-CH), 7.06−7.19 (m, 4H, H_{arom}), 7.26−7.33 (m, 2H, H_{arom}), 7.38−7.46 (m, 4H, H_{arom}); MS (FAB^+) *m*/*z* 434 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]-2-methylpropylphosphonate Trifluoroacetate (9.22). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74−0.78 (t, 1.5H, δ-CH_3), 0.82−0.86 (t, 1.5H, δ-CH_3), 0.93−0.97 (m, 3H, γ-CH_3), 1.09−1.14 (m, 6H, CH_3), 1.15−1.59 (m, 2H, γ-CH_2), 1.89−2.01 (m, 1H, β-CH), 2.38−2.49 (m, 1H, β-CH), 4.18−4.27 (m, 1H, α-CH), 4.67−4.77 (m, 1H, α-CH), 7.05−7.31 (m, 10H, H_{arom}); MS (FAB^+) *m*/*z* 419 $(M + H)^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]-2-methylbutylphosphonate Trifluoroacetate (9.23). ^1H NMR ($CDCl_3$, 400

MHz) δ 0.75−1.00 (m, 9H, CH_3), 1.07−1.53 (m, 7H, CH_2, CH_3), 1.88−2.00 (m, 1H, β-CH), 2.12−2.22 (m, 1H, β-CH), 4.15−4.22 (m, 1H, α-CH), 4.90−5.02 (m, 1H, α-CH), 7.02−7.36 (m, 10H, H_{arom}); MS (FAB$^+$) *m/z* 433 (M + H)$^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]-3-methylbutylphosphonate Trifluoroacetate (9.24). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70−0.1.29 (m, 14H, CH_3, CH_2), 1.49−1.51 (m, 1H, γ-CH), 1.65−2.00 (m, 3H, β-CH, β-CH_2), 4.10−4.24 (m, 1H, α-CH), 4.75−4.88 (m, 1H, α-CH), 7.05−7.31 (m, 10H, H_{arom}); MS (FAB$^+$) *m/z* 433 (M + H)$^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]-2-ethylbutylphosphonate Trifluoroacetate (9.25). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.76−1.00 (m, 12H, CH_3), 1.03−1.98 (m, 8H, γ-CH_2, β-CH), 4.10−4.23 (m, 1H, α-CH), 4.95−5.08 (m, 1H, α-CH), 7.07−7.32 (m, 10H, H_{arom}); MS (FAB$^+$) *m/z* 447 (M + H)$^+$.

Diphenyl (*R,S*)-[(*S*-Cyclohexylalanyl)amino](cyclohexyl)-methylphosphonate Trifluoroacetate (9.26). ^{1}H NMR(CD_3-OD, 400 MHz) δ 0.85−1.46 (m, 11H, CH_2), 1.58−1.83 (m, 10H, CH_2), 1.94−2.19 (m, 3H, CH_2, CH), 3.98−4.08 (m, 1H, α-CH), 4.68−4.78 (dd, 1H, α-CH), 7.06−7.09 (m, 1H, H_{arom}), 7.14−7.28 (m, 5H, H_{arom}), 7.32−7.42 (m, 4H, H_{arom}); MS (FAB$^+$) *m/z* 499 (M + H)$^+$.

Diphenyl (*R,S*)-Cyclohexyl[(*S*-2.4-diaminobutanoyl)-amino]methylphosphonate Ditrifluoroacetate (9.27). ^{1}H NMR (D_2O, 400 MHz) δ 1.11−1.34 (m, 5H, CH_2), 1.58−1.79 (m, 3H, CH_2), 1.83−1.96 (m, 2H, CH_2), 2.08−2.36 (m, 3H, CH_2, CH), 3.03−3.16 (m, 2H, γ-CH_2), 4.21 (s, 1H, α-CH), 4.62−4.81 (m, 1H, α-CH), 7.04−7.20 (m, 4H, H_{arom}), 7.25−7.40 (m, 6H, H_{arom}); MS (FAB$^+$) 446 *m/z* (M + H)$^+$.

Diphenyl (*R,S*)-Cyclohexyl[(L-histidyl)amino]methylphosphonate Ditrifluoroacetate (9.28). ^{1}H NMR (D_2O, 400 MHz) δ 0.65−0.86 (m, 1H, CH_2), 0.94−1.28 (m, 4H, CH_2), 1.58−1.70 (m, 4H, CH_2), 1.82−1.89 (m, 1H, CH_2), 1.96−2.09 (m, 1H, CH), 3.24−3.42 (m, 2H, CH_2), 4.40 + 4.46 (t, 0.5H, α-CH), 6.97 (d, 1H, Harom), 6.94 (d, 1H, H_{arom}), 7.10−7.14 (m, 2H, H_{arom}), 7.22−7.47 (m, 7H, H_{arom}, 4H−His), 8.33 + 8.72 (s, 0.5H, 2H−His); MS (FAB$^+$) *m/z* 483 (M + H)$^+$.

Diphenyl (*R,S*)-Cyclohexyl[(L-isoleucyl)amino]methylphosphonate Trifluoroacetate (9.29). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74−0.87 (m, 3H, CH_3), 0.93 (d, 1.5H, γ-CH_3), 0.97 (d, 1.5H, γ-CH_3), 1.04−1.31 (m, 6H, CH_2), 1.58−2.12 (m, 8H, CH, CH_2), 4.16−4.24 (m, 1H, α-CH), 4.68−4.82 (m, 1H, α-CH), 7.05−7.32 (m, 10H, H_{arom}); MS (FAB$^+$) *m/z* 459 (M + H)$^+$.

Diphenyl (*R,S*)-[(L-Isoleucyl)amino](phenyl)methylphosphonate Trifluoroacetate (9.30). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.59−0.88 (m, 6H, CH_3), 1.15−1.55 (m, 2H, CH_2), 1.74−1.95 (m, 1H, CH), 4.15 (s, 1H, α-CH), 5.91 (dd, 1H, α-CH), 6.70−6.73 (m, 2H, H_{arom}), 7.02−7.16 (m, 6H, H_{arom}), 7.24−7.32 (m, 5H, H_{arom}), 7.48−7.50 (m, 2H, H_{arom}); MS (FAB$^+$) *m/z* 453 (M + H)$^+$.

Diphenyl 1(*R,S*)-[(L-Isoleucyl)amino]-2-phenylethylphosphonate Trifluoroacetate (9.31). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.50−0.75 (m, 6H, CH_3), 0.83−1.04 (m, 1.5H, CH_2), 1.24−1.38 (m, 0.5H, CH_2), 1.54−1.62 (m, 0.5H, β-CH), 1.71−1.81 (m, 0.5H, β-CH), 3.05−3.5 (m, 2H, CH_2), 3.79−3.84 (m, 0.5H, α-CH), 3.98−4.05 (m, 0.5H, α-CH), 4.49−5.12 (m, 1H, α-CH), 7.05−7.32 (m, 15H, H_{arom}); MS (FAB$^+$) *m/z* 467 (M + H)$^+$.

Diphenyl (*R,S*)-[(L-Isoleucyl)amino](4-cyanofenyl)methylphosphonate Trifluoroacetate (9.32). ^{1}H NMR (CD_3OD, 400 MHz) δ 0.83−1.11 (m, 6H, CH_3), 1.24−1.46 (m, 2H, γ-CH_2), 1.62−1.67 (m, 0.5H, β-CH), 1.92−2.07 (m, 0.5H, β-CH), 3.92−3.94 (m, 1H, α-CH), 4.82−4.88 (m, 1H, α-CH), 6.91−7.38 (m, 10H, H_{arom}), 7.75−7.85 (m, 4H, H_{arom}); MS (FAB$^+$) *m/z* 478 (M + H)$^+$.

Diphenyl (*R,S*)-[(L-Isoleucyl)amino](3-cyanophenyl)methylphosphonate Trifluoroacetate (9.33). MS (FAB$^+$) *m/z* 478 (M + H)$^+$.

Diphenyl (*R,S*)-(Cyclohexyl)[(*N*-cyclopentylglycyl)amino]methylphosphonate Trifluoroacetate (9.34). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13−1.28 (m, 6H, CH_2), 1.45−2.10 (m, 13H, CH_2, CH), 3.39−3.48 (m, 1H, CH), 3.84 (s, 2H, CH_2), 4.63−4.77 (m, 1H, α-CH), 7.09−7.31 (m, 10H, H_{arom}); MS (ES$^+$) *m/z* 471 (M + H)$^+$.

Diphenyl (*R,S*)-[(*N*-Cyclopentylglycyl)amino](phenyl)-methylphosphonate Trifluoroacetate (9.35). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47−1.71 (m, 6H, CH_2), 1.84−1.93 (m, 2H, CH_2), 3.29 (m, 1H, CH), 3.33−3.40 (m, 1H, CH_2), 3.65−3.78 (m, 1H, CH_2), 6.76−6.79 (m, 2H, H_{arom}), 6.98−7.01 (m, 2H, H_{arom}), 7.03−7.27 (m, 8H, H_{arom}), 7.29−7.35 (m, 3H, H_{arom}), 7.45−7.48 (m, 2H, H_{arom}); MS (FAB$^+$) *m/z* 465 (M + H)$^+$.

Diphenyl (*R,S*)-(Cyclohexyl)[(*N*-cyclohexylglycyl)amino]methylphosphonate Trifluoroacetate (9.36). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06−1.38 (m, 12H, CH_2), 1.57−2.10 (m, 9H, CH_2, CH), 2.90−3.00 (m, 1H, CH), 3.87 (dd, 2H, CH_2), 4.65−4.78 (m, 1H, α-CH), 7.08−7.34 (m, 10H, H_{arom}); MS (ES$^+$) *m/z* 485 (M + H)$^+$.

Diphenyl (*R,S*)-[(*N*-Benzylglycyl)amino](cyclohexyl)-methylphosphonate Trifluoroacetate (9.37). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09−1.28 (m, 6H, CH_2), 1.51−2.09 (m, 5H, CH_2, CH), 3.69 (dd, 2H, CH_2), 4.10 (s, 2H, CH_2), 4.64−4.71 (m, 1H, α-CH), 7.07−7.32 (m, 10H, H_{arom}); MS (ES$^+$) *m/z* 493 (M + H)$^+$.

Diphenyl (*R,S*)-[(*N*-*sec*-Butylaminoglycyl)amino](cyclohexyl)methylphosphonate Trifluoroacetate (9.38). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, 3H, CH_3), 1.05−1.32 (m, 8H, CH_2), 1.42−2.12 (m, 8H, CH_2,CH), 2.99−3.13 (m, 1H, CH), 3.74−3.97(m, 2H, CH_2), 4.65−4.79 (m, 1H, α-CH), 7.07−7.34 (m, 10H, H_{arom}); MS (ES$^+$) *m/z* 459 (M + H)$^+$.

Diphenyl (*R,S*)-(Cyclohexyl)[(*N*-isobutylaminoglycyl)-amino]methylphosphonate Trifluoroacetate (9.39). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, 6H, CH_3), 1.05−1.31 (m, 6H, CH_2), 1.59−2.09 (m, 6H, CH_2,CH), 2.67−2.79 (m, 2H, CH_2), 3.82 (s, 2H, CH_2), 4.69−4.77 (m, 1H, α-CH), 7.08−7.33 (m, 10H, H_{arom}); MS (ES$^+$) *m/z* 459 (M + H)$^+$.

Diphenyl 1-L-Alanylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.1). ^{1}H NMR (D_2O, 400 MHz) δ 1.48 (dd, 3H, CH_3), 2.05−2.58 (m, 4H, β-CH_2, γ-CH_2), 3.66−3.82 (m, 2H, δ-CH_2), 4.35−4.43 (m, 1H, α-CH), 4.89−4.95 (m, 0.5H, α-CH), 5.00−5.05 (m, 0.5H, α-CH), 7.07−7.12 (m, 4H, *o*-H_{arom}), 7.23−7.27 (m, 2H, *p*-H_{arom}), 7.34−7.39 (m, 4H, *m*-H_{arom}); MS (ES$^+$) *m/z* 375 (M + H)$^+$.

Diphenyl 1-L-Asparaginylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.2). ^{1}H NMR (D_2O, 400 MHz) δ

2.09−2.51 (m, 4H, β-CH_2, γ-CH_2), 2.67−2.94 (m, 2H, CH_2), 3.65−3.78 (m, 2H, δ-CH_2), 4.58−4.63 (m, 1H, α-CH), 4.97−5.04 (m, 1H, α-CH), 7.07−7.11 (m, 4H, *o*-H_{arom}), 7.21−7.25 (m, 2H, *p*-H_{arom}), 7.33−7.37 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 418 $(M + H)^+$.

Diphenyl 1-L-Aspartylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.3). ^1H NMR (D_2O, 400 MHz) δ 2.12−2.61 (m, 4H, β-CH_2, γ-CH_2), 2.81−3.12 (m, 2H, CH_2), 3.7−3.84 (m, 2H, δ-CH_2), 4.66−4.69 (m, 1H, α-CH), 4.92−4.97 (m, 0.5H, α-CH), 5.02−5.08 (m, 0.5H, α-CH), 7.08−7.13 (m, 4H, *o*-H_{arom}), 7.26 (t, 2H, *p*-H_{arom}), 7.35−7.39 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 419 $(M + H)^+$.

Diphenyl 1-L-Glycylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.4). ^1H NMR (D_2O, 400 MHz) δ 2.11−2.61 (m, 4H, β-CH_2, γ-CH_2), 3.59−3.63 (m, 2H, δ-CH_2), 3.90−4.04 (m, 2H, CH_2), 7.04−7.12 (m, 4H, *o*-H_{arom}), 7.23−7.39 (m, 2H, *p*-H_{arom}), 7.34−7.39 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 361 $(M + H)^+$.

Diphenyl 1-L-Histidylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.5). ^1H NMR (D_2O, 400 MHz) δ 2.16−2.69 (m, 4H, β-CH_2, γ-CH_2), 3.45−4.04 (m, 4H, CH_2, δ-CH_2), 5.03−5.10 (m, 1H, α-CH), 5.06−5.18 (m, 1H, α-CH), 7.19−7.22 (m, 4H, *o*-H_{arom}), 7.36−7.39 (m, 2.H, *p*-H_{arom}, 4H−His), 7.47−7.54 (m, 4.5H, *m*-H_{arom}, 4H-His), 8.52 (s, 0.5H, 2H-His), 8.75 (s, 0.5H, 2H-His); MS (ES^+) *m*/*z* 441 $(M + H)^+$.

Diphenyl 1-L-Lysylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.6). ^1H NMR (D_2O, 400 MHz) δ 1.31−1.41 (m, 1H), 1.45−1.56 (m, 2H), 1.66−1.76 (m, 1H), 1.83−1.99 (m, 2H), 2.11−2.99 (m, 6H, β-CH_2, γ-CH_2, ϵ-CH_2), 3.71−3.86 (m, 2H, δ-CH_2), 4.36−4.44 (m, 1H, α-CH), 4.93−4.98 (m, 0.5H, α-CH), 5.05−5.10 (m, 0.5H, α-CH), 7.11−7.14 (m, 4H, *o*-H_{arom}), 7.26−7.30 (m, 2H, *p*-H_{arom}), 7.37−7.42 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 432 $(M + H)^+$.

Diphenyl 1-L-Phenylalanylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.7). ^1H NMR (D_2O, 400 MHz) δ 1.83−2.41 (m, 4H, β-CH_2, γ-CH_2), 3.05−3.16 (m, 2H, CH_2), 3.40−3.59 (m, 2H, δ-CH_2), 4.46−4.54 (m, 1H, α-CH), 4.71−4.94 (m, 1H, α-CH), 6.99−7.07 (m, 4H, H_{arom}), 7.15−7.35 (m, 11H, H_{arom}); MS (ES^+) *m*/*z* 451 $(M + H)^+$.

Diphenyl 1-L-Serylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.8). ^1H NMR (D_2O, 400 MHz) δ 2.09−2.59 (m, 4H, β-CH_2, γ-CH_2), 3.67−4.03 (m, 4H, δ-CH_2, CH_2), 4.46 (t, 1H, α-CH), 4.91−4.96 (m, 0.5H, α-CH), 5.01−5.06 (m, 0.5H, α-CH), 7.07−7.12 (m, 4H, *o*-H_{arom}), 7.23−7.27 (m, 2H, *p*-H_{arom}), 7.34−7.38 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* *391* $(M + H)^+$.

Diphenyl 1-*S*-Thiaprolylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.9). ^1H NMR (D_2O, 400 MHz) δ 2.09−2.56 (m, 4H, β-CH_2, γ-CH_2), 2.94−2.99 (m, 0.5H, β-CH_2) 3.14−3.19 (m, 0.5H, β-CH_2), 3.56−3.77 (m, 3H, δ-CH_2, β-CH_2), 4.35−4.46 (m, 2H, δ-CH_2), 4.87−5.02 (m, 2H, α-CH), 7.03−7.10 (m, 4H, *o*-H_{arom}), 7.20−7.23 (m, 2H, *p*-H_{arom}), 7.31−7.35 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 419 $(M + H)^+$.

Diphenyl 1-L-Valylpyrrolidine-2(*R,S*)-phosphonate Trifluoroacetate (8.10). ^1H NMR (D_2O, 400 MHz) δ 1.00−1.09 (m, 6H, CH_3), 2.09−2.59 (m, 5H, β-CH_2, γ-CH_2, β-CH), 3.73−3.88 (m, 2H, δ-CH_2), 4.22 (d, 0.5H, α-CH), 4.27 (d, 0.5H, α-CH), 4.94−5.00 (m, 0.5H, α-CH), 5.05−5.11 (m, 0.5H, α-CH), 7.08−7.14 (m, 4H, *o*-H_{arom}), 7.27 (t, 2H, *p*-H_{arom}), 7.35−7.41 (m, 4H, *m*-H_{arom}); MS (ES^+) *m*/*z* 403 $(M + H)^+$.

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