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Diastereoselective synthesis of 5-iminooxazolines and their subsequent transformation to α,α-disubstituted dipeptide esters: a formal [4+1] cycloaddition reaction of cyclohexyl isocyanide and *Z*-alkyl-α-benzoyl amino-acrylates

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ABSTRACT

A novel atom economical diastereoselective synthesis of 5-iminooxazolines and their subsequent transformation to α,α-disubstituted dipeptide esters is described. Heating a mixture of cyclohexyl isocyanide and *Z*-α-benzoyl amino-acrylic acid alkyl esters under solvent-free conditions, afforded 5-iminooxazolines, which, upon specifications provided α,α-disubstituted dipeptide esters in good yield.

1. Introduction

Peptide containing drugs typically present higher bactericidal strength and a lower tendency for generating resistance compared to common antibiotics, such as penicillin and sulfonamides. Nevertheless, the use of peptide drugs is limited due to their low metabolic stability and poor pharmacokinetic properties.[1–3] The fast degradation by proteases, low lipophilicity, and the lack of direct transition into cells systems, are the major disadvantages of peptide drugs. Cell membranes generally resist the transport of most peptides, and peptide drugs are rapidly excreted through the liver and kidney. Conformational flexibility of peptides, which, allows a peptide to bind to more than one receptor, leads to undesired side effects, creating another problem.[4,5] Incorporation of conformationally constrained amino acids, such as α,α-disubstituted α-amino acids into key positions of peptides chains is an efficient strategy to retard proteolytic degradation and to stabilize secondary structure motifs.[6,7] As a result of such activities, the advantage of the modification of natural peptides has been showed by increasing the potency, and selectivity, decreasing the side effects, and improving the half-life of compound by minimizing enzymatic degradation.[8]

Isocyanides have been recognized as crucial building blocks in modern organic synthesis.[9] This unusual reactivity offers constructs substituted heterocyclic compound and has attracted significant attention in recent years. This reactivity involves the α-addition of both nucleophiles and electrophiles on the same carbon atom of the functional group.[9a] Five-membered, nitrogen-containing heterocycles are found in a broad number of biologically active compounds.[10] In terms of five-membered ring construction, a [4+1] mode, in which 1,3-conjugated systems act as four-atom assembling units, were reported as an interesting reaction of isocyanides. A variety of these [4+1] cycloaddition reactions involving a wide range of substrates, such as α,β-unsaturated carbonyl compounds,[11] quinonemethides,[12] thioxothiamides,[13] azadienes,[14] and vinyl isocyanates,[15] with isocyanides have been carried out. Among five-membered nitrogen-containing heterocycles, the 5-iminooxazolines, are infrequently reported in the literature, and besides its hydrolysis to dipeptides, little is known about their chemistry. Moreover, they are valuable synthetic intermediates due to the ease of hydrolyses to α,α-disubstituted dipeptide esters. Recently, Burger et al. reported that imines of hexafluoroacetone and methyl 3,3,3-trifluoropyruvate, can able to undergo [4+1] cycloaddition with α,α-disubstituted-α-isocyanatoesters, leading to the 5-iminooxazolines, which can be easily

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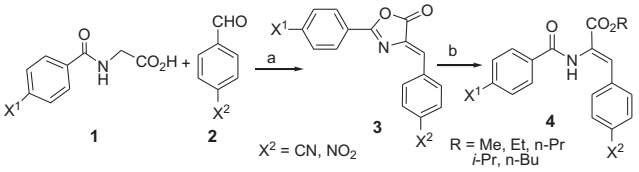
hydrolyzed under mild acidic conditions to give the corresponding α,α-disubstituted dipeptide esters.[16] In 2007, Zhu et al.[17] reported that three-component reaction of α,α-disubstituted α-isocyanoacetamide with an aldehyde and an amine, providing access to 5-iminooxazolines, which can be readily transformed into cyclic dipeptides under mild acidic conditions.

In last decade, the development in the field of solvent-free reactions have provided organic chemists with new simple efficient synthetic routes of great promise.[18]

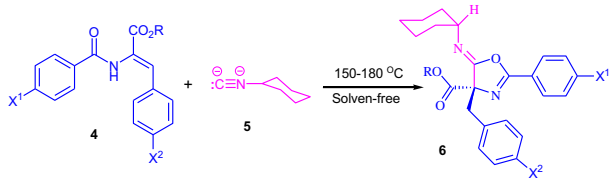
As part of our ongoing efforts on the development of new approaches to the preparation of heterocyclic compounds,[19] we report herein a new and efficient manner for synthesis of 5-iminoxazoline with potency transform to α,α-disubstituted α-amino acid derivatives. To the best of our knowledge, the formation of 5-iminooxazolines from the reaction of cyclohexyl isocyanide and *Z*-α-benzoylamino acrylates were unprecedented at the time of our studies.

For this purpose, we have utilized α-amidoacrylates building block **4**, (Scheme 1) resulting from the Erlenmeyer reaction of aromatic aldehydes with hippuric acid followed by an oxazolone ring opening alcoholysis, in the reaction with cyclohexyl isocyanide at 140–210 °C, under solvent-free conditions (Table 1). On the basis of our experience in the introduction of 5-iminooxazolines **6**, we decided to test these five-membered rings scaffolds with the goal of obtaining a small library *N*-benzoyl-*N*-cyclohexyl phenylalaninamides as peptidomimetics scaffold **7** (Table 2).



Scheme 1. General synthesis of alkyl *Z*-α-benzoylamino acrylate, reagent: (a) CH_3CO_2Na/Ac_2O and (b) RONa, ROH.

Table 1
Syntheses of 5-iminooxazolines **6** from reaction of *Z*-α-benzoyl amino-acrylic acid alkyl esters **4** and cyclohexyl isocyanide **5**



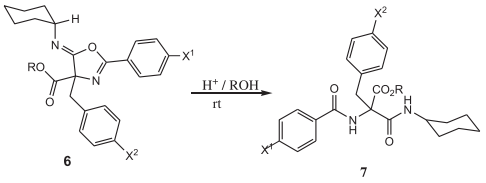
Product	X^1	X^2	R	*T* (°C)[a]	Time (h)	Yield[b]
6a	H	NO_2	Me	190	0.5	55%
6b	H	NO_2	Et	175	1.5	79%
6c	H	NO_2	Pr	175	2	93%
6d	H	NO_2	*i*-Pr	180	2.5	60%
6e	H	NO_2	Bu	150	6	54%
6f	H	CN	Me	175	1	69%
6g	H	CN	Et	155	1.25	52%
6h	H	CN	Pr	170	2	78%
6i	H	CN	*i*-Pr	210	1.25	68%
6j	H	CN	Bu	140	2.5	65%
6k	OMe	NO_2	Me	185	0.25	51%
6l	OMe	NO_2	Pr	193	2.5	40%

[a] Reaction Temperature.
[b] Isolated yields.

2. Results and discussion

In a model reaction, *Z*-methyl-2-(benzamido)-3-(4-nitrophenyl) acrylate **4**,[20,21] and cyclohexyl isocyanide were stirred under solvent-free condition at 190 °C. The reaction was completed within 0.5 h to produce (5*Z*)-ethyl 4-(4-nitrobenzyl)-5-(cyclohexylimino)-4,5-dihydro-2-phenyloxazole-4-carboxylate **6a** in 55% yield (Table 1, entry 1). To explore the scope of this reaction further, *Z*-alkyl 2-(benzamido)-3-(4-X^2-phenyl)acrylates **4**, were used under similar conditions; however the reaction did not proceed for X^2=H and X^2=EDG. It is worth noting that an electron withdrawing group on the para position of Ph-CH=moiety (X^2=EWG) had an important role in the reaction pathway and presence of this moiety is essential for reaction to proceed. Two other isocyanides, *tert*-butylisocyanide and 1,1,3,3-tetramethylbutylisocyanide were also examined, but no conversion occurred.

Table 2
Syntheses of α,α-disubstituted α-amino acid amides **7** fromhydrolysis of 5-iminooxazolines **6** with alcoholic hydrochloric acid



Product	X^1	X^2	R	Yield (%)[a]
7a	H	NO_2	Pr	55
7b	H	NO_2	Bu	85
7c	H	CN	Me	96
7d	H	CN	*i*-Pr	75

[a] Isolated yields.

The structures of compounds **6a–j** were deduced from their elemental analysis, mass, IR, and high-field ^{1}H and ^{13}C NMR spectra (see Supplementary data). The mass spectrum of **6a** displayed the molecular ion peak at *m*/*z* 435, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the one NO_2 group at 1347, and 1518 cm^{-1}, two C=N groups at 1645, 1738 cm^{-1} and the carbonyl group at 1748 cm^{-1}. The ^{1}H NMR spectrum of **6a**, exhibited mutiplet signals for the cyclohexyl ring (δ=1.09–1.75 ppm), two doublet for diastereotopic methylene protons of CH_2Ph moity (δ=3.52 and 3.69 ppm), a mutiplet for NCH of cyclohexyl ring (δ=3.59 ppm), a singlet for methoxy group (δ=3.77 ppm), and two multiplets for the aromatic protons (δ=7.36–7.46 and 7.50–7.99 ppm). The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 20 distinct resonances in agreement with the suggested structure, partial assignment of these resonances is given in the experimental section. Charactristic ^{13}C NMR signals were showed due to one ester carbonyl at δ=154.02 and two C=N groups at δ=163.6 and 168.3. The ^{1}H and ^{13}C NMR of **6b–j** are similar to those for **6a** except for ester and aromatic moieties. Unambiguous evidence for the structure and stereochemistry of **6d** was obtained from a single-crystal X-ray analysis. An ORTEP[22] diagram of **6d** is shown in Fig. 1. The

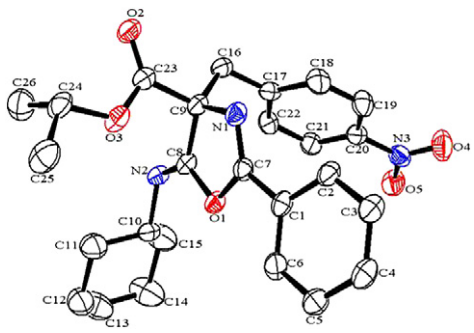
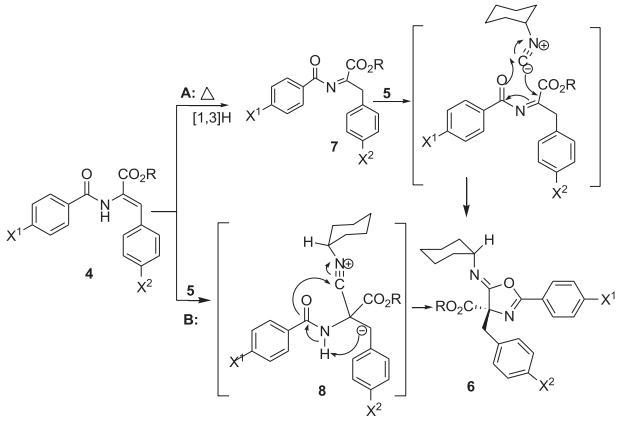


Fig. 1. Single-crystal X-ray structure (ORTEP) of **6d**.

stereochemistry was deduced from the crystallographic data and the same configuration was assumed for the other products on account of their NMR spectroscopic similarities.

A mechanistic rationalization for this reaction is provided in Scheme 2. Initially, isomerization of species **4**, gives *N*-benzoylimine intermediate **7**, followed by [4+1] cycloaddition reaction with cyclohexyl isocyanide affords the products (path A). Addition of isocyanide **5** to α-amidoacrylate **4**, forms intermediate **8**, then intramolecular cyclization rapidly produces product **6** (path B). The efficient conversion of α-amidoacrylate **4**, involving electron windrowing (EW) substituent in the para position of phenyl group (X^2=NO_2 and CN), supported the mechanism reaction sequence outlines in path B.



Scheme 2. Proposed mechanisms for the formation of compound **6**.

The synthetic scope of this new reaction is increased by the potential for hydrolysis of the 5-iminooxazolines. For instance, hydrolysis of 5-iminooxazolines **6c**, **6e**, **6f** and **6i** with alkoholic hydrochloric acid[16] at room temperature provides corresponding α,α-disubstituted α-amino acid esters **7a**–**d** in good yields (Table 2).

The structures of compounds **7a**–**d** were deduced from their elemental analysis, mass, IR, and high-field ^{1}H and ^{13}C NMR spectra (see Supplementary data). The mass spectrum of **7a** displayed the molecular ion peak at *m*/*z* 481, which is in agreement with the proposed structure. The IR spectrum of this compound showed two NH groups at 3349, absorption bands due to the one NO_2 group at 1320, and 1500 cm^{-1}, two carbonyl groups at 1654 and 1725 cm^{-1}. The ^{1}H NMR spectrum of **7a**, exhibited triplet signal of $OCH_2CH_2CH_3$ at 0.88 ppm, mutiplet signals for the cyclohexyl ring and $OCH_2CH_2CH_3$ (δ=1.15–1.97 ppm), two diastereotopic doublet for methylene protons of CH_2Ph moiety (δ=3.64 and 4.13 ppm), a mutiplets for NCH of cyclohexyl ring (δ=3.59 ppm), a doublet for NHCH (δ=6.20 ppm), a singlet for NH-CO (7.62 ppm), along with the aromatic protons (δ=7.36–7.46 and 7.5–7.99 ppm). The ^{1}H-decoupled ^{13}C NMR spectrum of **7a** showed 22 distinct resonances in agreement with the recommended structure, partial assignment of these resonances is given in the experimental section. Characteristic ^{13}C NMR signals were due to two ester carbonyl at δ=154.0 and 166.4 and one ester carbonyl group at δ=170.7. The ^{1}H and ^{13}C NMR of **7b**–**d** are similar to those for **7a** except for ester and aromatic moieties.

In summary, we have introduced a new and efficient method for the diastereoselective synthesis of 5-iminooxazolines, which could be easily hydrolyzed under alcoholic acidic conditions to afford the corresponding α,α-disubstituted α-amino acid esters with the potential to undergo further hydrolysis for incorporation into key position of peptides for use in the retardation of proteolytic degradation and to stabilize secondary structure motifs. Main advantages of our method are: (1) All atoms of two reactants are incorporated into the desired 5-iminooxazolines, that is, this reaction is 100% atom-economic; (2) A formal [4+1] Cycloaddition reaction of cyclohexyl isocyanide and *Z*-alkyl-α-benzoyl aminoacrylates, provides an efficient route to diastereoselective synthesis of 5-Iminooxazolines in good yeilds; (3) The use of simple and ready available isocyanide along with the simplicity of its method makes it a novel route for syntheses of 5-iminooxazolines.

3. Experimental

3.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN–*O*-Rapid analyzer. IR spectra were measured on a Perkin–Elmer 783 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.46 MHz, respectively. Mass spectra were recorded on a Shimadzu GC–MS-QP5050 mass spectrometer operating at an ionization potential of 70 eV isocyanides were obtained from Merck (Germany) and Fluka (Buchs, Switzerland), (*Z*)-alkyl 2-(benzamido)-3-aryl acrylates (α-amidoacrylate) prepared by known method[20,21] and all materials were used without further purification. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV254 plates.

3.2. General procedure for the synthesis of products 6

(*Z*)-Alkyl 2-(benzamido)-3-aryl acrylate (1 mmol) was placed in a capped test tube, and was heated to its melting point. Then cyclohexyl isocyanide (1 mmol) was added. The mixture was stirred for 5 min, then the temperature was increased to those stated and stirring was continued for an appropriate time (Table 1). The reaction mixture was cooled to room temperature. Pure product **6** was isolated by preparative plate chromatography eluted with *n*-hexane:EtOAc.

*3.2.1. Methyl (5Z)-5-(cyclohexylimino)-4-(4-nitrobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6a**).* Brown oil, 0.24 g, Yield 55%. R_f (25% EtOAc/*n*-hexane) 0.34; IR (KBr) (ν_{max}, cm^{-1}): 1748 (C=O), 1738, 1645 (C=N), 1518, 1347 (NO_2). Anal. calcd for $C_{24}H_{25}N_3O_5$ (436): C, 66.19; H, 5.79; N, 9.65% found: C, 65.88; H, 5.82; N, 9.68% MS (EI, 70 eV): *m*/*z* (%)=436 (M^++1, 1.46), 435 (M^+, 4.36), 376 ($M^+-CH_3CO_2$, 2.59), 299 ($M^+-CH_2C_6H_4NO_2$, 23.13), 217 (M^++1-$C_6H_{11}-CH_2C_6H_4NO_2$, 41.19), 105 (PhCO, 100),77 (Ph, 19.81). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H=1.09–1.75 (10H, m, 5 CH_2 of cyclohexyl), 3.52 (1H, d, $^2J_{HH}$=13.4 Hz, $CH_AH_BC_6H_4NO_2$), 3.59 (1H, m, HC–N), 3.69 (1H, d, $^2J_{HH}$=13.4 Hz, $CH_AH_BC_6H_4NO_2$), 3.77 (3H, s, OCH_3), 7.36–7.47 (4H, m, arom), 7.50–7.55 (1H, m, arom), 7.86 (2H, m, arom), 7.99 (2H, d, $^3J_{HH}$=8.70 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=24.5, 24.6, 25.5, 33.3, 33.5 (5 CH_2 of cyclohexyl), 40.6 ($CH_2-C_6H_4NO_2$), 53.5 (OCH_3), 58.0 (HC–N), 76.7 (C), 122.8 (2 CH_{arom}), 125.4 (C_{arom}), 128.1, 128.7, 131.9 (3 CH_{arom}), 133.2 (CH_{arom}), 142.4 (C_{arom}), 147.1 (C_{arom}), 154.0 (C=O), 163.6, 168.3 (2C=N).

*3.2.2. Ethyl (5Z)-5-(cyclohexylimino)-4-(4-nitrobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate(**6b**).* Yellow crystal, 0.35 g, Yield 79%; mp: 104–106 °C. R_f (50% EtOAc/n-hexane) 0.47; IR (KBr) (ν_{max}, cm^{-1}): 1745 (C=O), 1730, 1639 (C=N), 1514, 1341 (NO_2). Anal. Calcd for $C_{25}H_{27}N_3O_5$ (449): C, 66.80; H, 6.05; N, 9.35%, found: C, 67.12; H, 6.24; N, 9.45%. MS (EI, 70 eV): *m*/*z* (%)=449 (M^+, 1.17), 376 ($M^+-CH_3CH_2CO_2$, 1.98), 313 ($M^+-CH_2C_6H_4NO_2$, 8.45), 231 (M^++1-$C_6H_{11}-CH_2C_6H_4NO_2$, 14.57), 105 (PhCO, 100), 77 (Ph, 22.60). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H=1.23 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2CH_3), 1.26–1.82 (10H, m, 5 CH_2 of cyclohexyl), 3.52 (1H, d, $^2J_{HH}$=13.5 Hz,

CH_AH_B–$C_6H_4NO_2$), 3.60 (1H, m, HC–N), 3.69 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–$C_6H_4NO_2$), 4.15 (1H, m, $OCH_AH_BCH_3$), 4.33 (1H, m, $OCH_AH_BCH_3$), 7.37–7.44 (4H, m, arom) 7.53 (1H, m, arom), 7.87 (2H, d, $^3J_{HH}$=7.3 Hz, arom), 7.99 (2H, d, $^3J_{HH}$=8.6 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=14.0 (OCH_2CH_3), 24.5, 24.6, 25.6, 33.3, 33.5, (5 CH_2 of cyclohexyl), 40.4 (CH_2–$C_6H_4NO_2$), 57.9 (OCH_2CH_3), 62.5 (HC–N), 76.7 (C), 122.8 (2 CH_{arom}), 125.5 (C_{arom}), 128.1, 128.7, 131.8 (6 CH_{arom}), 132.8 (C_{arom}), 142.6 (CH_{arom}), 147.1 (C_{arom}), 154.3 (C=O), 163.6, 167.7 (2C=N).

*3.2.3. n-Propyl (5Z)-5-(cyclohexylimino)-4-(4-nitrobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6c**).* Brown solid, 0.43 g, Yield 93%; mp: 108–110 °C. R_f (50% EtOAc/n-hexane) 0.50; IR (KBr) (ν_{max}, cm^{-1}): 1747 (C=O), 1729, 1638 (C=N), 1515, 1341 (NO_2). Anal. calcd for $C_{26}H_{29}N_3O_5$ (463): C, 67.37; H, 6.31; N, 9.07% found: C, 67.47; H, 6.32; N, 9.25%. MS (EI, 70 eV): *m*/*z* (%)=464 (M^++1, 1.53), 463 (M^+, 3.93), 376 (M^+–$CO_2CH_2CH_2CH_3$, 4.92), 327 (M^+–$CH_2C_6H_4NO_2$, 15.90), 245 (M^++1-C_6H_{11}–$CH_2C_6H_4NO_2$, 22.50), 105 (PhCO, 100), 77 (Ph, 14.48). ^{1}H NMR (300.13 MHz, acetone-d_6): δ_H=0.88 (3H, t, $^3J_{HH}$=7.4 Hz, $OCH_2CH_2CH_3$), 1.28–1.81 (12H, m, 5 CH_2 of cyclohexyl, $OCH_2CH_2CH_3$), 3.51 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–$C_6H_4NO_2$), 3.66 (1H, m, HC–N), 3.70 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–$C_6H_4NO_2$), 4.07 (1H, m, $OCH_AH_BCH_2CH_3$), 4.22 (1H, m, $OCH_AH_BCH_2CH_3$), 7.47–7.53 (4H, m, arom), 7.61 (1H, m, arom), 7.90–7.94 (2H, m, arom), 8.04–7.08 (2H, m, arom). ^{13}C NMR (75.47 MHz, acetone-d_6): δ_C=10.5 ($OCH_2CH_2CH_3$), 22.5 ($OCH_2CH_2CH_3$), 25.0, 25.0, 26.3, 34.1, 34.5 (5 CH_2 of cyclohexyl), 40.9 (CH_2-$C_6H_4NO_2$), 58.2 ($OCH_2CH_2CH_3$), 68.2 (HC–N), 77.5 (C), 123.4 (2 CH_{arom}), 126.6 (C_{arom}), 128.8, 129.7, 133.0 (6 CH_{arom}), 133.7 (C_{arom}), 143.8 (CH_{arom}), 148.0 (C_{arom}), 155.1 (C=O), 164.2, 168.5 (2C=N).

*3.2.4. Isopropyl (5Z)-5-(cyclohexylimino)-4-(4-nitrobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate(**6d**).* Yellow crystals, 0.28 g, Yield 60%; mp: 140–143 °C. R_f (40% EtOAc/n-hexane) 0.46; IR (KBr) (ν_{max}, cm^{-1}): 1742 (C=O), 1732, 1637 (C=N), 1514, 1339 (NO_2). Anal. calcd for $C_{26}H_{29}N_3O_5$ (463): C, 67.37; H, 6.31; N, 9.07% found: C, 67.15; H, 6.12; N, 9.21% MS (EI, 70 eV): *m*/*z* (%)=464 (M^++1, 1.83), 463 (M^+, 3.74), 376 (M^+–$(CH_3)_2CHCO_2$, 7.71), 327 (M^+–$CH_2C_6H_4NO_2$, 12.57), 245 (M^++1-C_6H_{11}, $CH_2C_6H_4NO_2$, 7.97), 105 (PhCO, 100), 77 (Ph, 15.12). ^{1}H NMR (300.13 MHz, acetone-d_6): δ_H=1.18 (3H, d, $^3J_{HH}$=6.3 Hz, CH_3), 1.21 (3H, d, $^3J_{HH}$=6.23 Hz, CH_3), 1.26–1.76 (10H, m, 5 CH_2 of cyclohexyl), 3.49 (1H, d, $^2J_{HH}$=13.4 Hz, CH_AH_B–$C_6H_4NO_2$), 3.67 (1H, m, HC–N), 3.68 (1H, d, $^2J_{HH}$=13.4 Hz, $CH_AH_BC_6H_4NO_2$), 5.06 (1H, sep, $^3J_{HH}$=6.24 Hz, $(CH_3)_2CHCO_2$), 7.47–7.53 (4H, m, arom), 7.61 (1H, m, arom), 7.90–7.93 (2H, m, arom), 8.04–8.08 (2H, m, arom). ^{13}C NMR (75.47 MHz, acetone-d_6): δ_C=21.5, 21.6 [$(CH_3)_2CHCO_2$], 25.0, 26.4, 34.1, 34.3, (5 CH_2 of cyclohexyl), 40.8 (CH_2–$C_6H_4NO_2$), 58.1 [$(CH_3)_2CHCO_2$], 70.6 (HC-N), 77.5 (C), 123.4 (2 CH_{arom}), 126.7 (C_{arom}), 128.8, 129.7, 133.0 (6 CH_{arom}), 133.7 (C_{arom}), 144.0 (CH_{arom}), 148.0 (C_{arom}), 155.2 (C=O), 164.1, 167.9 (2C=N).

*3.2.5. n-Butyl (5Z)-5-(cyclohexylimino)-4-(4-nitrobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6e**).* Yellow precipitation, 0.26 g, Yield 54%; mp: 99–101 °C. R_f (40% EtOAc/n-hexane) 0.41; IR (KBr) (ν_{max}, cm^{-1}): 1740 (C=O), 1726, 1640 (C=N), 1512, 1335 (NO_2). Anal. Calcd for $C_{27}H_{31}N_3O_5$ (477): C, 67.91; H, 6.54; N, 8.80% found: C, 68.01; H, 6.34; N, 8.71%. MS (EI, 70 eV): *m*/*z* (%)=478 (M^++1, 1.72), 477 (M^+, 3.68), 376 (M^+–$CO_2CH_2CH_2CH_2CH_3$, 4.75), 341 (M^+–$CH_2C_6H_4NO_2$, 13.97), 259 (M^+–C_6H_{11}–$CH_2C_6H_4NO_2$, 17.05), 105 (PhCO, 100), 77 (Ph, 11.70). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=0.87 (3H, t, $OCH_2CH_2CH_2CH_3$, $^3J_{HH}$=7.37 Hz), 1.21–1.78 (14H, m, 5CH_2 of cyclohexyl, $OCH_2CH_2CH_2CH_3$), 3.52 (1H, d, $^2J_{HH}$=13.51 Hz, CH_AH_B–$C_6H_4NO_2$), 3.59 (1H, m, HC–N), 3.70 (1H, d, $^2J_{HH}$=13.48 Hz, CH_AH_B–$C_6H_4NO_2$), 4.11 (1H, m, $OCH_AH_BCH_3CH_2CH_2$), 4.28 (1H, m, OCH_AH_B–$CH_3CH_2CH_2$), 7.37–7.45 (4H, m, arom), 7.54 (1H, m, arom), 7.86 (2H, m, arom), 7.99 (2H, d, $^3J_{HH}$=8.63 Hz, arom) ppm ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=13.6 ($OCH_2CH_2CH_2CH_3$), 18.9 ($OCH_2CH_2CH_2CH_3$), 24.6, 24.6, 25.6 (3 CH_2 of cyclohexyl), 30.4 ($OCH_2CH_2CH_2CH_3$) 33.3, 33.5 (2 CH_2 of cyclohexyl), 40.4 (CH_2–$C_6H_4NO_2$), 57.9 ($OCH_2CH_2CH_2CH_3$), 66.3 (HC–N), 77.1 (C), 122.8 (2 CH_{arom}), 125.5 (C_{arom}), 128.1, 128.7, 131.9 (6 CH_{arom}), 132.8 (C_{arom}), 142.6 (CH_{arom}), 147.0 (C_{arom}), 154.2 (C=O), 163.6, 167.8 (2C=N).

*3.2.6. Methyl (5Z)-5-(cyclohexylimino)-4-(4-cyanobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6f**).* Yellow crystal, 0.29 g, Yield 69%; mp: 102–104 °C. R_f (25% EtOAc/n-hexane) 0.38; IR (KBr) (ν_{max}, cm^{-1}): 2213 (CN), 1748 (C=O), 1730, 1639 (C=N). Anal. calcd for $C_{25}H_{25}N_3O_3$ (415): C, 72.27; H, 6.06; N, 10.11% found: C, 72.51; H, 6.23; N, 10.28%. MS (EI, 70 eV): *m*/*z* (%)=416 (M^++1, 3.81), 415 (M^+, 5.84), 400 (M^+–CH_3, 0.58), 356 (M^+–CO_2CH_3, 3.29), 299 (M^+–$CH_2C_6H_4CN$, 35.04), 217 (M^++1-C_6H_{11}–$CH_2C_6H_4CN$, 61.82), 105 (PhCO, 100), 77 (Ph, 20.28). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H=1.21–1.76 (10H, m, 5 CH_2 of cyclohexyl), 3.47 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–C_6H_4CN), 3.56 (1H, m, HC–N), 3.64 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–C_6H_4CN), 3.77 (3H, s, OCH_3), 7.32 (2H, d, $^3J_{HH}$=8.0 Hz, arom), 7.41–7.45 (4H, m, arom), 7.51–7.56 (1H, m, arom), 7.87 (2H, d, $^3J_{HH}$=7.3 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=24.55, 24.7, 25.6, 33.3, 33.5 (5 CH_2 of cyclohexyl), 41.0 ($CH_2C_6H_4CN$), 53.5 (OCH_3), 58.0 (HC–N), 76.7 (C), 111.0 (CN), 118.8, 125.5 (2C_{arom}), 128.1, 128.7, 131.5, 131.8 (8 CH_{arom}), 132.9 (C_{arom}), 140.3 (CH_{arom}), 154.1(C=O), 163.5, 168.3 (2C=N).

*3.2.7. Ethyl (5Z)-5-(cyclohexylimino)-4-(4-cyanobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6g**).* Yellow precipitation, 0.22 g, Yield 52%; mp: 117–118 °C. R_f (25% EtOAc/n-hexane) 0.40; IR (KBr) (ν_{max}, cm^{-1}): 2218 (CN), 1745 (C=O), 1728, 1640 (C=N). Anal. Calcd for $C_{26}H_{27}N_3O_3$ (429): C, 72.71; H, 6.34; N, 9.78% found: C, 73.00; H, 6.46; N, 9.87%. MS (EI, 70 eV): *m*/*z* (%)=430 (M^++1, 1.18), 429 (M^+, 6.13), 400 (M^+–CH_2CH_3, 1.16), 356 (M^+–$CH_2CH_3CO_2$, 5.35), 313 (M^+–$CH_2C_6H_4CN$, 23.55), 231 (M^++1-C_6H_{11}–$CH_2C_6H_4CN$, 37.29), 105 (PhCO, 100), 77 (Ph, 15.12). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H=1.11–2.01 (13H, m, 5 CH_2 of cyclohexyl, OCH_2CH_3), 3.48 (1H, d, $^2J_{HH}$=13.49 Hz, CH_AH_B–C_6H_4CN), 3.57 (1H, m, HC–N), 3.65 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–C_6H_4CN), 4.17 (1H, m, $OCH_AH_BCH_3$), 4.34 (1H, m, $OCH_AH_BCH_3$), 7.31–7.59 (7H, m, arom), 7.88 (2H, d, $^3J_{HH}$=7.5 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=14.0 (OCH_2CH_3), 24.6, 24.6, 25.6, 33.3, 33.6 (5 CH_2 of cyclohexyl), 40.8 ($CH_2C_6H_4CN$), 57.9 (OCH_2CH_3), 62.5 (HC–N), 76.7 (C), 110.9 (CN), 118.9, 125.6 (2C_{arom}), 128.1, 128.7, 131.4, 131.8 (8 CH_{arom}), 132.8 (C_{arom}), 140.4 (CH_{arom}), 154.3 (C=O), 163.5, 167.8 (2C=N).

*3.2.8. n-Propyl (5Z)-5-(cyclohexylimino)-4-(4-cyanobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6h**).* Yellow solid, 0.34 g, Yield 78%; mp: 122–125 °C. R_f (25% EtOAc/n-hexane) 0.38; IR (KBr) (ν_{max}, cm^{-1}): 2208 (CN), 1741 (C=O), 1731, 1641 (C=N). Anal. Calcd for $C_{27}H_{29}N_3O_3$ (443): C, 73.11; H, 6.59; N, 9.47% found: C, 73.33; H, 6.72; N, 9.39%. MS (EI, 70 eV): *m*/*z* (%)=444 (M^++1, 2.15), 443 (M^+, 4.63), 400 (M^+–$CH_2CH_2CH_3$, 1.22), 356 (M^+–$CO_2CH_2CH_2CH_3$, 6.16), 327 (M^+–$CH_2C_6H_4CN$, 20.27), 245 (M^++1-C_6H_{11}, $CH_2C_6H_4CN$, 30.29), 105 (PhCO, 100), 77 (Ph, 16.24). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=0.88 (3H, t, $^3J_{HH}$=7.4 Hz, $OCH_2CH_2CH_3$), 1.21–1.78 (12H, m, 5 CH_2 of cyclohexyl, $OCH_2CH_2CH_3$), 3.48 (1H, d, $^2J_{HH}$=13.5 Hz, CH_AH_B–$C_6H_4NO_2$), 3.58 (1H, m, HC–N), 3.65 (1H, d, $^2J_{HH}$=13.4 Hz, CH_AH_B–$C_6H_4NO_2$), 4.06 (1H, m, $OCH_AH_BCH_2CH_3$), 4.23 (1H, m, $OCH_AH_BCH_2CH_3$), 7.33 (2H, d, $^3J_{HH}$=8.1 Hz, arom), 7.42–7.46 (4H, m, arom), 7.54 (1H, m, arom), 7.87 (2H, d, $^3J_{HH}$=7.3 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=10.2 ($OCH_2CH_2CH_3$), 21.8 ($OCH_2CH_2CH_3$), 24.6, 24.7, 25.6, 33.3, 33.5 (5 CH_2 of cyclohexyl), 40.7 (CH_2–C_6H_4CN), 57.9 ($OCH_2CH_2CH_3$), 67.9 (HC–N), 76.7 (C), 110.8 (CN), 118.9, 125.6

($2C_{arom}$),128.1, 128.7, 131.4, 131.8 (8 CH_{arom}), 132.8 (C_{arom}), 140.4 (CH_{arom}), 154.3 (C=O), 163.5, 167.9 (2C=N).

*3.2.9. Isopropyl (5Z)-5-(cyclohexylimino)-4-(4-cyanobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6i**).* Brown solid, 0.30 g, Yield 68%; mp: 130–133 °C. R_f (30% EtOAc/n-hexane) 0.50; IR (KBr) (ν_{max}, cm^{-1}): 2213 (CN), 1743 (C=O), 1730, 1640 (C=N).). Anal. Calcd for $C_{27}H_{29}N_3O_3$ (443): C, 73.11; H, 6.59; N, 9.47% found: C, 72.81; H, 6.45; N, 9.60%. MS (EI, 70 eV): *m/z* (%)=443 (M^+, 1.03), 356 ($M^+-(CH_3)_2CHCO_2$, 3.97), 327 ($M^+-CH_2C_6H_4CN$, 5.21), 245 (M^++1-$C_6H_{11}-CH_2C_6H_4CN$, 5.61), 77 (Ph, 21.42). ^1H NMR (300.13 MHz, acetone-d_6): δ_H=1.17 [3H, AB system, $^3J_{HH}$=6.3 Hz, $OCH(CH_3)_A(CH_3)_B$], 1.20 [3H, AB system, $^3J_{HH}$=6.3 Hz, $OCH(CH_3)_A(CH_3)_B$], 1.25–1.81 (10H, m, 5 CH_2 of cyclohexyl), 3.43 (1H, d, $^2J_{HH}$=13.5 Hz, $CH_AH_B-C_6H_4CN$), 3.62 (1H, d, $^2J_{HH}$=13.5 Hz, $CH_AH_BC_6H_4CN$), 3.68 (1H, m, HC–N), 5.05 [1H, sep., $^3J_{HH}$=6.2 Hz, $OCH(CH_3)_2$], 7.43 (2H, d, $^3J_{HH}$=8.2 Hz, CH_{arom}), 7.51 (4H, m, arom), 7.61 (1H, m, arom), 7.91 (2H, m, arom). ^{13}C NMR (75.47 MHz, acetone-d_6): δ_C=21.6, 21.6 ($OCH(CH_3)_2$), 25.0, 26.3, 34.1, 34.2, (5 CH_2 of cyclohexyl), 41.1 ($CH_2-C_6H_4CN$), 58.0 ($OCH(CH_3)_2$), 70.5 (HC–N), 77.5 (C), 111.5 (CN), 119.2, 126.7 ($2C_{arom}$),128.7, 129.7, 132.2, 132.8 (8 CH_{arom}), 133.7 (C_{arom}), 141.7 (CH_{arom}), 155.2 (C=O), 164.0, 167.9 (2C=N).

*3.2.10. n-Butyl (5Z)-5-(cyclohexylimino)-4-(4-cyanobenzyl)-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (**6j**).* Yellow solid, 0.29 g, Yield 65%; mp: 124–126 °C. R_f (40% EtOAc/n-hexane) 0.44; IR (KBr) (ν_{max}, cm^{-1}): 2213 (CN), 1748 (C=O), 1722, 1642 (C=N). Anal. Calcd for $C_{28}H_{31}N_3O_3$ (457): C, 73.50; H, 6.83; N, 9.18% found: C, 73.64; H, 6.94; N, 9.34%. MS (EI, 70 eV): *m/z* (%)=458 (M^++1, 1.24), 457 (M^+, 2.25), 356 ($M^+-CO_2CH_2CH_2CH_2CH_3$, 4.05), 341 ($M^+-CH_2C_6H_4CN$, 12.18), 259 (M^++1-$C_6H_{11}-CH_2C_6H_4CN$, 21), 105 (PhCO, 100), 77 (Ph, 25.02). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H=0.87 (3H, t, $^3J_{HH}$=7.3 Hz, $OCH_2CH_2CH_2CH_3$), 1.25–1.78 (14H, m, 5 CH_2 of cyclohexyl, $OCH_2CH_2CH_2CH_3$), 3.47 (1H, d, $^2J_{HH}$=13.5 Hz, $CH_AH_B-C_6H_4NO_2$), 3.57 (1H, m, HC–N), 3.65 (1H, d, $^2J_{HH}$=13.5 Hz, $CH_AH_B-C_6H_4NO_2$), 4.10 (1H, m, $OCH_AH_BCH_3CH_2CH_2$), 4.28 (1H, m, $OCH_AH_BCH_3CH_2CH_2$), 7.32 (2H, d, $^3J_{HH}$=8.18 Hz, arom), 7.41–7.46 (4H, m, arom), 7.54 (1H, m, arom), 7.85–7.88 (2H, m, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=13.7 ($OCH_2CH_2CH_2CH_3$), 18.9 ($OCH_2CH_2CH_2CH_3$), 24.6, 24.7, 25.6 (3 CH_2 of cyclohexyl), 30.4 ($OCH_2CH_2CH_2CH_3$), 33.3, 33.5 (2 CH_2 of cyclohexyl), 40.7 ($CH_2-C_6H_4CN$), 57.88 ($OCH_2CH_2CH_2CH_3$), 66.24 (HC–N), 77.1 (C), 110.8 (CN), 118.6, 125.6 ($2C_{arom}$),128.1, 128.7, 131.4, 131.8 (8 CH_{arom}), 132.8 (C_{arom}), 140.5 (CH_{arom}), 154.3 (C=O), 163.5, 167.9 (2C=N).

*3.2.11. Methyl (5Z)-5-(cyclohexylimino)-2-(4-methoxyphenyl)-4-(4-nitrobenzyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (**6k**).* Brown oil, 0.24 g, Yield 51%. R_f (30% EtOAc/n-hexane) 0.37; IR (KBr) (ν_{max}, cm^{-1}): 1735 (C=O), 1726, 1612 (C=N), 1510, 1320 (NO_2). Anal. Calcd for $C_{25}H_{27}N_3O_6$ (465): C, 64.50; H, 5.85; N, 9.03% found: C, 64.20; H, 5.95; N, 8.96%. MS (EI, 70 eV): *m/z* (%)=465 (M^+, 4.13), 450 (M^+-CH_3, 2.58), 406 ($M^+-CO_2CH_3$, 3.29), 344 ($M^+-CH_2C_6H_4OMe$, 25.04), 105 (PhCO, 100), 77 (Ph, 23.28). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H=1.15–1.74 (10H, m, 5 CH_2 of cyclohexyl), 3.50 (1H, d, $^2J_{HH}$=13.4 Hz, $CH_AH_BC_6H_4NO_2$), 3.57 (1H, m, HC–N), 3.66 (1H, d, $^2J_{HH}$=13.4 Hz, $CH_AH_BC_6H_4NO_2$), 3.76 (3H, s, OCH_3), 3.82 (3H, s, CO_2CH_3), 6.90 (2H, d, $^3J_{HH}$=8.9 Hz, arom), 7.37 (1H, d, $^3J_{HH}$=8.6 Hz, arom), 7.80 (2H, d, $^3J_{HH}$=8.8 Hz, arom), 7.98 (2H, d, $^3J_{HH}$=8.6 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=24.6, 24.7, 25.6, 33.3, 33.5 (5 CH_2 of cyclohexyl), 40.7 ($CH_2-C_6H_4NO_2$), 53.4 (CO_2CH_3), 55.5 (OCH_3), 57.9 (HC–N), 76.5 (C), 114.1 (2 CH_{arom}), 117.6 (C_{arom}), 122.8, 130.0, 131.9 (6 CH_{arom}), 142.6, 147.0 ($3C_{arom}$), 154.3 (C=O), 163.3, 168.5 (2C=N) ppm.

*3.2.12. Propyl (5Z)-5-(cyclohexylimino)-2-(4-methoxyphenyl)-4-(4-nitrobenzyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (**6l**).* Brown solid, 0.19 g, Yield 40%; mp: 58.5–61.5 °C. R_f (25% EtOAc/n-hexane) 0.45; IR (KBr) (ν_{max}, cm^{-1}): 1739 (C=O), 1712, 1621 (C=N), 1512, 1335 (NO_2). Anal. Calcd for $C_{27}H_{31}N_3O_6$ (493): C, 65.71; H, 6.33; N, 8.51% found: C, 66.01; H, 6.22; N, 8.62%. MS: *m/z* (%)=493 (M^+, 1.03), 407 ($M^+-CO_2CH_2CH_2CH_3$, 39.28), 358 (M^++1− $CH_2C_6H_4NO_2$, 87.50), 274 ($M^+-CO_2CH_2CH_2CH_3$–MeO-PhCO, 66.07), 135 (MeO–PhCO, 100). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H=0.88 (3H, t, $^3J_{HH}$=7.5 Hz, $OCH_2CH_2CH_3$), 1.21–1.69 (1.78) (10H, m, 5 CH_2 of cyclohexyl), 3.51 (1H, d, $^2J_{HH}$=13.5 Hz, $CH_AH_B-C_6H_4NO_2$), 3.55–3.60 (1H, m, HC–N), 3.68 (1H, d, $^2J_{HH}$=13.5 Hz, $CH_AH_B-C_6H_4NO_2$), 3.85 (3H, s, CH_3O), 4.03–4.11 (1H, m, $OCH_AH_BCH_2CH_3$), 4.20–4.28 (1H, m, $OCH_AH_BCH_2CH_3$), 6.91 (2H, d, $^3J_{HH}$=8.6 Hz, arom), 7.39 (2H, d, $^3J_{HH}$=8.4 Hz, arom), 7.82 (2H, d, $^3J_{HH}$=8.5 Hz, arom), 7.99 (2H, d, $^3J_{HH}$=8.2 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=10.2 ($OCH_2CH_2CH_3$), 21.8 ($OCH_2CH_2CH_3$), 24.6, 24.7, 25.6, 33.3, 33.6 (5 CH_2 of cyclohexyl), 40.4 ($CH_2-C_6H_4NO_2$), 55.5 (OCH_3), 57.9 ($OCH_2CH_2CH_3$), 67.9 (HC–N), 76.6 (C), 114.1 (2 CH_{arom}), 117.6 (C_{arom}), 122.8, 130.0, 131.9 (6 CH_{arom}), 142.8, 147.0 ($3C_{arom}$), 154.5 (C=O), 163.3, 168.1 (2C=N) ppm.

3.3. General procedure for the synthesis of 7a

A solution of **6** (1 mmol) in corresponding alcohol (3 mL) was stirred with 4 drops of 1 N HCl at rt. The progress of the reaction was monitored by TLC (ethyl acetate/hexanes). After evaporation of the solvent, the residue was dissolved in methylene chloride and washed with $NaHCO_3$ solution, with water and dried over Na_2SO_4. After evaporation of the solvent, produce the desired products **7**.

*3.3.1. N-Benzoyl-N-cyclohexyl-4-nitro-α-(propoxycarbonyl) phenylalaninamide (**7a**).* Yellow solid, 0.27 g, Yield 55%; mp: 162–164 °C. IR (KBr) (ν_{max}, cm^{-1}): 3349 (NH), 1725, 1654 (C=O), 1500, 1320 (NO_2). Anal. Calcd for $C_{26}H_{31}N_3O_6$ (481): C, 64.85; H, 6.49; N, 8.73% found: C, 65.03; H, 6.50; N, 8.5%. MS: *m/z* (%)=481 (1.03) [M^+], 356 (29.09) (M^++1-$C_6H_{11}NHCO$), 279 (54.53) ($M^+-C_6H_{11}NHCO-Ph$), 137 (100) ($CH_2C_6H_4NO_2$), 105 (55.62) (PhCO). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H=0.88 (3H, t, $^3J_{HH}$=7.5 Hz, $OCH_2CH_2CH_3$), 1.15–1.99 (12H, m, 5 CH_2 of cyclohexyl, $OCH_2CH_2CH_3$), 3.64 (1H, d, $^2J_{HH}$=14.0 Hz, $CH_AH_B-C_6H_4NO_2$), 3.71–3.82 (1H, m, HC–N), 4.13 (1H, d, $^2J_{HH}$=14.0 Hz, $CH_AH_B-C_6H_4NO_2$), 4.14–4.25 (2H, m, $OCH_2CH_2CH_3$), 6.20 (1H, d, $^3J_{HH}$=8.0 Hz, CHNH), 7.24 (2H, t, $^3J_{HH}$=8.7 Hz, arom), 7.45 (2H, m, arom), 7.55 (1H, m, arom), 7.62 (1H, s, NH), 7.74 (2H, m, arom), 8.07 (2H, d, $^3J_{HH}$=8.7 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=10.3 ($OCH_2CH_2CH_3$), 21.8 ($OCH_2CH_2CH_3$), 24.6, 24.7, 25.3, 32.7, 32.9 (5 CH_2 of cyclohexyl), 38.7 ($CH_2-C_6H_4NO_2$), 49.5 (HC–N), 66.7 (C), 68.6 ($OCH_2CH_2CH_3$), 123.4, 127.0, 128.8, 130.8 (8 CH_{arom}), 132.2 (CH_{arom}), 133.4, 142.9, 147.3 ($3C_{arom}$), 164.5, 166.4, 170.2 (3C=O).

*3.3.2. N-Benzoyl-α-(butoxycarbonyl)-N-cyclohexyl-4-nitrophenylalaninamide (**7b**).* Yellow Oil, 0.43 g, Yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 3354 (NH), 1653, 1730 (C=O), 1502, 1345 (NO_2). Anal. Calcd for $C_{28}H_{33}N_3O_6$ (495): C, 65.44; H, 6.71; N, 8.48% found: C, 65.63; H, 6.54; N, 8.31%. MS: *m/z* (%)=495 (M^+, 1.75), 370 (M^++1-$C_6H_{11}NHCO$, 42.11), 296 ($M^+-C_6H_{11}NHCO$, $OCH_2CH_2CH_2CH_3$, 29.82), 149 ($CH_2CH_2C_6H_4NO_2$, 100), 105 (PhCO, 75.43). ^1H NMR (300.13 MHz, $CDCl_3$): δ_H=0.86 (3H, t, $^3J_{HH}$=7.4 Hz, $OCH_2CH_2CH_2CH_3$), 1.12–1.94 (14H, m, 5 CH_2 of cyclohexyl, $OCH_2CH_2CH_2CH_3$), 3.64 (1H, d, $^2J_{HH}$=14.0 Hz, $CH_AH_B-C_6H_4NO_2$), 3.71–3.83 (1H, m, HC–N), 4.13 (1H, d, $^2J_{HH}$=14.1 Hz, $CH_AH_B-C_6H_4NO_2$), 4.18–4.26 (2H, m, $OCH_2CH_2CH_2CH_3$), 6.2 (1H, d, $^3J_{HH}$=8.0 Hz, CHNH), 7.2 (2H, d, $^3J_{HH}$=8.6 Hz, arom), 7.4–7.6 (3H, m, arom), 7.6 (1H, s, NH), 7.74 (2H, d, $^3J_{HH}$=7.2 Hz, arom), 8.1 (2H, d, $^3J_{HH}$=8.6 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=13.5 ($OCH_2CH_2CH_2CH_3$), 18.9 ($OCH_2CH_2CH_2CH_3$), 24.6, 24.7, 25.3 (3 CH_2 of cyclohexyl), 30.3 ($OCH_2CH_2CH_2CH_3$), 32.7, 32.9 (2 CH_2 of cyclohexyl), 38.7

(CH_2–$C_6H_4NO_2$), 49.5 (HC–N), 66.7 (C),66.8 ($OCH_2CH_2CH_2CH_3$), 123.4, 127.0, 128.8, 130.8 (8 CH_{arom}), 132.2 (CH_{arom}), 133.4, 142.9, 147.3 ($3C_{arom}$), 164.5, 166.4, 170.2 (3C=O).

*3.3.3. N-Benzoyl-4-cyano-N-cyclohexyl-α-(methoxycarbonyl) phenylalaninamide (**7c**).* Yellow Oil, 0.43 g, Yield 96%. IR (KBr) (ν_{max}, cm^{-1}): 3354 (NH), 2213 (CN), 1735, 1649 (C=O). Anal. Calcd for $C_{25}H_{27}N_3O_4$ (433): C, 69.27; H, 6.28; N, 9.69% found: C, 69.01; H, 6.44; N, 9.78%. MS: *m*/*z* (%)=433 (1.03) [M^+], 308 (24.06) (M^++1-$C_6H_{11}NHCO$), 230 (44.53) (M^+–$C_6H_{11}NHCO$, Ph), 137 (100) ($CH_2C_6H_4NO_2$), 105 (55.62) (PhCO). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H=1.16–1.92 (10H, m, 5 CH_2 of cyclohexyl), 3.61 (1H, d, $^2J_{HH}$=14.0 Hz, CH_AH_B–C_6H_4CN), 3.75 (1H, m, HC–N), 3.81 (3H, s, OCH_3), 4.06 (1H, d, $^2J_{HH}$=14.0 Hz, CH_AH_B–C_6H_4CN), 6.22 (1H, d, $^3J_{HH}$=9.0 Hz, CHNH), 7.16 (2H, d, $^3J_{HH}$=8.1 Hz, arom), 7.42–7.57 (5H, m, arom), 7.61 (1H, s, NH), 7.74 (2H, d, $^3J_{HH}$=7.2 Hz, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=24.6, 24.7, 25.3, 32.6, 32.8 (5 CH_2 of cyclohexyl), 38.9 (CH_2–C_6H_4CN), 49.5 (HC–N), 53.8 (C), 66.7 (OCH_3), 111.3 (CN), 118.7 (C_{arom}), 127.1, 128.8, 130.7, 132.0 (8 CH_{arom}), 132.2 (CH_{arom}), 133.3, 140.6 ($2C_{arom}$), 164.4, 166.4, 170.8 (3C=O).

*3.3.4. N-Benzoyl-4-cyano-N-cyclohexyl-α-(isopropoxycarbonyl) phenylalaninamide (**7d**).* Yellow solid, 0.35 g, Yield 75%; mp: 175–177 °C, IR (KBr) (ν_{max}, cm^{-1}): 3349 (NH), 2213 (CN), 1731, 1653 (C=O). Anal. Calcd for $C_{27}H_{31}N_3O_4$ (461): C, 70.26; H, 6.77; N, 9.10% found: C, 70.35; H, 6.84; N, 9.21%. MS: *m*/*z* (%)=461 (M^+, 3.57), 336 (M^++1-$C_6H_{11}NHCO$, 87.50), 276 [M^+–$C_6H_{11}NHCO$, $OCH(CH_3)_2$, 63.63], 231 ($CH_2C_6H_4NO_2$, PhCO, 32.72), 105 (PhCO, 100).^{1}H NMR (300.13 MHz, $CDCl_3$): δ_H=1.10–1.96 [16H, m, 5 CH_2 of cyclohexyl, $(CH_3)_2CHO$], 3.58 (1H, d, $^2J_{HH}$=14.0 Hz, CH_AH_B–C_6H_4CN), 3.77 (1H, m, HC–N), 4.05 (1H, d, $^2J_{HH}$=14.0 Hz, CH_AH_B–C_6H_4CN), 5.13 [1H, sep, $^3J_{HH}$=6.3 Hz, $(CH_3)_2CHO$], 6.16 (1H, d, $^3J_{HH}$=8.2 Hz, CHNH), 7.17 (2H, d, $^3J_{HH}$=8.26 Hz, arom), 7.42–7.57 (6H, m, arom, NH), 7.71 (2H, m, arom). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ_C=21.4, 21.5 [$(CH_3)_2CHO$], 24.7, 24.7, 25.3, 32.7, 32.9 (5 CH_2 of cyclohexyl), 38.8 (CH_2–C_6H_4CN), 49.3 (HC–N), 66.7 (C), 70.8 [$(CH_3)_2CHO$], 111.2 (CN), 118.7 (C_{arom}), 126.9, 128.8, 130.7, 132.0 (8 CH_{arom}), 132.1 (CH_{arom}), 133.7, 140.9 ($2C_{arom}$), 164.6, 166.4, 169.5 (3C=O).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.073.

References and notes

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22. Crystal data for **6d** $C_{26}H_{29}N_3O_5$ (CCDC 823597): M_W=463.52, monoclinic, space group 'P 21/c, a=10.440(2) Å, b=14.726(3) Å, c=16.917(3) Å, α=90.00 β=105.59(3), γ=90.00, V=2505.1(9) $Å^3$, Z=4, Dc=1.229 mg/m^3, F (000)=984, crystal dimension 0.5×0.6×0.4 mm, radiation, Mo Kα (λ=0.71073 Å), 2.45≤2θ≤29.19, intensity data were collected at 120(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of −14≤h≤10, −19≤k≤20, −23≤l≤23; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 4456 observed reflections with R (into)=0.1750 by a full-matrix least-squares technique converged to R=0.1358and Raw=0.3567 [$I>2\sigma(I)$].