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Rapid access to reverse-turn peptidomimetics by a three-component Ugi reaction of 3,4-dihydroisoquinoline

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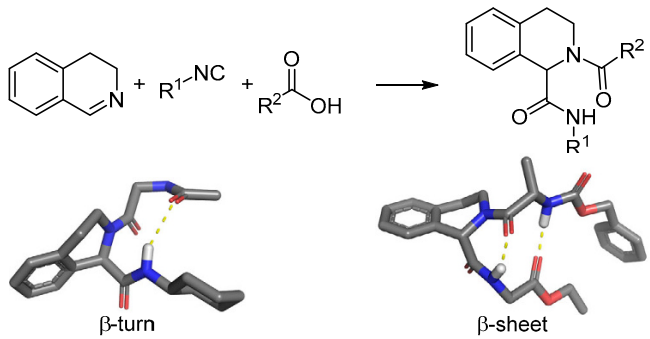


Peptidomimetics have raised a considerable attention in the last decades due to their potential application as therapeutic agents. In this perspective, multicomponent reactions are an excellent tool to rapidly afford a large number of drug candidates having a great structural diversity. We report here on the use of the three-component Ugi reaction for the synthesis of a library of potential reverse-turn mimetics, based on the constrained tetrahydroisoquinoline heterocyclic scaffold. The ability of the target compounds to mimic secondary structure of peptides was evaluated by means of computational tools and NMR studies. We were able to demonstrate that by using the appropriate starting materials, a β-turn or a β-sheet mimetic is obtained.

Keywords: peptidomimetics, tetrahydroisoquinoline, multicomponent reaction, Ugi reaction.

In the last decades, the field of peptidomimetics has been thoroughly investigated as a promising access to novel and efficient therapeutic agents.[1–6] Many strategies toward the reproduction of the most relevant secondary structures have been proposed. Reverse turns have been identified as a main target in the relevant PPI (protein-protein interactions) process.[2,4,7–11] In particular, γ-turns and β-turns have been studied both as a recognition motif and a β-sheet inducer toward more complex structures. A common way to obtain the desired geometry of a secondary structure mimetics is to design rigid scaffolds able to correctly arrange the residues in the space, this way promoting the binding to the desired target. Heterocyclic scaffolds have been extensively used to this goal.[12,13]

The exploitation of constrained peptidomimetics in medicinal chemistry is often limited by the fact that long and inefficient synthetic sequences are often required. With this regards, multicomponent reactions[14–18] can be very effective in the synthesis of complex and highly functionalized scaffolds in few steps and often in high yields. Recently some examples of multicomponent approaches to the synthesis of potential peptidomimetics have been reported,[19–21] mainly based on the Ugi reaction. The Ugi reaction is a well-known and much exploited four-component reaction involving the use of an amine, an aldehyde, a carboxylic acid, and an isocyanide to produce an amino acid derivative.[22,23]

Following the above considerations and based on our experience in the preparation of peptidomimetics,[24–32] we have designed the synthesis of a reverse-turn mimetics, easily achievable applying this strategy, starting from tetrahydroisoquinoline scaffolds. Tetrahydroisoquinoline

moiety is present in a large number of natural compounds and pharmacologically active molecules.[33] The great structural diversity of this class of molecules is often due to the presence of many different substituents and functional groups on the piperidine ring. These heterocyclic scaffolds are most often prepared by cyclization procedures (e.g., Pictet–Spengler and Bischler–Napieralski reactions) allowing the formation of the piperidine ring with the concomitant introduction of substituent in the key C-1 position. Further elaborations of these structures lead to a variety of derivatives. Beside the interest for their biological activities that spread from antimalarials to opioid mimetics, tetrahydroisoquinolines have been proposed, due to their rigid polycyclic structures, as efficient peptide secondary structure inducers in the field of peptidomimetics.[28]

Following these observations we became interested in the design of a new library of peptidomimetics **1a**–**l** based on the 1-carboxytetrahydroisoquinoline scaffold by means of a three-component Ugi reaction[34–36] (Scheme 1) using the preformed imine **2**. The starting material **2** could be easily obtained by a Bischler–Napieralski cyclization of the related formamide precursor.

In order to set up the reaction conditions, we first tested compound **2** with acetic acid and benzyl isocyanide in different solvents and temperature, stirring the mixture for 24 h to afford compound **1a** (Table 1). The use of dichloromethane and acetonitrile produced moderate yields (58 and 54%), whereas with toluene and THF only a 23–34% yield could be observed. The best results were achieved when using methanol at room temperature (84%). Increasing the temperature did not provide any improvement.

By using these reaction conditions, we prepared a small combinatorial library of compounds **1a**–**l** with different side chains attached to the tetrahydroisoquinoline ring system. Three alkyl isocyanides were used, *viz*. benzyl isocyanide, cyclohexyl isocyanide, and *tert*-butyl isocyanide. In order to better test the reverse-turn capability of the final products, ethyl isocyanoacetate was also used as a mimetic of a glycine residue. For the acidic component, two *N*-protected amino acids were employed, *N*-acetylglycine and *N*-Cbz-L-alanine. Moreover, 1-pentenoic acid was selected because of its expectedly easy removal from the final product, thus allowing the possibility of further decoration on the tetrahydroisoquinoline nitrogen. In addition, chloroacetic acid was also employed in order to explore the possibility to obtain a fused diketopiperazine ring by a post-Ugi cyclization (Scheme 2). The isolated final products are listed in Figure 1.

Scheme 1

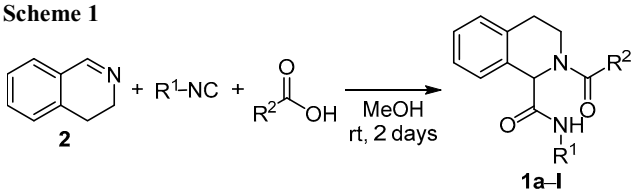
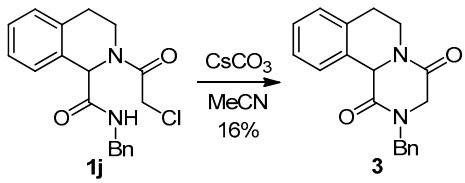


Table 1. Optimization of the reaction conditions for the preparation of compound **1a**

Solvent	*T*, °C	Conversion*, %	Solvent	*T*, °C	Conversion*, %
CH_2Cl_2	25	44	MeOH	60	79
CH_2Cl_2	60	58	MeCN	25	51
THF	25	31	MeCN	60	54
THF	60	34	PhMe	25	23
MeOH	25	84	PhMe	60	27

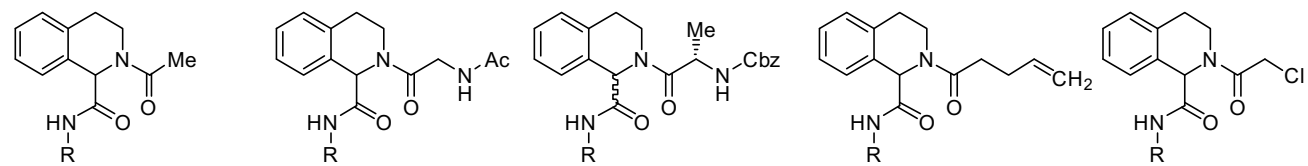
* Conversion was measured by GC/MS analysis or by ^{1}H NMR of the crude product.

Scheme 2



In most of the cases, the reactions proceeded smoothly, and after 24–48 h the solvent was evaporated and the crude product purified by column chromatography. In a few cases, a solid precipitated out or could be easily recovered after treatment of the crude product with a methanol–hexane mixture. All products could be isolated in moderate to good yields. When *N*-Cbz-L-alanine was used, a 1:1 diastereoisomeric mixture was obtained (products **1e**,**f**). The two diastereoisomers could be efficiently separated by column chromatography.

To explore the possibility to obtain a diketopiperazine derivative as a useful modification toward more complex scaffolds, compound **1j** was reacted with a base to promote the intramolecular cyclization (Scheme 2). The use of strong bases (NaH or *t*-BuOK) yielded a mixture of inseparable products. Methanolic NaOH afforded the product in a 12% conversion yield (measured from GC/MS and ^{1}H NMR of the crude product), whereas with cesium



1a R = Bn (84%) **1b** R = CH_2COOEt (68%) **1c** R = Cy (72%) **1d** R = *t*-Bu (66%) **1e** R = Bn (55%) **1f** R = CH_2COOEt (48%) **1g** R = Bn (81%) **1h** R = Cy (74%) **1i** R = CH_2COOEt (64%) **1j** R = Bn (79%) **1k** R = Cy (81%) **1l** R = *t*-Bu (68%)

Figure 1. Structures and isolated yields of compounds **1a**–**l** prepared according to Scheme 1.

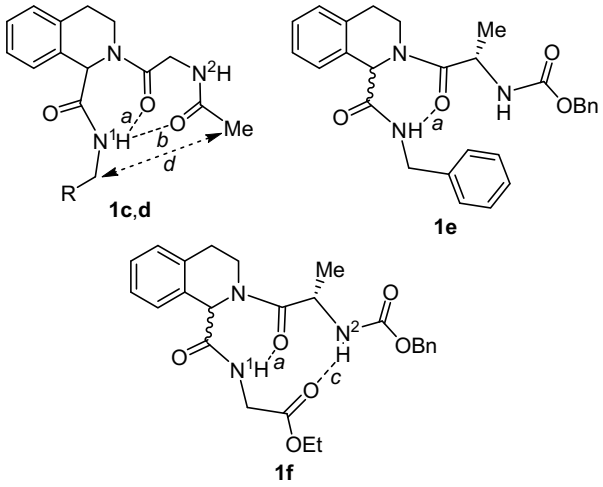


Figure 2. Definition of the geometrical parameters for the reverse-turn evaluation of compounds **1c**–**f**.

carbonate in acetonitrile the conversion was 16%. In the ^{1}H NMR spectrum, we could observe the disappearance of the CH_2Cl signal at 4.15 ppm and the presence of a new AB system of the diketopiperazine ring CH_2 group in the form of two doublets (J = 14.3 Hz) at 4.22 and 4.35 ppm. Also the chemical shifts of other signals in the aliphatic region of the spectrum were altered. In the GC/MS chromatogram, a peak having the *m*/*z* value of the molecular ion of compound **3** (306) was also detected. However, due to the presence of a great number of by-products we could not isolate the pure product.

We then investigated the ability to adopt a reverse turn-like conformation for compounds **1c**–**f** by means of computational tools. A conformational analysis was performed with the use of a Monte Carlo search and a molecular mechanics energy minimization with the MMFF94 force field (as implemented in the Spartan'08 software suite).[37] Reverse turns of the γ (seven-membered H-bond ring) and β (ten-membered H-bond ring) type are stabilized by intramolecular hydrogen bonds and defined according to the H-bonds pattern. In addition, for the β-turn, a favorable condition is d < 7 Å (the distance between α-carbon atoms separated by three amino acid residues, see Fig. 2). We could identify three most common hydrogen bonds in our models: the *a* and *b* hydrogen bond patterns, related to the γ- and β-turn, respectively, and the H-bond *c*. Interestingly this latter pattern is found in antiparallel β-sheet motifs.[38] Attention has been turned to these structures in recent years because of their possible implication in protein aggregation diseases.[39]

Detailed analysis of the results is presented in Table 2. Only conformers within 6 kcal/mol from the global minimum were considered. All the scaffolds are able to adopt a classic γ-turn-like conformation through the presence of the *a* H-bond. The presence of a *N*-acetylglycine residue (compounds **1c**,**d**) promoted the formation of a β-turn, in particular for compound **1c** (81% of conformers with d < 7 Å); in all cases, the analysis of the dihedral angles established the presence of a type II β-turn. As expected, for compounds **1e**,**f** some differences between

Table 2. Conformational analysis of amino acis derivatives **1c**–**f**. Results are reported as percentage of conformers containing the indicated bond or distance

Compound	Total conformers*	*a* bond, %	*b* bond, %	*c* bond, %	*d* < 7 Å, %
1c	58	16	40	n.a.**	81
1d	39	31	36	n.a.	54
(*S*,*S*)-**1e**	69	23	1	n.a.	n.a.
(*R*,*S*)-**1e**	21	76	0	n.a.	n.a.
(*S*,*S*)-**1f**	33	45	9	33	n.a.
(*R*,*S*)-**1f**	25	88	0	16	n.a.

* Number of conformers within 6 kcal/mol from the global minimum.
** Not applicable to the given structure.

the two diastereoisomers are observed: for the (*S*,*S*)-isomer there is a prevalence for type *a* bond, while in the (*R*,*S*)-isomer some tendency toward the β-turn conformation is also revealed. Notably, the presence of the *N*-Cbz-alanine in compound **1f** promoted the formation of the H-bond *c*.

In order to confirm the presence of the computationally predicted H-bonds, variable temperature NMR experiments were performed on compound **1c** and on one of the two diastereoisomers of compound **1f**. For compound **1c**, values of Δδ/ΔT corresponding to –7.7 ppb/K for N^{1}H and –6.3 ppb/K for N^{2}H were measured. Similarly, for compound **1f** the detected values of Δδ/ΔT were –6.1 ppb/K for N^{1}H and –5.4 ppb/K for N^{2}H. According to literature,[40–43] these values are in agreement with the presence of intramolecular hydrogen bonds, thus supporting the presence of stabilized secondary structures. Figure 3 shows the structures of compounds **1c**, (*S*,*S*)-**1f**, and (*R*,*S*)-**1f** as obtained from the calculations.

In this work, we reported the use of a three-component Ugi reaction as an effective tool for the rapid creation of new peptidomimetic scaffolds based on the tetrahydroisoquinoline moiety. By this approach, we could prepare a combinatorial library of derivatives with different components. For some of them, a computer-aided investigation of the conformational properties was performed, thus predicting their ability to mimic some classical reverse-turn peptide structures. Variable-temperature NMR studies finally supported the presence of intramolecular hydrogen

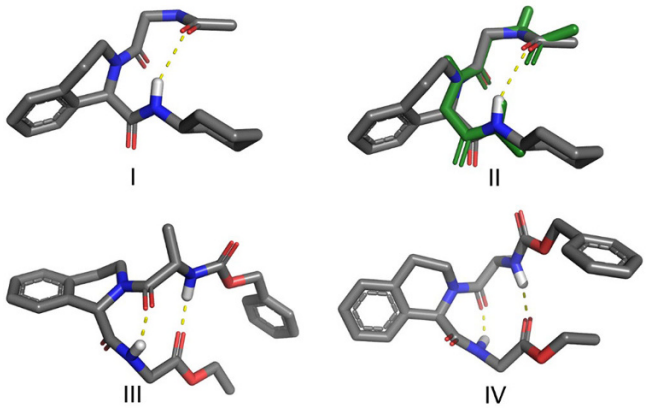


Figure 3. Compound **1c** (I) and its superimposition with a type II β-turn model (II). Structures of (*S*,*S*)-**1f** (III) and (*R*,*S*)-**1f** (IV).

bond patterns. According to the different residues present on the tetrahydroisoquinoline scaffold, a γ-turn, β-turn, or an antiparallel β-sheet could be recognized.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively). Chemical shifts are expressed in ppm relative to TMS for ^{1}H NMR spectra and relative to $CDCl_3$ (77.16 ppm) or DMSO-d_6 (39.51 ppm) signal for ^{13}C NMR spectra. Some ^{13}C NMR spectra have been recorded using the APT pulse sequence; the signals of CH and CH_3 are positive while those of CH_2 and quaternary carbons are negative. GC/MS analyses were performed on an Agilent instrument equipped with an EI source by using an HP-5 MS column (30 m × 0.25 mm × 0.25 μm, Agilent). The following temperature program was employed: 60°C (1 min)/6°C min^{-1}/150°C (1 min)/12°C min^{-1}/280°C (5 min). Elemental analyses were carried out on a PerkinElmer Series II analyzer. All reactions were monitored by TLC on precoated silica gel 60 F254; spots were visualized with UV light (254 nm) or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). The enantiomeric excess was determined by HPLC on a Chiralpak AD column (eluent 9:1, hexane–2-PrOH, 9:1, flow rate 0.75 ml/min). All solvents were distilled and dried over sodium or calcium chloride, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. Calculations were performed with the suite Spartan'08.[37]

3,4-Dihydroisoquinoline (2).[44] 2-Phenylethylamine (30.0 g, 0.248 mol) and ethyl formate were heated at reflux for 2 days. Removal of excess ethyl formate under vacuum gave the *N*-phenethylformamide in quantitative yield (37.0 g) as a colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.10 (1H, s, CHO); 7.29 (2H, t, *J* = 7.2, H Ar); 7.24–7.13 (3H, m, H Ar); 6.7–6.2 (1H, br. s, NH); 3.50 (2H, t, *J* = 7.0, CH_2); 2.81 (2H, t, *J* =7.0, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 161.4; 138.6; 128.8; 128.7; 126.6; 39.2; 35.5. Crude 2-phenylethylamine (7.0 g, 0.47 mol) and polyphosphoric acid (20 ml) were heated at 160°C overnight. The reaction mixture was cooled to room temperature and made basic with 5 M NaOH; a white precipitate formed. The precipitate was filtered off, and the filtrate was extracted three times with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield compound **2** (5.0 g, 81%) as a pale-yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.31 (1H, t, *J* = 2.3, H Ar); 7.36–7.20 (3H, m, H Ar); 7.19–7.05 (1H, m, H Ar); 3.83–3.70 (2H, m, CH_2); 2.81–2.69 (2H, m, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 160.7; 136.7; 131.7; 128.9; 127.8; 127.6; 127.5; 47.8; 25.4

Synthesis of peptidomimetics 1a–l by three-component Ugi reaction (General method). The carboxylic acid (4.27 mmol) and the isocyanide (4.27 mmol) were added to a stirred solution of compound **2** (0.560 g, 4.27 mmol) in methanol (10 ml). The reaction mixture was stirred at room temperature for 2 days and concentrated *in vacuo*. A crude oil was obtained. After purification by silica gel column chromatography (eluent varied from *n*-hexane–EtOAc, 7:3, to pure EtOAc), the desired product was obtained as oil or foamy solid.

2-Acetyl-*N*-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1a).[45] ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.36–7.10 (9H, m, H Ar); 6.84 (1H, br. s, NH); 5.94 (1H, s, CH); 4.48–4.32 (2H, m, CH_2Ph); 3.81 (1H, ddd, *J* = 12.8, *J* = 8.2, *J* = 4.7) and 3.74–3.64 (1H, m, CH_2); 3.06 (1H, dt, *J* = 15.8, *J* = 4.7) and 2.95–2.85 (1H, m, CH_2); 2.18 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 170.7; 170.6; 138.4; 134.9; 132.2; 128.5; 128.2 (2C); 127.9; 127.6 (2C); 127.4; 127.1; 126.7; 57.4; 43.5; 43.1; 28.8; 21.7. Found, %: C 74.11; H 6.61; N 9.11. $C_{19}H_{20}N_2O_2$. Calculated, %: C 74.00; H 6.54; N 9.08.

Ethyl (2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl-carbonyl)glycinate (1b). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.43 (1H, br. s, NH); 7.39–7.32 (1H, m, H Ar); 7.25–7.14 (3H, m, H Ar); 6.05 (1H, s, CH); 4.17 (2H, q, *J* = 7.2, C<u>H</u>$_2$CH$_3$); 4.00–3.96 (2H, m, CH_2); 3.90 (1H, ddd, *J* = 12.7, *J* = 8.2, *J* = 4.9) and 3.74 (1H, ddd, *J* = 12.2, *J* = 6.5, *J* = 5.1, CH_2); 3.14–3.02 (1H, m) and 2.97–2.90 (1H, m, CH_2); 2.23 (3H, s, CH_3); 1.25 (3H, t, *J* = 7.2, CH$_2$C<u>H</u>$_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 170.7; 170.5; 169.4; 134.6; 131.6; 128.0; 127.9; 127.5; 126.5; 61.1; 56.7; 42.9; 41.3; 28.6; 21.5; 13.9. Found, %: C 63.11; H 6.64; N 9.21. $C_{16}H_{20}N_2O_4$. Calculated, %: C 63.14; H 6.62; N 9.20.

2-(Acetylglycyl)-*N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1c). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.09 (1H, d, *J* = 7.9, NH); 8.00 (1H, t, *J* = 5.6, NH); 7.35–7.12 (4H, m, H Ar); 5.62 (1H, s, CH); 4.05 (2H, d, *J* = 5.6, CH_2); 4.02–3.91 (1H, m) and 3.61 (1H, ddd, *J* = 12.1, *J* = 7.3, *J* = 4.8, CH_2); 3.02 (1H, ddd, *J* = 15.5, *J* = 7.3, *J* = 4.9) and 2.87–2.78 (1H, m, CH_2); 1.87 (3H, s); 1.72–1.67 (1H, m), 1.65–1.60 (2H, d, *J* = 10.9), 1.56–1.51 (2H, m), and 1.28–1.06 (6H, m, $CH(CH_2)_5$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 169.9; 169.8; 168.8; 135.6; 133.2; 128.5; 127.7; 127.5; 126.6; 57.6; 48.2; 41.4; 32.8; 32.6; 28.6; 25.7; 25.0; 24.9; 24.7; 22.9. Found, %: C 67.22; H 7.59; N 11.77. $C_{20}H_{27}N_3O_3$. Calculated, %: C 67.20; H 7.61; N 11.76.

2-(Acetylglycyl)-*N*-(*tert*-butyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1d). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.43–7.08 (4H, m, H Ar); 6.66 (1H, br. s, NH); 6.08 (1H, br. s); 5.75 (1H, s, CH); 4.25–4.18 (1H, m) and 4.13 (1H, dd, *J* = 17.5, *J* = 4.5, CH_2); 3.85 (1H, dd, *J* = 7.1, *J* = 5.1) and 3.61 (1H, ddd, *J* = 12.3, *J* = 7.1, *J* = 5.1, CH_2); 3.06 (1H, ddd, *J* = 15.9, *J* = 7.2, *J* = 5.3) and 2.94–2.80 (1H, m, CH_2); 2.06 (3H, s, CH_3); 1.30 (9H, s, *t*-Bu). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 170.3; 168.8; 168.3; 134.6; 131.8; 128.5; 128.0; 127.4; 126.9; 60.2; 58.6; 41.8; 41.3; 28.6 (3C); 28.4; 23.0. Found, %: C 65.20; H 7.61; N 12.71. $C_{18}H_{25}N_3O_3$. Calculated, %: C 65.23; H 7.60; N 12.68.

Benzyl {(2*S*)-1-[1-(benzylcarbamoyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]-1-oxopropan-2-yl}carbamate (1e).

Diastereoisomer A. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.38–7.13 (14H, m, H Ar); 6.99 (1H, br. s, NH); 5.92 (1H, s, CH); 5.56 (1H, d, *J* = 7.1, NH); 5.10 (1H, d, *J* = 12.1) and 4.88 (1H, d, *J* = 12.1, CH_2); 4.73 (1H, quin, *J* = 6.9, CH); 4.58–4.32 (2H, m, CH_2); 4.12–3.88 (1H, m) and 3.84–3.72 (1H, m, CH_2); 3.05 (1H, dt, *J* = 15.9, *J* = 5.8) and 2.92 (1H, ddd, *J* = 15.2, *J* = 9.0, *J* = 6.3, CH_2); 1.33 (3H, d, *J* = 6.9, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 173.0; 169.6; 138.4; 136.3; 134.3; 131.9; 128.6; 128.5; 128.4; 128.2 (3C); 128.1 (3C); 127.8 (3C); 127.4; 127.2; 126.8; 66.9; 60.3; 58.0; 47.2; 43.6; 28.8; 14.2. Found, %: C 71.33; H 6.20; N 8.90. $C_{28}H_{29}N_3O_4$. Calculated, %: C 71.32; H 6.20; N 8.91.

Diastereoisomer B. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.37–7.13 (14H, m, H Ar); 6.67 (1H, br. s, NH); 5.92 (1H, s, CH); 5.68–5.51 (1H, m, NH); 5.21–4.90 (2H, m, CH_2); 4.78–4.67 (1H, m, CH); 4.51–4.29 (2H, m, CH_2); 3.86–3.72 (2H, m, CH_2); 3.10–2.85 (2H, m, CH_2); 1.32 (3H, d, *J* = 6.9, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 172.5; 170.1; 155.6; 138.4; 136.4; 134.6; 131.5; 128.6 (2C); 128.5; 128.3 (2C); 128.1 (2C); 128.0; 127.7 (2C); 127.5; 127.3; 127.1; 126.7; 66.8; 57.5; 47.2; 43.6; 41.9; 28.8; 18.6. Found, %: C 71.31; H 6.23; N 8.94. $C_{28}H_{29}N_3O_4$. Calculated, %: C 71.32; H 6.20; N 8.91.

Ethyl 2-{[(benzyloxycarbonyl)-L-alanyl]-1,2,3,4-tetrahydroisoquinolin-1-ylcarbonyl}glycinate (1f). **Diastereoisomer A**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.45–7.19 (8H, m, H Ar); 7.19–7.12 (1H, m, NH); 6.03 (1H, d, *J* = 7.5, NH); 5.99 (1H, s, CH); 5.09 (2H, s, CH_2); 4.78 (1H, t, *J* = 7.0, CH); 4.20–4.12 (1H, m, CH_2); 4.12 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.07–3.93 (2H, m, CH_2); 3.88–3.75 (2H, m, CH_2); 3.10 (1H, dd, *J* = 13.9, *J* = 7.8) and 2.95–2.82 (1H, m, CH_2); 1.34 (3H, d, *J* = 6.8, CH_3); 1.19 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 172.8; 170.0; 169.5; 156.0; 136.4; 134.4; 131.5; 128.4; 128.0 (2C); 127.9; 127.8 (2C); 126.7 (2C); 61.1; 57.6; 47.3; 42.2; 41.4; 28.6; 20.8; 18.2; 14.1; 14.0. Found, %: C 64.25; H 6.23; N 9.01. $C_{25}H_{29}N_3O_6$. Calculated, %: C 64.23; H 6.25; N 8.99.

Diastereoisomer B. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.39–7.16 (9H, m, H Ar); 6.79 (1H, br. s, NH); 6.00 (1H, s, CH); 5.71 (1H, br. s, NH); 5.12–5.02 (2H, m, CH_2); 4.77 (1H, br. s, CH); 4.17 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.04 (1H, dd, *J* = 18.2, *J* = 5.2) and 3.92 (1H, dd, *J* = 18.2, *J* = 5.2, CH_2); 3.86–3.71 (2H, m, CH_2); 3.01–2.91 (2H, m, CH_2); 1.45 (3H, d, *J* = 6.8, CH_3); 1.29 (3H, t, *J* = 7.1, CH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 172.7; 170.0; 169.4; 156.6; 134.5; 131.0; 128.5; 128.4 (2C); 128.0; 127.9 (2C); 127.8; 126.8; 66.8; 61.6; 61.4; 57.0; 47.3; 41.9; 41.5; 40.0; 28.7; 18.8; 14.1. Found, %: C 64.24; H 6.26; N 9.02. $C_{25}H_{29}N_3O_6$. Calculated, %: C 64.23; H 6.25; N 8.99.

***N*-Benzyl-2-(pent-4-enoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1g)**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.33–7.14 (9H, m, H Ar); 6.89 (1H, br. s, NH); 5.96 (1H, s, CH); 5.92–5.77 (1H, m, $C\underline{H}=CH_2$); 5.12–4.94 (2H, m, $CH=C\underline{H}_2$); 4.42 (2H, d, *J* = 5.9, CH_2); 3.81–3.68 (2H, m, CH_2); 3.06 (1H, dt, *J* = 15.7, *J* = 5.5) and 2.95–2.85 (1H, m, CH_2); 2.60–2.36 (4H, m, $C\underline{H}_2C\underline{H}_2CH=CH_2$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 172.5; 170.4; 138.3; 137.1; 134.8; 132.0; 128.5; 128.2 (2C); 127.9 (2C); 127.6; 127.4; 127.2; 126.6; 115.3; 57.4; 43.6; 42.2; 32.9; 28.9; 28.8. Found, %: C 75.80; H 6.93; N 8.06. $C_{22}H_{24}N_2O_2$. Calculated, %: C 75.83; H 6.94; N 8.04.

***N*-Cyclohexyl-2-(pent-4-enoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1h)**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.25–7.13 (4H, m, H Ar); 6.47 (1H, d, *J* = 8.3, NH); 5.92–5.80 (2H, m, CH and $C\underline{H}=CH_2$); 5.12–4.94 (2H, m, $CH=C\underline{H}_2$); 3.84–3.64 (3H, m, CH_2, $C\underline{H}(CH_2)_5$); 3.03 (1H, dt, *J* = 15.7, *J* = 5.2) and 2.89 (1H, ddd, *J* = 15.7, *J* = 8.5, *J* = 5.3, CH_2); 2.64–2.39 (4H, m, $C\underline{H}_2C\underline{H}_2CH=CH_2$); 1.86–1.79 (1H, m), 1.70–1.52 (2H, m), 1.35–1.10 (3H, m), and 1.40–1.10 (4H, m, $CH(C\underline{H}_2)_5$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 172.3; 169.4; 137.1; 134.7; 132.1; 128.3; 127.8; 127.6; 126.6; 115.5; 57.4; 48.3; 42.2; 32.9; 32.8 (2C); 29.1; 28.9; 25.5; 24.6 (2C). Found, %: C 74.07; H 8.32; N 8.25. $C_{21}H_{28}N_2O_2$. Calculated, %: C 74.08; H 8.29; N 8.23.

Ethyl [2-(pent-4-enoyl)-1,2,3,4-tetrahydroisoquinolin-1-ylcarbonyl]glycinate (1i). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.32–7.15 (4H, m, H Ar); 7.12 (1H, br. s, NH); 6.02 (1H, s, CH); 5.86 (1H, dtt, *J* = 16.6, *J* = 10.0, *J* = 6.1, $CH=CH_2$); 5.11–4.96 (2H, m, $CH=CH_2$); 4.16 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.97 (2H, AB system, *J* = 18.1, *J* = 5.5, CH_2); 3.83 (1H, ddd, *J* = 12.8, *J* = 8.1, *J* = 4.8) and 3.75 (1H, dt, *J* = 12.3, *J* = 5.7, CH_2); 3.04 (1H, dt, *J* = 15.7, *J* = 5.6) and 2.89 (1H, ddd, *J* = 15.6, *J* = 8.2, *J* = 5.1, CH_2); 2.65–2.36 (4H, m, $C\underline{H}_2C\underline{H}_2CH=CH_2$); 1.24 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 172.6; 170.7; 169.4; 137.1; 134.7; 131.7; 128.1; 128.0; 127.7; 126.6; 115.3; 61.2; 57.0; 42.2; 41.4; 32.9; 28.9; 28.8; 14.0. Found, %: C 66.24; H 7.04; N 8.10. $C_{19}H_{24}N_2O_4$. Calculated, %: C 66.26; H 7.02; N 8.13.

***N*-Benzyl-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1j)**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.31–7.16 (9H, m, H Ar); 6.90 (1H, br. s, NH); 5.88 (1H, s, CH); 4.40 (2H, d, *J* = 5.8, CH_2); 4.20–4.09 (2H, m, CH_2); 3.91 (1H, ddd, *J* = 12.9, *J* = 8.4, *J* = 4.7) and 3.76 (1H, dt, *J* = 12.5, *J* = 5.6, CH_2); 3.09 (1H, dt, *J* = 15.8, *J* = 5.3) and 2.97 (1H, ddd, *J* = 16.0, *J* = 8.4, *J* = 5.1, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 169.7; 166.7; 138.0; 134.4; 131.2; 128.6 (2C); 128.4; 127.9; 127.7; 127.5 (2C); 127.4; 126.9; 58.0; 43.7; 42.8; 41.3; 28.7. Found, %: C 66.55; H 5.56; N 8.14. $C_{19}H_{19}ClN_2O_2$. Calculated, %: C 66.57; H 5.59; N 8.17.

2-(2-Chloroacetyl)-*N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1k). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.28–7.15 (4H, m, H Ar); 6.27 (1H, d, *J* = 8.1, NH); 5.79 (1H, s, CH); 4.24–4.11 (2H, m, CH_2); 3.95–3.77 (2H, m, $C\underline{H}(CH_2)_5$ and CH_2); 3.76–3.68 (1H, m, CH_2); 3.10–2.88 (2H, m, CH_2); 1.93–1.80 (2H, m), 1.67–1.50 (2H, m), 1.40–1.27 (2H, m), and 1.25–1.10 (4H, m, $CH(C\underline{H}_2)_5$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.7; 166.8; 134.3; 133.6; 128.5; 127.8; 127.7; 126.8; 57.9; 48.5; 42.7; 41.2; 32.8 (2C); 28.8; 25.5; 24.6 (2C). Found, %: C 64.59; H 6.88; N 8.35. $C_{18}H_{23}ClN_2O_2$. Calculated, %: C 64.57; H 6.92; N 8.37.

***N*-(*tert*-Butyl)-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (1l)**. ^{1}H NMR spectrum ($CDCl_3$),

δ, ppm (*J*, Hz): 7.35–7.10 (4H, m, H Ar); 6.24 (1H, br. s, NH); 5.75 (1H, s, CH); 4.27–4.10 (2H, m, CH_2); 3.93–3.77 (2H, m, CH_2); 3.09–2.93 (2H, m, CH_2); 1.32 (9H, s, *t*-Bu). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 167.1; 161.4; 134.2; 131.4; 128.7; 128.5; 127.8; 126.8; 58.3; 51.6; 42.7; 41.1; 28.8; 28.7 (3C). Found, %: C 62.25; H 6.82; N 9.10. $C_{16}H_{21}ClN_2O_2$. Calculated, %: C 62.23; H 6.85; N 9.07.

The Supplementary information file containing the ^1H and ^{13}C NMR spectra of compounds **1a**–**l** is available at the journal website at http://link.springer.com/journal/10593.

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