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Synthesis and characterization of peptidomimetics containing oxazolidin-2-one and oxazolidine scaffolds

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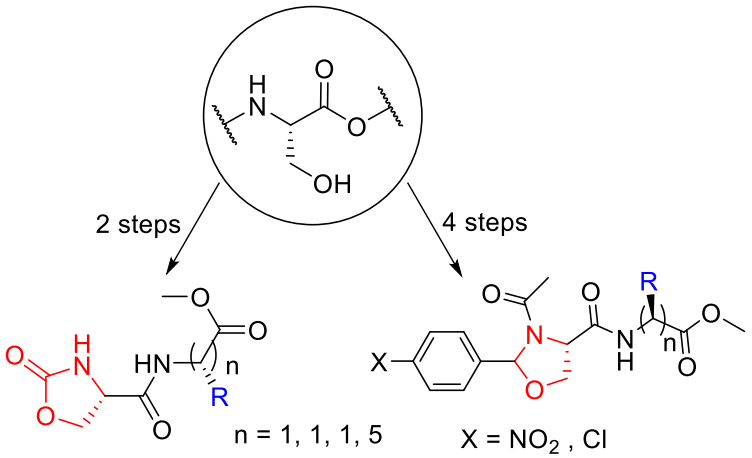
Abstract

In this paper, we report the synthesis of peptidomimetics containing oxazolidin-2-one and oxazolidine rings. The two of these heterocyclic peptidomimetics novel series were obtained from serine as starting material through an efficient intramolecular cyclization. In the case of oxazolidine, the formation of only one diastereoisomer was observed.



R = -CH(CH$_3$)$_2$, -CH$_2$-CH(CH$_3$)$_2$, -CH$_2$-Ph.

Keywords: Amino acids, peptidomimetics, oxazolidin-2-one, oxazolidine

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Introduction

Peptides are regaining interest in drug discovery.[1] However, their use is limited by proteases degradation and by low membrane permeability.[2] Peptidomimetics have been developed in order to improve their bioavailability. [3-8]

We have focused our attention on peptidomimetics with heterocyclic rings. Indeed, five-membered heterocyclic rings resulting from intramolecular condensation of amino acids side chains such as: cysteine, threonine or serine are usually found in cyclic peptides isolated from marine organisms.[9,10] Amino acids containing these rings and their analogous oxazoles or thiazoles have already been employed as precursors of peptidomimetics[11,12] and as building blocks of macrocyclic compounds.[13] Current research in this field is mainly concentrated on discovering novel compounds with biological activities such as antibacterial properties.

Peptides containing oxazolidinone and oxazolidine rings constitute an infrequent but remarkable class of peptidomimetics, the cyclic residue can be regarded as suitable constrained pseudo-proline.[14] They have found use in medicinal chemistry as precursors in the construction of foldamers and oligomers with constrained bioactive structures.[14-16] Oxazolidine ring is less likely to be found in peptidomimetics than oxazolidinone. In natural or synthetic molecules, the latter is a central part of a promising class of antibacterial agents (Figure 1).[17-20]

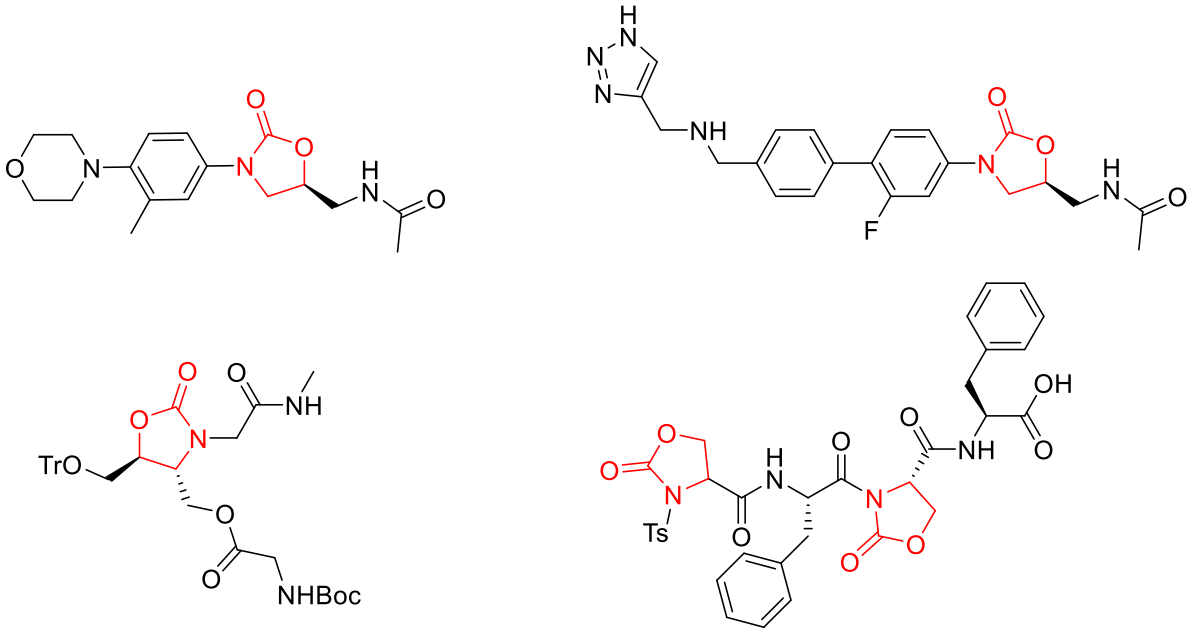


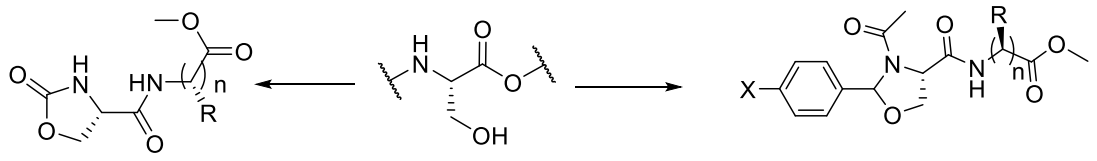
Figure 1. Examples of peptidomimetics containing oxazolidinone.

In this area, our work is focused on generating new peptidomimetics with restricted conformation. We have been interested in developing a set of new peptidomimetics with oxazolidinone and oxazolidine ring as constrained pseudo-proline residues.

Results and Discussion

Here we report the synthesis of new peptidomimetics that result from the incorporation of oxazolidinone or oxazolidine heterocyclic backbone into a dipeptide structure. These heterocycles can be incorporated into the structure either at the beginning or at the end of the synthesis, by intramolecular cyclization of the serine side chain.

Oxazolidin-2-ones can be simply introduced from a dipeptide containing a *N*-Boc L-serine residue (Scheme 1). This approach is based on the condensation reactions of the amino alcohol, described in literature.[21-24] In the same context, we discovered a simple synthesis of oxazolidine-derivatives using the same approach with another serine derivative: the *N*-acetyl-L-serine methyl ester hydrochloride (Scheme 1).



1a n = 1, R = *i*Pr
1b n = 1, R = *i*Bu
1c n = 5, R = **-**
1d n = 1, R = Bn

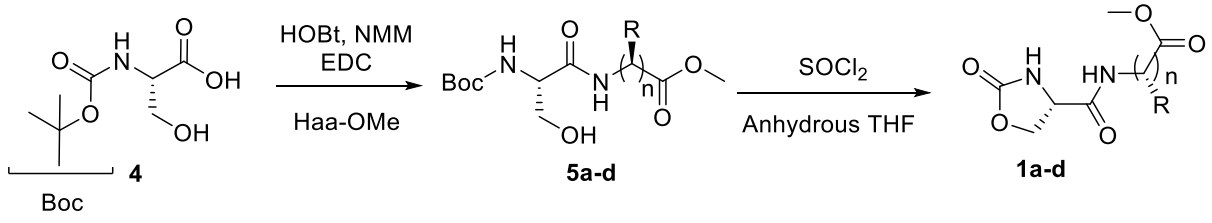
2a X = NO_2, n = 1, R = *i*Pr
2b X = NO_2, n = 1, R = *i*Bu
2c X = NO_2, n = 5, R = -
2d X = NO_2, n = 1, R = Bn

3a X = Cl, n = 1, R = *i*Pr
3b X = Cl, n = 1, R = *i*Bu
3c X = Cl, n = 5, R = -
3d X = Cl, n = 1, R = Bn

Scheme 1. Formation of oxazolidinones and oxazolidines dipeptide mimetics via serine derivatives.

Several studies have exploited β-amino alcohols cyclization, especially for the synthesis of oxazolidinones.[25-28] In the first part of this article, we describe an application of this method to the synthesis of conformational constrained dipeptide mimetic from derivatives containing serine fragment. Thus, the cyclization was performed directly on the dipeptide resulting from peptide coupling with different amino acids: Val, Leu, Phe and aminocaproic acid. On the other hand, stable oxazolidines were obtained using also a serine derivative; but the cyclization was carried out at the first step using *N*-acetyl-L-serine methyl ester.

The synthetic procedure leading to dipeptide mimetic derivatives containing an oxazolidinone moiety **1a-d**, is reported in table 1. It started with a condensation between *N*-Boc-L-serine **4** and methyl ester hydrochloride amino acids, according to a classical peptide synthesis method (EDC/HOBt/NMM),[29] affording the dipeptides **5a-d** in excellent yields (ranging from 83 to 98 %).

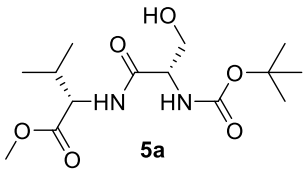
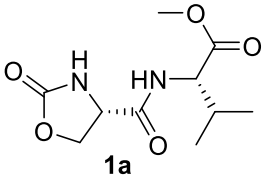
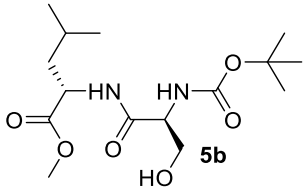
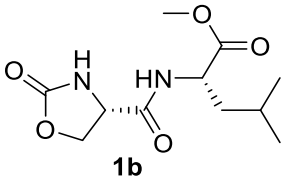
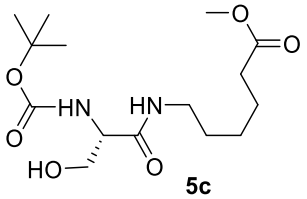
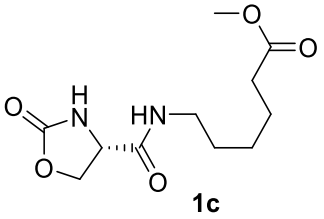
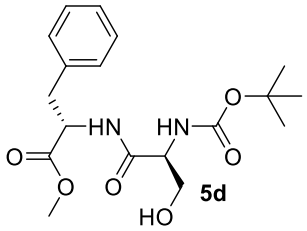
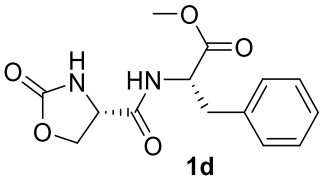


Scheme 2. Synthesis of oxazolidin-2-one **1a-d.**

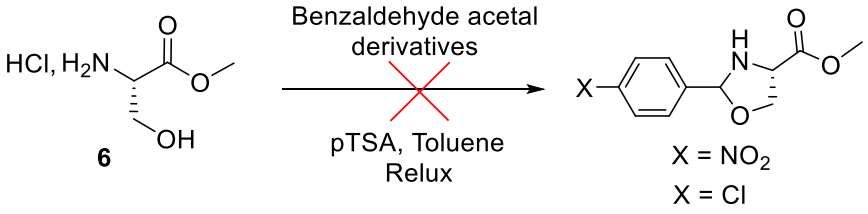
The oxazolidinones **1a-d** were formed following Miyata *et al* [30] methodology. *N-tert*-butoxycarbonyl dipeptides **5a-d** were simply treated with thionyl chloride in anhydrous THF (Scheme 2). We thought that, after the substitution of the hydroxyl group by chlorine atom, **1a-d** were obtained *via* displacement of this

leaving group by the carbamate oxygen moiety. The obtained yields, ranging from moderate to good (61% to 90%), are summarized in table 1.

Table 1. Synthesis of dipeptides **5a-d** and oxazolidin-2-one **1a-d**

Entry	Amino acids	Product 5	Yield (%)	Product 1	Yield (%)
1	L-Val-OMe·HCl	 **5a**	92	 **1a**	90
2	L-Leu-OMe·HCl	 **5b**	83	 **1b**	72
3	Amino caproic-OMe·HCl	 **5c**	98	 **1c**	61
4	L-Phe-OMe·HCl	 **5d**	86	 **1d**	62

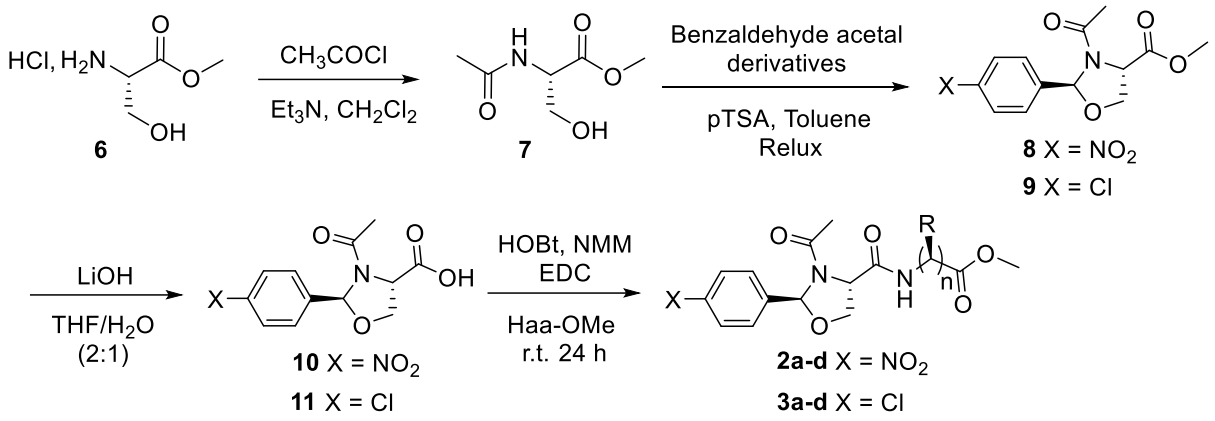
Turning to oxazolidine in the second part of this work, condensation was tried in the first place between L-serine methyl ester hydrochloride **6** and benzaldehyde acetal derivatives catalyzed by para-toluene sulfonic acid (pTSA), following Bedürftig *et al*.[31] No detectable oxazolidine was formed as determined by ^{1}H NMR spectroscopy (Scheme 3).



Scheme 3. No detectable oxazolidine.

As prescribed by Bedürftig *et al*[31] in order to circumvent the heterocyclic instability induced by the free amine function, the cyclization was achieved by prior *N*-acetylation of L-serine methyl ester hydrochloride **6**

using acetyl chloride and triethyl amine (Et_3N) and giving acetamide product **7** with excellent yield 99% (Scheme 4).[32]



Scheme 4. Synthesis of oxazolidine **2a-d** and **3a-d**.

As shown previously, the cyclization reaction based on the serine derivative was accomplished with benzaldehyde acetal derivatives in acidic medium[31] and yielded oxazolidines **8** and **9** in 64 and 62% yield, respectively. Afterwards, dipeptide mimetics were obtained in two steps keeping the heterocyclic ring safe. The methyl ester was removed by treatment with a lithium hydroxide solution in THF/H_2O (2/1). The carboxylic acids **10** and **11** were obtained in 44 and 62% yield, respectively. Following standard peptide coupling procedure (EDC/HOBt/ NMM)[29] compounds **10** and **11** were condensed with various methyl ester amino acids to give oxazolidines **2a-d** and **3a-d** with moderate to excellent yields (Table 2).

Rotamers of compounds **8**, **9** and **2a-d**, **3a-d** were observed by ^{1}H NMR spectroscopy. This was confirmed by heating, as shown by the ^{1}H NMR spectra of compound **2b** at different temperatures: 298K, 323K, 348K, 363K and 378K (Figure 2 and Figure 3).

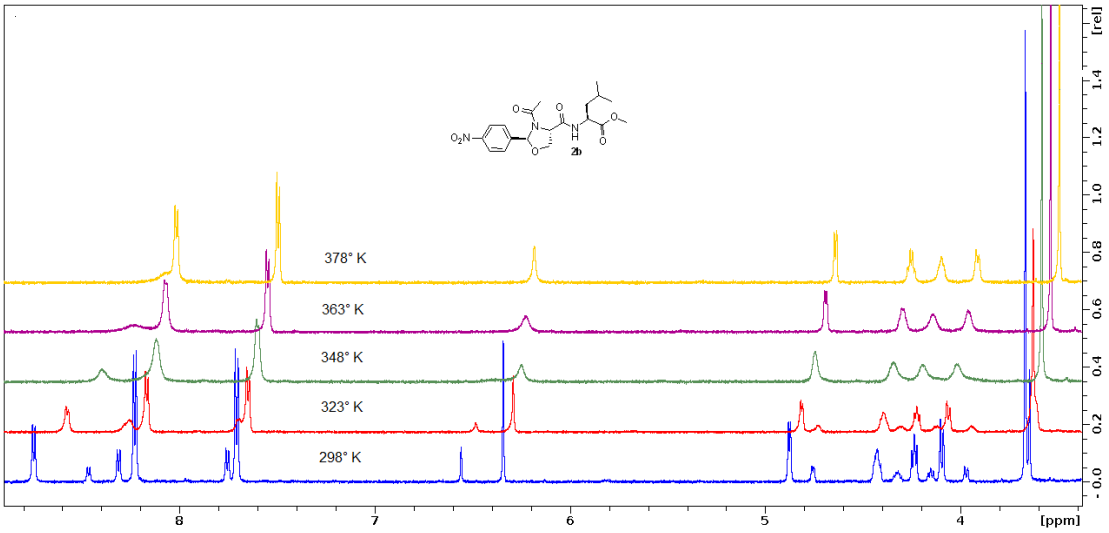


Figure 2. ^{1}H NMR spectra of compound **2b** in DMSO-d_6 at different temperatures (3.5-9 ppm) at 600 MHz.

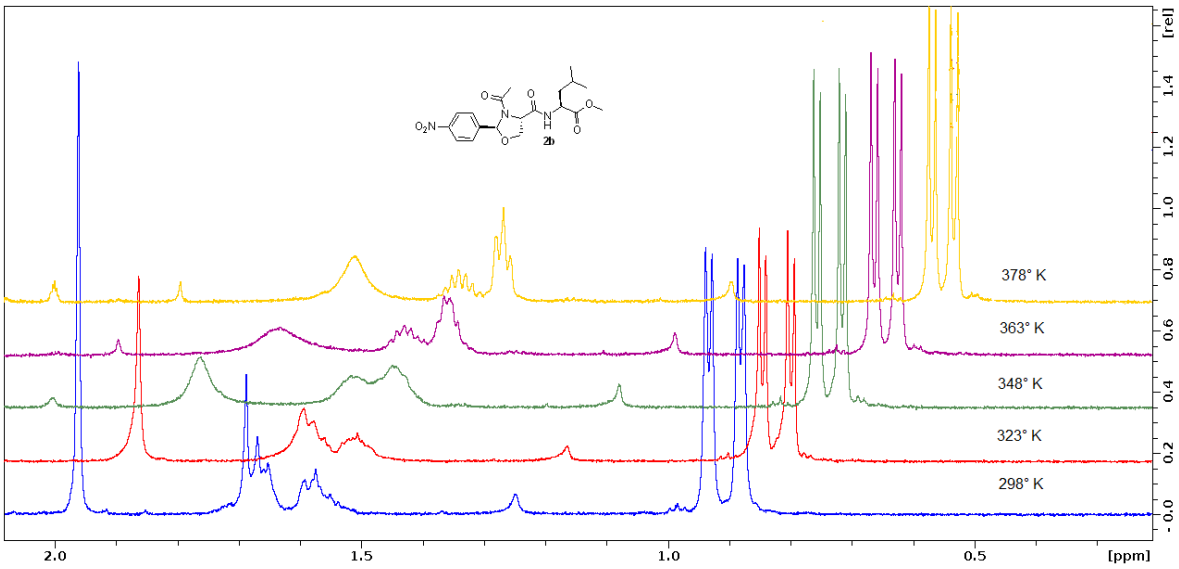


Figure 3. ^{1}H NMR spectra of compound **2b** in DMSO-d_6 at different temperatures (0-2ppm) at 600 MHz.

Nevertheless, a single diastereoisomer was obtained, nOe experiment allowed us to establish the configuration of the new tertiary asymmetric carbon 2 (Figure 4).

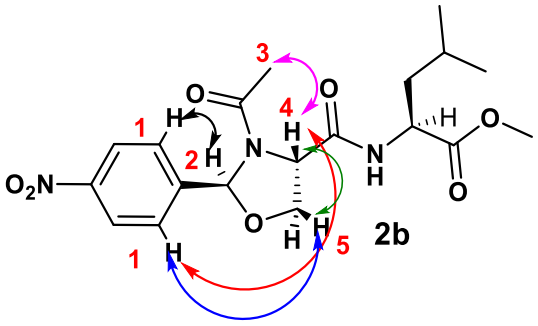
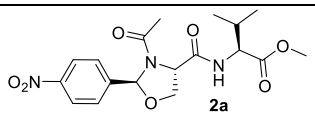
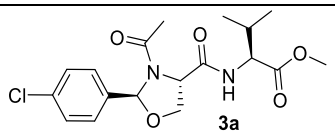
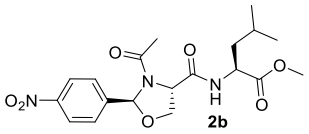
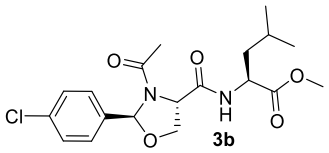
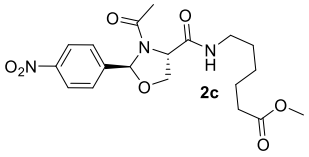
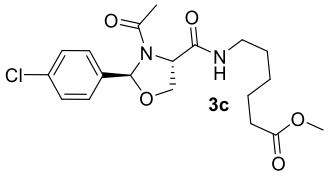
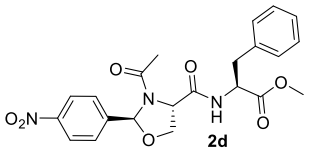
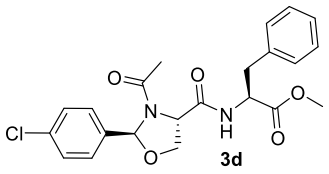


Figure 4. nOe of **2b.**

Table 2. Synthesis of dipeptide mimetics with oxazolidine moiety **2a-d** and **3a-d**

Entry	Amino acids	Product 2	Yield (%)	Product 3	Yield (%)
1	L-Val-OMe·HCl	 **2a**	99	 **3a**	76
2	L-Leu-OMe·HCl	 **2b**	81	 **3b**	99
3	Amino caproic-OMe·HCl	 **2c**	63	 **3c**	91
4	L-Phe-OMe·HCl	 **2d**	90	 **3d**	83

Conclusions

In conclusion, we have developed two efficient strategies to obtain series of dipeptide mimetics analogues using simple and cheap methods in good yields. Oxazolidinones **1a-b** were obtained in two steps from *N*-Boc-L-serine **4** (61 to 90%). Oxazolidines **2a-d** and **3a-d** were synthesized in three steps from *N*-acetyl-L-serine **7** (63 to 99%). These products are useful scaffolds to be introduced in peptide mimetics.

Experimental Section

General. All reagents were purchased from commercial suppliers and used without further purification. The reactions were monitored by TLC. TLC analyses were performed using aluminum plates coated with silica gel 60F 254 from Macherey-Nagel and revealed under ultraviolet light (254 nm) and with a 5% ethanolic phosphomolybdic acid bath and a solution of 1% sulfuric vanillin in ethanol. Common silica gel (40–70 mesh) was used for column chromatography purifications. On a Bruker Avance spectrometer operating at 300 or 600 MHz for ^{1}H and ^{13}C. For ^{1}H and ^{13}C NMR spectra analyses, $CHCl_3$ (7.26 ppm) and $^{13}CDCl_3$ (77.0 ppm), CH_3OH (3.31 - 4.78 ppm) and $^{13}CH_3OH$ (49.1 ppm), Dimethyl sulfoxide (2.50 ppm) and (39.5 ppm) for ^{13}C were used as the internal references, respectively. High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform or on a LCT premier

Waters. Optical rotation data were obtained on a Perkin Elmer 541 polarimeter at ambient temperature using a 100 mm cell with a 1 mL capacity.

General procedure for amino acid coupling. *N*-Boc-L-serine (500 mg, 2.4 mmol), EDC (550 mg, 2.9 mmol), and hydroxybenzotriazole (HOBt) (520 mg, 3.9 mmol) were dissolved in CH_2Cl_2 (50 mL). After 1 h the opportune amino acid; for valine (450 mg, 2.6 mmol) and *N*-methylmorpholine (800 µL, 7.3 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. The solution was washed with 10% $NaHCO_3$ (2×10 mL), 5% $KHSO_4$ (2×10 mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was used without further purification.

Methyl (*tert*-butoxycarbonyl)-L-seryl-L-valinate (5a).[33] Yield 716 mg, 92%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.93 (d, *J* 6.9 Hz, 3H), 0.97 (d, *J* 6.9 Hz, 3H), 1.48 (s, 9H), 2.00 (s, 1H) 2.19-2.29 (m, 1H), 3.63-3.72 (m, 2H), 3.77 (s, 3H), , 4.10 (d, *J* 9.2 Hz, 1H), 4.53 (t, *J* 3.4 Hz, 1H), 5.71 (NH, 1H), 7.31 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 19.05, 28.3, 30.8, 52.3, 54.6, 57.4, 62.7, 80.5, 156.2, 171.7, 172.3.

Methyl (*tert*-butoxycarbonyl)-L-seryl-L-leucinate (5b)[33] was prepared from 500 mg (2.4 mmol) of *N*-Boc-L-serine, 550 mg (2.9 mmol) of EDC, 520 mg (3.9 mmol) of HOBt, 490 mg (2.7 mmol) of L-leucine methyl ester hydrochloride and 800 µL (7.3 mmol) of *N*-methyl morpholine in 50 mL of CH_2Cl_2 to provide 671 mg, 83% as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.96 (d, *J* 1.7 Hz, 3H), 0.97 (d, *J* 1.9 Hz, 3H), 1.49 (s, 9H), 1.53 (s, 1H), 1.57-1.65 (m, 1H), 1.67-1.74 (m, 2H), 3.78 (s, 3H), 4.23 (t, *J* 6.1 Hz, 1H), 4.50-4.70 (m, 2H), 5.63 (NH, 1H), 7.07 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.9, 24.8, 28.3, 40.8, 50.9, 52.5, 53.4, 62.9, 80.5, 156.1, 171.6, 173.5.

Methyl (*S*)-6-(2-((*tert*-butoxycarbonyl) amino)-3-hydroxypropanamido)hexanoate (5c) was prepared from 1.006 g (4.9 mmol) of N-Boc-L-serine, 1.4 g (7.3 mmol) of EDC, 1.04 g (7.7 mmol) of HOBt, 960 mg (5.3 mmol) of methyl 6-aminohexanoate hydrochloride and *N*-methyl morpholine (1.6 mL, 14.7 mmol) in 80 mL of CH_2Cl_2 to provide 1.582 g, 98% as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.25-1.30 (m, 2H), 1.35-1.43 (m, 2H), 1.49 (s, 9H), 1.59 (s, 1H), 1.65-1.72 (m, 2H), 2.34 (t, *J* 7.2 Hz, 2H), 3.29 (t, *J* 6.0 Hz, 2H), 3.70 (s, 3H), 4.08-4.16 (m, 2H), 5.34 (NH, 1H), 6.81 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 24.3, 26.2, 28.3, 29.0, 33.8, 39.2, 51.6, 54.8, 62.9, 80.5, 156.3, 171.4, 174.1.

Methyl *(tert*-butoxycarbonyl)-L-seryl-L-phenylalaninate (5d)[33] was prepared by reacting 500 mg (2.4 mmol) of *N*-Boc-L-serine, 550 mg (2.9 mmol) of EDC, 520 mg (3.9 mmol) of HOBt, 580 mg (2.6 mmol) of L-phenylalanine methyl ester hydrochloride and (800 µL, 7.3 mmol) of *N*-methyl morpholine in 50 mL of CH_2Cl_2 to provide 765 mg, 86% as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.47 (s, 9H) , 2.80 (s, 1H), 3.10 (q, *J* 7.4, 6.8 Hz, 1H), 3.19 (q, *J* 8.2, 5.6 Hz, 1H), 3.61-3.67 (m, 1H), 3.75 (s, 3H), 3.96-4.05 (m, 1H), 4.21 (d, *J* 9.2 Hz, 1H), 4.87 (q, *J* 7.6, 6.4 Hz, 1H), 5.57 (NH, 1H), 7.10-7.31 (m, 5H, Ar), 7.32 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 28.3, 37.7, 52.5, 53.4, 55.1, 62.9, 80.4, 127.2-128.6-129.2-135.7 (Ar), 155.9, 171.0, 171.9.

General procedure for oxazolidinone cyclisation

To **5a** (100 mg, 0.3 mmol) dissolved in 10 mL of absolute THF, was added dropwise thionyl chloride (180 µL, 2.5 mmol) at room temperature. The mixture was refluxed for 5 h. The reaction mixture was washed with $NaHCO_3$ 10%, the aqueous phase was extracted twice by EtOAc. The organic phase was dried with $MgSO_4$ and concentrated under vacuum, thereafter the residue was purified by flash chromatography on silica gel (EtOAc, 100%).

Methyl ((*S*)-2-oxooxazolidine-4-carbonyl)-L-valinate (1a). Yield 69 mg, 90%, yellow oil, R_f = 0.29 (AcOEt 100%).^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.94 (d, *J* 1.6 Hz, 3H), 0.96 (d, *J* 1.6 Hz, 3H), 2.16-2.28 (m, 1H), 3.74 (s, 3H), 4.44 (q, *J* 5.6, 2.6 Hz, 1H), 4.53 (q, *J* 5.8, 3.0 Hz, 2H), 4.70 (t, *J* 8.4 Hz, 1H), 7.34 (NH, 1H), 7.60 (NH, 1H). ^{13}C NMR

(300 MHz, $CDCl_3$): δ_C 19.0, 31.0, 52.3, 55.3, 57.3, 68.5, 160.1, 170.6, 172.4. [α] $^{20}_D$= - 26.5 (c = 0.15, CH_2Cl_2). HRMS (ES-: *m/z* [M-H]$^-$): Calcd for $C_{10}H_{15}N_2O_5$ 243.0981 Found 243.0978.

Methyl ((*S*)-2-oxooxazolidine-4-carbonyl)-L-leucinate (1b) was prepared from 378 mg (1.1 mmol) of **5b** and 660 µL (9.1 mmol) of Thionyl chloride in 36 mL of tetrahydrofuran to provide 208 mg, 72% as yellow oil. R_f = 0.34 (AcOEt 100%).^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.94 (d, *J* 1.5 Hz, 3H), 0.96 (d, *J* 1.7 Hz, 3H), 1.58-1.65 (m, 1H), 1.71-1.76 (m, 2H), 3.73 (s, 3H), 4.40 (dd, *J* 5.5, 2.9 Hz, 1H), 4.51 (t, *J* 9.7, 5.5 Hz, 2H), 4.69 (q, *J* 8.7Hz, 2H), 7.37 (NH, 1H), 7.68 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.8, 24.9, 40.6, 50.6, 52.5, 55.3, 68.6, 160.2, 170.7, 173.8.

[α] $^{20}_D$= - 45.1 (c = 0.25, CH_2Cl_2). HRMS (ES-: m/z [M-H]$^-$): Calcd for $C_{11}H_{17}N_2O_5$ 257.1137 Found 257.1145.

Methyl (*S*)-6-(2-oxooxazolidine-4-carboxamido)hexanoate (1c) was prepared from 393 mg (1.2 mmol) of **5c** and 700 µL (9.5 mmol) of Thionyl chloride in 37 mL of tetrahydrofuran to provide 185 mg, 61% as yellow oil. R_f = 0.25 (AcOEt/MeOH 99.9/0.1).^{1}H NMR (300 MHz, $CDCl_3$): δ_H1.1.31-1.41 (m, 2H), 1.51-1.59 (m, 2H), 1.62-1.69 (m, 2H), 2.33 (t, *J* 7.3 Hz, 2H), 3.28 (t, *J* 6.1 Hz, 2H), 3.68 (s, 3H), 4.43 (q, *J* 7.0, 5.3 Hz, 2H), 4.66 (t, *J* 7.5 Hz, 1H), 7.23 (NH, 1H), 7.26 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 24.3, 26.1, 28.7, 33.7, 39.3, 51.6, 54.9, 68.6, 160.1, 170.3, 174.3.

[α] $^{20}_D$= - 41.0 (c = 0.3, CH_2Cl_2). HRMS (ES-: *m/z* [M-H]$^-$): Calcd for $C_{11}H_{17}N_2O_5$ 257.1137 Found 257.1144.

Methyl ((*S*)-2-oxooxazolidine-4-carbonyl)-L-phenylalaninate (1d) was prepared by reacting 325 mg (0.9 mmol) of **5d** and 510 µL (7.1 mmol) of Thionyl chloride in 28 mL of tetrahydrofuran to provide 173 mg, 62% as yellow oil. R_f = 0.43 (AcOEt 100%).^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.08 (dd, *J* 10.6, 2.7 Hz, 1H), 3.25 (dd, *J* 9.0, 4.4 Hz, 1H), 3.69 (t, *J* 1.9 Hz, 1H), 3.72 (s, 3H), 4.46 (q, *J* 7.9, 5.1 Hz, 2H), 5.00 (dt, *J* 6.0, 4.3 Hz, 1H), 7.26-7.38 (m, 5H, Ar), 7.65 (NH, 1H), 8.10 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 38.3, 52.5, 52.6, 55.7, 68.8, 127.0-128.3-129.5-136.6 (Ar), 160.6, 170.5, 172.1. [α] $^{20}_D$= + 7.2 (c = 0.5, CH_2Cl_2). HRMS (ES+: *m/z* [M+Na]$^+$): Calcd for $C_{14}H_{16}N_2O_5Na$ 315.0957 Found 315.0956.

Methyl acetyl-L-serinate (7). To a solution of serine methyl ester hydrochloride (4g, 25.7 mmol) in anhydrous CH_2Cl_2 (40 mL) and triethylamine (6.9 mL, 51.4 mmol) was added dropwise acetyl chloride (1.7 mL, 24.4 mmol) at -5°C, reaction mixture was stirred at -5°C for 3h. Precipitated Et_3N, HCl has been filtered and the solvent was removed under reduce pressure and the residue was purified by column chromatography on silica gel (ethyl acetate/ MeOH, 97:3, R_f= 0.76) to afford 4.1 g of desired product as colorless oil (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.96 (s, 3H), 3.66 (s, 3H), 3.75 (dd, *J* 8.0, 3.2 Hz, 1H), 3.85 (dd, *J* 7.9, 3.3 Hz, 1H), 4.50 (t, *J* 3.9Hz, 1H), 7.29 (NH, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.6, 52.5, 54.7, 62.3, 171.1, 171.4.

Methyl (2*S*,4*S*)-3-acetyl-2-(4-nitrophenyl)oxazolidine-4-carboxylate (8). A solution of **7** (253 mg, 1.6 mmol), 4-nitro benzaldehyde dimethyl acetal (960 mg, 4.8 mmol) and *p*-toluenesulfonic acid (6 mg, 0.03 mmol) in toluene (10 mL) was refluxed for 2h30 and then the solvent was evaporated to a volume of 2 mL. The residue was dissolved in ethyl acetate (50 mL), washed with $NaHCO_3$ saturated, and then the collected organic layer was dried over $MgSO_4$. After evaporation, the residue was purified by chromatography column ethyl acetate/cyclohexane (7:3) to afford 298 mg of **8** as orange oil (64%). R_f = 0.79 (ethyl acetate/cyclohexane 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.87 (s, 3H, rotamer 1), 2.12 (s, 3H, rotamer 2), 3.82 (s, 3H, rotamer 1), 3.89 (s, 3H, rotamer 2), 4.18 (q, *J* 6.0, 4.5 Hz, 2H, rotamer 1), 4.32 (q, *J* 8.3, 6.1 Hz, 2H, rotamer 2), 4.70 (d, *J* 5.9 Hz, 1H, rotamer 1), 4.84 (t, *J* 4.3 Hz, 1H, rotamer 2), 6.40 (s, 1H, rotamer 1), 6.48 (s, 1H, rotamer 2), 7.55-7.63, 8.19-8.32 (m, 8H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.8 (rotamer 1), 23.1 (rotamer 2), 52.8 (rotamer 1), 53.3 (rotamer 2), 58.5 (rotamer 1), 59.5 (rotamer 2), 67.8 (rotamer 1), 69.8 (rotamer 2), 89.2 (rotamer 1), 89.4 (rotamer 2), 123.6-124.3-127.6-127.8-144.5-145.1-148.0-148.7, (Ar) 168.0 (rotamer 1), 169.4 (rotamer 2) 170.0 (rotamer 1), 170.3 (rotamer 2).

(2*S*,4*S*)-3-acetyl-2-(4-nitrophenyl)oxazolidine-4-carboxylic acid (10). Oxazolidine **8** (129 mg, 0.4 mmol) was dissolved in THF (2 mL). At 0°C the mixture was cooled to 0°C and then 0.2 N LiOH (2 mL, 0.4 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solution was extracted by ethyl acetate, then acidified aqueous layer with $KHSO_4$ (5%) till pH 1–2, and then extracted with ethyl acetate. The combined organic layers were washed with 2 N NaCl, dried and concentrated to give 53 mg (44%) of **10** as light yellow oil. The crude product was used without further purification. ^{1}H NMR (300 MHz, MeOD): δ_H 1.86 (s, 3H, rotamer 1), 2.15 (s, 3H, rotamer 2), 4.26 (q, *J* 9.7, 6.6 Hz, 2H, rotamer 1), 4.36 (q, *J* 8.7, 3.0 Hz, 1H, rotamer 2), 4.84 (d, *J* 8.3 Hz, 1H, rotamer 1), 4.96 (d, *J* 5.8 Hz, 1H, rotamer 2), 6.38 (s, 1H, rotamer 1), 6.55 (s, 1H, rotamer 2), 7.65-7.75, 8.25-8.36 (m, 8H, Ar). ^{13}C NMR (300 MHz, MeOD): δ_C 7.6 (rotamer 1), 9.6 (rotamer 2) 46.8 (rotamer 1), 48.6 (rotamer 2), 56.0 (rotamer 1), 57.9 (rotamer 2), 77.5 (rotamer 1), 77.7 (rotamer 2), 111.4-112.0-115.8-116.2-133.6-135.8-136.4-138.0 (Ar), 157.3 (rotamer 1), 159.1 (rotamer 2), 159.8 (rotamer 1), 161.3 (rotamer 2).

Methyl ((2*S*,4*S*)-3-acetyl-2-(4-nitrophenyl)oxazolidine-4-carbonyl)-L-valinate (2a) was prepared from 49 mg (0.18 mmol) of **10,** 60 mg (0.31 mmol) of EDC, 37.8 mg (0.28 mmol) of HOBt, 32 mg (0.2 mmol) of L-valine methyl ester hydrochloride and 57 µL (0.5 mmol) of *N*-methyl morpholine in 4 mL of CH_2Cl_2 to provide 70 mg, 99% as yellow oil.

R_f = 0.69 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.95 (d, *J* 6.8 Hz, 6H, rotamer 1), 0.99 (d, *J* 6.8 Hz, 6H, rotamer 2), 1.85 (s, 3H, rotamer 1), 2.17 (s, 3H, rotamer 2), 1.89-1.96 (m, 1H, rotamer 1), 2.23-2.27 (m, 1H, rotamer 2), 3.18 (d, *J* 6.4 Hz, 1H), 3.29 (d, *J* 5.8 Hz, 1H), 3.75 (s, 6H), 4.11 (q, *J* 8.8, 5.3 Hz, 2H, rotamer 1), 4.36 (d, *J* 9.7 Hz, 1H, rotamer 1), 4.51 (q, *J* 4.8, 3.0 Hz, 2H, rotamer 2), 4.89 (d, *J* 5.5Hz, 1H, rotamer 2), 6.41 (s, 1H, rotamer 1), 6.60 (s, 1H, rotamer 2), 7.05 (NH, 1H, rotamer 1), 7.24 (NH, 1H, rotamer 2), 7.31-7.59, 8.20-8.31 (m, 8H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 17.7 (rotamer 1), 19.0 (rotamer 2), 22.7 (rotamer 1), 23.3 (rotamer 2), 30.7 (rotamer 2), 31.1 (rotamer 1), 52.2 (rotamer 1), 52.3 (rotamer 2), 57.4 (rotamer 1), 57.6 (rotamer 2), 59.5 (rotamer 2), 60.6 (rotamer 1), 67.4 (rotamer 1), 70.5 (rotamer 2), 89.5 (rotamer 1), 89.6 (rotamer 2), 123.6-124.3-127.6-127.8-144.5-145.1-148.0-148.7 (Ar), 168.5 (rotamer 2), 169.0 (rotamer 1), 169.5 (rotamer 1), 169.8 (rotamer 2), 172.0 (rotamer 1), 172.2 (rotamer 2).

[α] $^{20}_D$= - 86.9 (c = 0.7, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{18}H_{24}N_3O_7$ 394.1609 Found 394.1607.

Methyl ((2*S*,4*S*)-3-acetyl-2-(4-nitrophenyl)oxazolidine-4-carbonyl)-L-leucinate (2b) was prepared from 48 mg (0.17 mmol) of **10**, 59 mg (0.3 mmol) of EDC, 37 mg (0.27 mmol) of HOBt, 34 mg (0.18 mmol) of L-leucine methyl ester hydrochloride and *N*-methyl morpholine (94 µL, 0.5 mmol) in 4 mL of CH_2Cl_2 to provide 65 mg, 81% as yellow oil.

R_f = 0.74 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.89 (d, *J* 5.7 Hz, 6H, rotamer 1), 0.93 (d, *J* 6.2 Hz, 6H, rotamer 2), 1.55-1.63 (m, 2H), 1.66 (t, *J* 4.1 Hz, 4H), 1.85 (s, 3H, rotamer 2), 2.25 (s, 3H, rotamer 1), 3.75 (s, 6H), 4.08 (q, *J* 9.0, 6.9 Hz, 2H, rotamer 2), 4.23 (q, *J* 9.9, 7.1 Hz, 2H, rotamer 1), 4.38 (d, *J* 5.3 Hz, 1H, rotamer 1), 4.65 (dd, *J* 10.6, 5.1 Hz, 2H), 4.85 (d, *J* 8.8 Hz, 1H, rotamer 2), 6.41 (s, 1H, rotamer 1), 6.59 (s, 1H, rotamer 2), 7.11 (NH, 1H, rotamer 1), 7.14 (NH, 1H, rotamer 2), 7.51-7.59, 8.22-8.32 (m, 8H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 21.3 (rotamer 1), 21.9 (rotamer 2), 22.7 (rotamer 1), 22.8 (rotamer 2), 24.9 (Crotamer 1), 29.6 (rotamer 2), 40.2 (rotamer 1), 41.1 (rotamer 2), 51.0 (rotamer 1), 51.2 (rotamer 2), 52.4 (rotamer 1), 52.5 (rotamer 2), 59.5 (rotamer 2), 60.7 (rotamer 1), 67.3 (rotamer 2), 70.3 (rotamer 1), 89.5 (rotamer 2), 89.6 (rotamer 1), 123.8-124.3-127.5-127.7-144.4-144.6-148.1-148.6 (Ar), 168.5 (rotamer 1), 168.9 (rotamer 2), 169.7 (rotamer 1), 169.8 (rotamer 2), 172.9 (rotamer 1), 173.2 (rotamer 2).

[α] $^{20}_D$= - 101.8 (c = 0.4, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{19}H_{25}N_3O_7$ 408.176527 Found 408.176580.

Methyl 6-((2*S*,4*S*)-3-acetyl-2-(4-nitrophenyl)oxazolidine-4-carboxamido)hexanoate (2c) was prepared from 100 mg (0.36 mmol) of **10,** 130 mg (0.68 mmol) of EDC, 77 mg (0.57 mmol) of HOBt, 71 mg (0.39 mmol) of

methyl 6-aminohexanoate hydrochloride and 110 µL (1.07 mmol) of *N*-methyl morpholine in 8 mL of CH_2Cl_2 to provide 91.7 mg, 63%, as yellow oil.

R_f = 0.76 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.21-1.31 (m, 4H), 1.36-1.45 (m, 4H), 1.69-1.80 (m, 4H), 1.98 (s, 3H, rotamer 1), 2.17 (s, 3H, rotamer 2), 2.34 (t, *J* 7.3 Hz, 4H), 2.48 (t, *J* 5.7 Hz, 2H, rotamer 1), 3.24 (t, *J* 3.8 Hz, 2H, rotamer 2), 3.68 (s, 6H), 4.15 (q, *J* 8.3, 7.4 Hz, 2H rotamer 1), 4.54 (d, *J* 9.7 Hz, 1H, rotamer 1), 4.67 (q, *J* 5.2, 3.4 Hz, 2H, rotamer 2), 4.82 (d, *J* 6.5 Hz, 1H, rotamer 2), 6.17 (s, 1H, rotamer 1), 6.41 (s, 1H, rotamer 2), 7.23 (NH, 1H, rotamer 1), 7.31 (NH, 1H, rotamer 2), 7.69-7.86, 8.22-8.31 (m, 8H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 23.0 (rotamer 1), 23.2 (rotamer 2), 24.3 (rotamer 1), 26.3 (rotamer 2), 29.1 (rotamer 1), 29.7 (rotamer 2), 30.6 (rotamer 1), 33.6 (rotamer 2), 33.8 (rotamer 1), 36.6 (rotamer 2), 39.5 (romater 1), 42.9 (rotamer 2), 51.6 (rotamer 1), 51.7 (rotamer 2), 58.8 (rotamer 1), 60.9 (rotamer 2), 67.5 (rotamer 1), 70.9 (rotamer 2), 89.6 (rotamer 1), 90.2 (rotamer 2), 123.5-123.6-124.1-128.5-144.2-148.1-148.6-148.7 (Ar), 168.6 (rotamer 2), 168.8 (rotamer 1), 170.1 (rotamer 1), 171.0 (rotamer 2), 174.0 (rotamer 1), 179.0 (rotamer 2).

$[\alpha]$ $^{20}_D$= - 12.6 (c = 0.2, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{19}H_{26}N_3O_7$ 408.1765 Found 408.1766.

Methyl ((2*S*,4*S*)-3-acetyl-2-(4-nitrophenyl)oxazolidine-4-carbonyl)-L-phenylalaninate (2d) was prepared by reacting 50 mg (0.17 mmol) of **10**, 60 mg (0.32 mmol) of EDC, 38 mg (0.28 mmol) of HOBt, 40 mg (0.2 mmol) of L-phenylalanine methyl ester hydrochloride and (100 µL, 0.53 mmol) of *N*-methyl morpholine in 4 mL of CH_2Cl_2 to provide 71 mg, 90% as yellow oil.

R_f = 0.55 (ethyl acetate 100%). ^{1}H NMR (300 MHz, DMSO): δ_H 1.66 (s, 3H, rotamer 1), 1.68 (s, 3H, rotamer 2), 2.94 (q, *J* 10.8, 3.0 Hz, 2H, rotamer 1), 3.15 (dd, *J* 9.3, 4.6 Hz, 2H, rotamer 1), 3.60 (s, 3H, rotamer 1), 3.68 (s, 3H, rotamer 2), 3.93 (dd, *J* 8.5, 0.9 Hz, 2H, rotamer 2), 4.15 (q, *J* 6.7, 2.6 Hz, 2H, rotamer 2), 4.65 (t, *J* 8.4, 4.5 Hz, 2H), 4.71 (d, *J* 6.5 Hz, 1H, rotamer 1), 4.76 (d, *J* 6.6 Hz, 1H, rotamer 2), 6.29 (s, 1H, rotamer 1), 6.56 (s, 1H, rotamer 2), 7.21-7.31 (m, 10H, Ar), 7.66-7.76, 8.19-8.29 (m, 8H, Ar), 8.84 (NH, 1H, rotamer 1), 8.86 (NH, 1H, rotamer 2). ^{13}C NMR (300 MHz, DMSO): δ_C 22.5 (rotamer 1), 26.8 (rotamer 2), 36.7 (rotamer 1), 36.8 (rotamer 2), 52.6 (rotamer 1), 52.7 (rotamer 2), 53.6 (rotamer 1), 53.7 (rotamer 2), 59.7 (rotamer 1), 59.8 (rotamer 2), 70.5 (rotamer 1), 70.6 (rotamer 2), 88.9 (rotamer 1), 89.5 (rotamer 2), 123.8-124.4-126.9-127.0-128.4-128.6-128.7-128.8-129.5-129.6-137.6-137.8-146.5-146.7-147.9 (Ar), 168.9 (rotamer 1), 169.7 (rotamer 2), 169.9 (rotamer 1), 170.0 (rotamer 2), 172.1 (rotamer 1), 172.2 (rotamer 2).

$[\alpha]$ $^{20}_D$= -43.3 (c = 0.25, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{22}H_{24}N_3O_7$ 442.1608 Found 442.1606.

Methyl (2*S*,4*S*)-3-acetyl-2-(4-chlorophenyl)oxazolidine-4-carboxylate (9). The oxazolidine **9** was obtained by reacting 320 mg (2 mmol) of **7**, 4-chloro benzaldehyde dimethyl acetal (1.12 g, 5.9 mmol) and *p*-toluenesulfonic acid (7.8 mg, 0.045 mmol) in toluene (13 mL) to provide 351 mg, 62% as yellow oil. R_f = 0.83 ethyl acetate/cyclohexane (7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.85 (s, 3H, rotamer 1), 2.11 (s, 3H, rotamer 2), 3.82 (s, 3H, rotamer 1), 3.88 (s, 3H, rotamer 2), 4.15 (d, *J* 2.6 Hz, 1H, rotamer 1), 4.20 (q, *J* 6.6, 2.8 Hz, 2H, rotamer 1), 4.30 (d, *J* 5.6 Hz, 1H, rotamer 2), 4.82 (q, *J* 4.0, 2.6 Hz, 2H, rotamer 2), 6.28 (s, 1H, rotamer 1), 6.44 (s, 1H, rotamer 2), 7.32-7.35, 7.42-7.45 (m, 8H, Ar). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.8 (rotamer 1), 23.0 (rotamer 2) 52.7 (rotamer 1), 53.2 (rotamer 2), 58.4 (rotamer 1), 59.5 (rotamer 2), 67.5 (rotamer 1), 69.3 (rotamer 2), 89.8 (rotamer 1), 89.9 (rotamer 2), 127.8-128.1-128.6-129.3-134.6-135.8-136.3-136.6 (Ar), 168.3 (rotamer 1), 169.0 (rotamer 2) 170.2 (rotamer 1), 170.5 (rotamer 2).

(2*S*,4*S*)-3-acetyl-2-(4-chlorophenyl)oxazolidine-4-carboxylic acid (11). The product **11** was obtained by reacting of **9** (300 mg, 1 mmol) and 6.3 mL of lithium hydroxide (1.2 mmol) in 6.3 mL of tetrahydrofuran/H_2O (1:1) to give carboxylic acid as yellow oil (173 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.90 (s, 3H, rotamer 1), 2.20 (s, 3H, rotamer 2), 4.24 (q, *J* 6.1, 2.7 Hz, 2H), 4.36 (d, *J* 9.3Hz, 1H, rotamer 1), 4.65 (d, *J* 6.0 Hz, 1H, rotamer 2), 4.84 (q, *J* 3.2, 2.4 Hz, 2H, rotamer 2), 6.32 (s, 1H, rotamer 1), 6.46 (s, 1H, rotamer 2), 7.30-7.47 (m, 8H, Ar), 7.71 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.8 (rotamer 1), 22.9 (rotamer 2), 58.5 (rotamer 1), 59.4

(rotamer 2), 67.5 (rotamer 1), 69.3 (rotamer 2), 89.8 (rotamer 1), 89.9 (rotamer 2), 127.8-128.1-128.6-129.4-134.7-135.8-135.9-136.3 (Ar), 169.7 (rotamer 1), 170.6 (rotamer 2) 171.9 (rotamer 1), 172.1 (rotamer 2).

Methyl ((2*S*,4*S*)-3-acetyl-2-(4-chlorophenyl)oxazolidine-4-carbonyl)-L-valinate (3a) was prepared from 52 mg (0.19 mmol) of **11,** 66 mg (0.35 mmol) of EDC, 42 mg (0.30 mmol) of HOBt, 35 mg (0.21 mmol) of L-valine methyl ester hydrochloride and 64 µL (0.58 mmol) of *N*-methyl morpholine in 4.3 mL of CH_2Cl_2 to provide 56 mg, 76% as yellow oil. R_f = 0.73 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.94 (d, *J* 7.0 Hz, 6H, rotamer 1), 1.01 (d, *J* 6.8 Hz, 6H, rotamer 2), 1.84 (s, 3H, rotamer 1), 2.07 (s, 3H, rotamer 2), 2.14-2.29 (m, 2H), 3.48 (d, *J* 7.0 Hz, 1H), 3.70 (d, *J* 7.9 Hz, 1H), 3.77 (s, 6H), 3.78 (s, 6H), 4.09 (q, *J* 6.8, 2.1 Hz, 2H, rotamer 1), 4.38 (d, *J* 9.5 Hz, 1H, rotamer 1), 4.57 (q, *J* 5.1, 3.7 Hz, 2H, rotamer 2), 4.85 (d, *J* 5.4 Hz, 1H, rotamer 2), 6.29 (s, 1H, rotamer 1), 6.59 (s, 1H, rotamer 2), 7.31-7.59, 8.20-8.31 (m, 8H, Ar), 7.46 (NH, 1H, rotamer 1), 7.66 (NH, 1H, rotamer 2). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 17.7 (rotamer 1), 19.1 (rotamer 2), 30.7 (rotamer 1), 31.1 (rotamer 2), 52.2 (rotamer 1), 52.5 (rotamer 2), 57.3 (rotamer 1), 57.9 (rotamer 2), 59.5 (rotamer 1), 60.9 (rotamer 2), 66.7 (rotamer 1), 68.1 (rotamer 2), 89.9 (rotamer 1), 90.1 (rotamer 2), 127.7-128.0-128.7-128.8-129.0-129.3-135.7-136.1 (Ar), 168.8 (rotamer 1), 169.1 (rotamer 2), 170.0 (rotamer 1), 170.1 (rotamer 2), 171.9 (rotamer 1), 172.2 (rotamer 2).

[α] $^{20}_D$= - 61.9 (c = 0.25, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{18}H_{24}ClN_2O_5$ 382.1368 Found 383.1362.

Methyl ((2*S*,4*S*)-3-acetyl-2-(4-chlorophenyl)oxazolidine-4-carbonyl)-L-leucinate (3b) was prepared from 51 mg (0.19 mmol) of **11**, 65 mg (0.34 mmol) of EDC, 41 mg (0.3 mmol) of HOBt, 38 mg (0.2 mmol) of L-leucine methyl ester hydrochloride and *N*-methyl morpholine (100 µL, 0.57 mmol) in 4.3 mL of CH_2Cl_2 to provide 75 mg, 99% as yellow oil.

R_f = 0.78 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.97 (d, *J* 5.4Hz, 6H, rotamer 1), 1.15 (d, *J* 7.1 Hz, 6H, rotamer 2), 1.60-1.71 (m, 2H), 1.82 (s, 3H, rotamer 1), 1.88-2.15 (m, 2H, rotamer 1), 2.23 (s, 3H, rotamer 2), 2.32-2.50 (m, 2H, rotamer 2), 3.74 (s, 6H), 4.05 (d, *J* 6.9 Hz, 1H, rotamer 1), 4.10 (d, *J* 6.9 Hz, 1H, rotamer 2), 4.35 (d, *J* 9.1 Hz, 1H, rotamer 1), 4.59 (dd, *J* 8.4 Hz, 2H, rotamer 1), 4.64 (dd, *J* 6.6 Hz, 2H, rotamer 2), 4.82 (d, *J* 6.3 Hz, 1H, rotamer 2), 6.28 (s, 1H, rotamer 1), 6.54 (s, 1H, rotamer 2), 7.14-7.31 (m, 8H, Ar), 7.68 (NH, 1H, rotamer 1), 8.00 (NH, 1H, rotamer 2).^{13}C NMR (300 MHz, $CDCl_3$): δ_C 22.0 (rotamer 1), 22.8 (rotamer 2), 23.3 (rotamer 1), 24.9 (rotamer 2), 40.2 (rotamer 1), 41.2 (rotamer 2), 50.9 (rotamer 1), 51.0 (rotamer 2), 51.2 (rotamer 1), 51.8 (rotamer 2), 52.3 (rotamer 1), 52.4 (rotamer 2), 59.4 (rotamer 1), 60.8 (rotamer 2), 66.9 (rotamer 1), 69.8 (rotamer 2), 90.1 (rotamer 1), 90.2 (rotamer 2), 127.8-128.0-128.7-129.3-135.7-135.8-136.2-136.3 (Ar), 168.8 (rotamer 1), 169.0 (rotamer 2), 169.3 (rotamer 1), 169.4 (rotamer 2), 173.1 (rotamer 1), 173.2 (rotamer 2).

[α] $^{20}_D$= - 69.8 (c = 0.25, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{19}H_{26}ClN_2O_5$ 397.1524 Found 397.1521.

Methyl 6-((2*S*,4*S*)-3-acetyl-2-(4-chlorophenyl)oxazolidine-4-carboxamido)hexanoate (3c) was prepared from 38 mg (0.14 mmol) of **11,** 48 mg (0.25 mmol) of EDC, 30 mg (0.23 mmol) of HOBt, 28 mg (0.16 mmol) of methyl 6-aminohexanoate hydrochloride and 46 µL (0.42 mmol) of *N*-methyl morpholine in 3.2 mL of CH_2Cl_2 to provide 51 mg, 91% as yellow oil.

R_f = 0.80 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.35-1.42 (m, 4H), 1.53-1.58 (m, 4H), 1.61-1.69 (m, 4H), 1.82 (s, 3H, rotamer 1), 2.17 (s, 3H, rotamer 2), 2.34 (t, *J* 7.1Hz, 4H), 3.24 (t, *J* 5.9 Hz, 4H), 3.68 (s, 3H, rotamer 1), 3.69 (s, 3H, rotamer 2), 4.07 (q, *J* 6.5, 2.5 Hz, 2H, rotamer 1), 4.40 (d, *J* 6.3 Hz, 1H, rotamer 1), 4.55 (q, *J* 5.0 Hz, 2H, rotamer 2), 4.77 (d, *J* 9.0 Hz, 1H, rotamer 2), 6.30 (s, 1H, rotamer 1), 6.56 (s, 1H, rotamer 2), 7.23-7.41 (m, 8H, Ar), 7.43 (NH, 1H, rotamer 1), 7.46 (NH, 1H, rotamer 2). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 23.0 (rotamer 1), 23.1 (rotamer 2), 23.4 (rotamer 1), 24.4 (rotamer 2), 26.2 (rotamer 1), 28.9 (rotamer 2), 29.7 (rotamer 1), 30.5 (rotamer 2), 33.8 (rotamer 1), 36.4 (rotamer 2), 39.5 (rotamer 1), 42.9 (rotamer 2), 51.6 (rotamer 1), 51.7 (rotamer 2), 59.6 (rotamer 1), 61.0 (rotamer 2), 66.8 (rotamer 1), 66.9 (rotamer 2), 89.9

(rotamer 1), 90.1 (rotamer 2), 110.8-117.7-125.8-126.6-128.0-129.3-135.7-136.1 (Ar), 169.1 (rotamer 1), 169.3 (rotamer 2), 171.5 (rotamer 1), 171.6 (rotamer 2), 174.1 (rotamer 1), 174.2 (rotamer 2). [α] $^{20}_{D}$= - 60.0 (c = 0.2, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{19}H_{26}ClN_2O_5$ 396.1523 Found 396.1524.

Methyl ((2*S*,4*S*)-3-acetyl-2-(4-chlorophenyl)oxazolidine-4-carbonyl)-L-phenylalaninate (3d) was prepared by reacting 55 mg (0.2 mmol) of **11**, 71 mg (0.36 mmol) of EDC, 44 mg (0.32 mmol) of HOBt, 48 mg (0.22 mmol) of L-phenylalanine methyl ester hydrochloride and (62 µL, 0.61 mmol) of *N*-methyl morpholine in 4.6 mL of CH_2Cl_2 to provide 73 mg, 83% as yellow oil.

R_f = 0.62 (ethyl acetate 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.77 (s, 3H, rotamer 1), 2.14 (s, 3H, rotamer 2), 3.17 (dd, *J* 8.2, 6.0 Hz, 2H, rotamer 1), 3.26 (dd, *J* 8.5, 5.4 Hz, 2H, rotamer 2), 3.79 (s, 6H), 4.03 (q, *J* 6.8, 1.3 Hz, 2H, rotamer 1), 4.15 (d, *J* 7.1Hz, 1H, rotamer 1), 4.42 (t, *J* 9.3, 6.9 Hz, 2H), 4.81 (d, *J* 5.4 Hz, 1H, rotamer 2), 4.95 (q, *J* 6.7, 5.9 Hz, 2H, rotamer 2), 6.17 (s, 1H, rotamer 1), 6.47 (s, 1H, rotamer 2), 7.10 (NH, 1H, rotamer 1),7.21-7.43 (m, 18H, Ar), 7.46 (NH, 1H, rotamer 2). ^{13}C NMR (300 MHz, $CDCl_3$): δ_C 23.3 (rotamer 1), 23.4 (rotamer 2), 37.5 (rotamer 1), 37.7 (rotamer 2), 52.4 (rotamer 1), 52.6 (rotamer 2), 53.3 (rotamer 1), 53.4 (rotamer 2), 59.4 (rotamer 1), 59.5 (rotamer 2), 66.4 (rotamer 1), 66.3 (rotamer 2), 89.8 (rotamer 1), 89.9 (rotamer 2), 127.0-127.1-127.3-127.5-127.7-127.8-127.9-128.0-128.5-128.6-128.7-128.9-129.1-129.2-129.4-129.5 (Ar), 168.6 (rotamer 1), 168.8 (rotamer 2), 171.2 (rotamer 1), 171.3 (rotamer 2), 171.5 (rotamer 1), 171.6 (rotamer 2). [α] $^{20}_{D}$= - 54.2 (c = 0.4, CH_2Cl_2). HRMS (ES+: *m/z* $[M+H]^+$): Calcd for $C_{22}H_{24}ClN_2O_5$ 431.1368 Found 431.1189.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of compounds, noe of **2b** and HRMS of oxazolidinones and oxazolidines are given in the Supplementary Material file associated with this manuscript.

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