Synthesis and kinetic investigation of the selective acydolysis of *para*-substituted *N*-phenylacetyl-*N*-benzyl- and *N*-phenylacetyl-*N*-phenyl-α,α-dialkylglycine cyclohexylamides

Filipa C.S.C. Pinto,[a] Sílvia M.M.A. Pereira-Lima,[a] Cristina Ventura,[b] Lídia Albuquerque,[c] Raquel Gonçalves-Maia[c] and Hernâni L.S. Maia[a,*]

[a] *Centro de Química, University of Minho, Gualtar, P-4710-057 Braga, Portugal*
[b] *Advanced Institute of Education and Sciences, Alameda das Linhas de Torres, 179, P-1750-142 Lisboa, Portugal*
[c] *Department of Chemistry and Biochemistry, Faculty of Science, University of Lisbon, Campo Grande, P-1749-016 Lisboa, Portugal*

Abstract—Several derivatives of *N*-phenylacetyl-*N*-benzyl-α,α-dimethylglycine cyclohexylamide and their α,α-dibenzylglycine analogues were synthesised by a Ugi-Passerini reaction. In addition, a few analogues of the former but having an *N*-phenyl instead of a benzyl group at the nitrogen atom were synthesised. The compounds in each of these three sets differed from each other at the position 4 of the *N*-benzyl (and *N*-phenyl) group. These adducts were submitted to acidolysis with TFA to obtain the corresponding free acids, the reactions being monitored by HPLC and data collected for kinetic purposes. The kinetic data were submitted to Hammett uni- and biparametric relationships and the results analysed in terms of structure-reactivity in connection to the sensitivity of the reaction rates to the electronic contributions of the various substituents in position 4 of the aromatic rings. The results allowed comparison with information obtained in previous investigations and rationalise the contribution of the substituent at the nitrogen atom to the lability of the C-terminal amide bond.

Keywords: Acidolysis; α,α-Dialkylglycines; α,α-Trialkylglycines; Peptide synthesis; Ugi-Passerini reaction; Rate constant; Structure-reactivity relationships.

* Corresponding author. Tel.: +351-967-096-958; fax: +351 253 617 959; e-mail: h.maia@netcabo.pt

1. Introduction

Conformational rigidity increases potency and selectivity of bioactive peptides, improving their bioavailabitlity and enhancing resistance to peptidases.[1] Consequently, design of conformational constrained peptides is one of the approaches for development of bioactive species with high activity and selectivity towards a specific receptor.[2,3] Owing to steric crowding within the neighbourhood of the α-carbon atom of α,α-dialkyl glycines, conformational rigidity can be obtained by inserting one or more residue of these amino acids into the peptide chain. In addition, special conformational features imparted to the peptide backbone by these amino acid residues[4-7] may be used to modulate activity and selectivity. This can be best achieved by previous parametrisation of these amino acids[8] followed by molecular dynamics simulations of the bioactive peptides[9] as modified at strategic positions by one or more of these amino acid units. Once the most promising peptide sequences are predicted, it is necessary to synthesise the selected compounds. In most cases these amino acids are not commercially available and their synthesis is usually difficult due to steric hindrance of the required reactions. Nevertheless, the interest these amino acids have raised in late years led to the recent development of a few interesting and sometimes ingenious approaches for preparation of either symmetric[10-12] or asymmetric compounds.[13,14] Having obtained the required amino acids is not sufficient to reach ones goal, as again steric crowding makes their insertion into a peptide chain even more problematic than the amino acid synthesis; thus, conventional methods of peptide synthesis become unpractical as reflected by the low yields observed in the rare cases where a product is obtained. A promising way to overcome these difficulties would consist in synthesising the α,α-dialkyl glycine unit already incorporated into the peptide chain a route that in principal is offered by the four-component Ugi-Passerini reaction. This is particularly appropriate when no concern with asymmetric induction is required, such as in the case of symmetric α,α-dialkyl glycines, which are among the simplest and most widely used structural units in the construction of peptides with a predetermined secondary structure.[15] However, the above strategy is not exempt of difficulties, as it requires that (i) the unwanted alkyl group bound to the nitrogen atom of dialkylated centre be removed and (ii) the unavoidable racemization of the amino acid residue that follows the newly synthesised unit be overcome. We have shown that the former can be

achieved if the unwanted N-substituent is methoxybenzyl,[16] and that the latter can be overcome by taking advantage of the lability of the amide bond at the C-terminus of the α,α-dialkyl glycine unit.[17-19] This allows obtaining the amino acid unit at the peptide C-terminus ready for further elongation of the chain without any risk of racemization. The above can be achieved by treatment of the Ugi-Passerini adduct with trifluoroacetic acid (TFA), but this approach will prove useful only if the double cleavage can be performed under acceptable selectivity and in good yield, which depends on the nature and structure of this adduct. In order to assess the selectivity of the amide bond cleavage, we have further investigated its mechanism and evaluated the effect of the substituent bulk and structure at the N- and the C-terminus, and also at the α-carbon atom of the fully substituted amino acid (Scheme 1).[20,22] In order to complete this investigation, we now present the results of a similar evaluation concerning the nature of the alkyl substituent bound to the N-terminal nitrogen atom of the Ugi-Passerini adduct.

2. Results and discussion

2.1. Syntheses

In our previous work it was found that the bulk of the amino acid side chains may affect seriously not only the rate of the acidolyses but also the path of the reactions involved.[19] Compounds with methyl at the side chain reacted faster and behaved better as compared with the corresponding benzyl analogues where a larger steric effect had to be expected. Thus, for the present investigation we designed one set of compounds with methyl (substrates **1**) and another with benzyl (substrates **2**) at the amino acid side chain, with eight substrates in each set (Scheme 1). As in our previous work R^2 was always 4-methoxybenzyl, for these two sets we chose differently substituted benzyl groups (including the non-substituted group). In addition, we have also devised a third set of substrates with methyl at the amino acid side chain but in which R^2 was a phenyl group substituted or not in position 4 (substrates **3**); in this case only five compounds were envisaged. Thus, all compounds were synthesised by a Ugi-Passerini reaction using phenylacetic acid, cyclohexyl isonitrile, the appropriate amine and acetone (compounds **1a**–**1h** and **3a**–**3e**) or dibenzyl ketone (compounds **2a**–**2h**) according to the methodologies described elsewhere (Table 1).[18,19] As shown previously[17,19] and is

depicted in Scheme 1, these substrates undergo acidolysis, which proceeds via an oxazolone derivative to yield the corresponding open-chain *N*-acyl-*N*,α,α-trialkylglycine.

Each of the above substrate was treated at room temperature with 5% TFA in acetonitrile to give three new sets of compounds (**4**, **5** and **6**) homologous of the previous ones (**1**, **2** and **3**, respectively). With only one exception (**3a**), **PORQUÊ?** the acidolyses of the *N*-benzyl compounds **1** and **2** gave good to very good yields in the corresponding free acid. The comparably much lower yields obtained with the anilides were due to the reactions being so slow that they were not taken to completion, much of the starting material being collected during work-up. Nevertheless, no signs have been detected of any reaction or product other than those depicted in Scheme 1.

2.2. Acquisition and treatment of kinetic information

Having observed that the acidolysis of all substrates is selective, i. e. that only cleavage of the C-terminal amide bond takes place, each substrate was submitted to acidolysis with 2% TFA under controlled conditions for collection of kinetic data; this was assisted by HPLC according to the procedure described below in the Experimental section. As expected,[20-22] an excellent linear relationship between substrate concentration and HPLC peak areas was found, which allowed calculation of reaction rate constants directly from peak areas. All reactions exhibited pseudo-first order behaviour with respect to the amino acid derivative, which is shown by the linear variation of ln *A*, where *A* is an HPLC peak area, as a function of time. As an example, ln *A* vs *t* plots for experiments concerning substrates **1a** at two temperatures (25.00 and 40.00 ºC) and **2a** at 25.00 ºC are presented in Fig. 1. The observed rate constants, *k*, were calculated by the linear least squares methodology for a straight line. Four to five experiments were performed for each substrate in reactions carried out at 25.00 ºC, while only two to three were performed for reactions at other temperatures. The results presented in Tables 2 and 3 are the mean rate constant values (*k*) and their mean deviations (d*k*).

As in all compounds now under investigation R^2 is connected to the rest of the molecule through an aromatic moiety, it is appropriate to analyse the kinetic results at the light of a Hammett treatment. For this purpose, the uniparametric correlation $\log k = \log k_o + \rho\sigma$ was applied to all acidolyses, σ being the Hammett substituent constant for *para*-substituents and ρ the reaction constant reflecting the sensitivity of the reaction rate to the total electronic effect of the substituents. The values of the Hammett constants (σ) used to fit the observed rate constants (k) are listed in Table 4;[24] although the number of substituents used in each set of compounds is not large, it is worthwhile noting that they provide a wide range of electronic effects. Table 5 shows the parameters estimated (a_0 and a_1) for the Hammett plots by the least squares methodology for a straight line. The correlation coefficient (r) and the standard deviation (s) of the fits are also presented, together with the standard deviations of the estimated parameters. The confidence levels for the estimated parameters as well as those for the fits obtained in a test-F[25] were always better than 99.99%, except for the reactions with compounds **3a**–**3e**, which was 99.8%; this difference is most probably due to the small number of compounds (N = 5) available in the latter case. Fig. 2 shows the corresponding plots. The success obtained in the above treatment of the electronic effect of substituents on the rate of our reactions lead us to investigate the possibility to quantify field/inductive and resonance contributions. For this purpose, we extended our analysis of rate constants taking advantage of a biparametric relationship in order to evaluate these two main part components as follows: $\log k = a_0 + a_1 \sigma_R + a_2 \sigma_I$ (where σ_R and σ_I are the resonance constant and the field/inductive constant, respectively).[24] This treatment was applied only to those cases where the number of results available allowed the most meaningful statistical analysis, i.e. compounds **1a**–**1h** and **2a**–**2h** at 25.00 ºC. The values of the constants used in the regression analysis, σ_R and σ_I, are listed also in Table 4. It should be noted that for the range of the substituents studied these two constants are not collinear and can be used as independent variables since their correlation coefficient is as low as 0.148 (N = 8). The results of the biparametric equations are presented in Table 6.

2.3. Discussion of results

The yields obtained in the Ugi-Passerini reaction (Table 1) were usually good to very good, except in the case of the nitro derivatives. The behaviour observed with the nitro derivatives is possibly due to the large electron withdrawing effect of the nitro group, which should decrease substantially the nucleophilicity of the amine nitrogen atom as compared with the other substituents. This was so enhanced in the case of the nitroanilide **3e**, that it could not be obtained in a yield better than 9%. Acidolysis of the dimethylglycine derivatives **1** were faster (2.5-4 hours for substrates **1a**–**1g**) than those with the corresponding dibenzylglycine compounds **2** (20 to 27 hours for compounds **2a**–**2e**) and usually gave good yields (Table 1). However, reactions with the *N*-phenyl derivatives were much slower (27, 48, 119 and 168 hours for **3a**, **3b**, **3c** and **3d**, respectively). Is noteworthy that after treatment with 2% TFA for more than four days, much the chlorophenyl and the cyanophenyl derivatives **3c** and **3d** had not been completely transformed; this suggests that C-terminal amide bond of *N*-(4-chorophenyl)- and *N*-(4-cyanophenyl)-α,α-dialkylglycine peptides would be sufficiently stable to allow the use of these compounds in routine peptide synthesis. Acidolyses with nitrobenzyl derivatives were also very slow (26 and 48 hours for **1h** and **2h**, respectively), while the acidolysis of the nitrophenyl derivative **3e** was so slow that boiling in neat TFA for more than 1 hour was required for a yield of only 48%. We have shown[19] that at room temperature and low TFA concentration the 4-metoxybenzyl group is not cleaved, but that this can be achieved on boiling in neat TFA for 5 minutes. However, when compounds **1b** and **1d** were boiled in neat TFA for 20 minutes the substituent at R^2 was not eliminated, the corresponding trialkylglicine being the only product obtained. It was already known[23] that the N-substituent of *N*,α,α-tribenzylglycine resists to boiling in concentrated aqueous HBr for several hours and that its cleavage requires hydrogenation in hot butanol for 12 hours.

In general, the values of the rate constants for the compounds of *N*-benzyl derivatives of α,α-dimethylglycine **1a**–**1h** are about 2.5 times larger than those for their analogues in the α,α-dibenzylglycine series (**2a**–**2h**). This difference must be related to a larger steric contribution of the amino acid side chains (R^1) to the reaction rates in the case of compounds **2**. Nevertheless, both sets have approximately the same sensitivity to electronic contributions, which is particularly visible by comparing the values for a_1 in the Hammett plots (–0.91 and –0.86 for set **1** and set **2**, respectively, at 25.00 ºC; Table

5 and Fig. 2). However, a different behaviour is observed in the case of the *N*-phenyl derivatives of α,α-dimethylglycine **3a**–**3e**, where the rate constants are 40 to 150 times smaller than those found for similar compounds in set **1**. Now, the reactions are not only much slower but also much more sensitive to the electronic contribution of the substituent at the nitrogen atom than in the case of those above. This different behaviour becomes evident from the value of a_1 in the corresponding Hammett plot (–1.56), which differs significantly from those of the previous sets. The absence of a methylene group between the nitrogen atom and the aromatic ring allows the electronic contribution of the substituent to be passed on to the oxygen atom of the vicinal carbonyl group, thus tuning its nucleophilicity. It is clear that conjugation of the side chain phenyl ring of compounds **3** with the reaction centre contributes to its stabilisation, thus decreasing the nucleophilicity of the oxygen atom to make the reactions slower than with the benzyl derivatives. In their investigation of the effect of the substituent on the rate of acydolysis under similar conditions of various *para*-substituted *N*-benzoyl derivatives of *N*,α,α-trimethylglycine Chreighton *et al.*[18] have found the value –1.335. This suggests that the nucleophilicity of the oxygen atom is more sensitive to the electronic contribution of the substituent at the nitrogen atom than that at the *N*-carbonyl carbon atom. This may be interpreted as resulting from the additional interaction in our case between the substituent and the nucleophilic oxygen atom through the formation of an N-C double bond during the cyclisation process (Scheme 2 – A). The results presented in Table 5 and Fig. 2 for compounds **1** at different temperatures show a slope varying, although not much but steadily, with temperature, in agreement with what one would expect from the properties of a Hammett reaction constant. Fluorine derivatives **1d** and **2d**, are the less well behaved compounds; in fact, in the plots at the different temperatures they show systematic deviations to the same side of the lines (Fig. 2).

The biparametric relationships presented above for compounds **1a**–**1h** and **2a**–**2h** at 25.00 ºC are excellent, the significance of the estimated parameters and of the fit obtained by the test-F were always better than 99.99%. In order to further demonstrate the validity of these correlations, the values observed for log *k* were plotted against those calculated by the equations, as shown in Fig. 3. The sixteen points (eight for **1a**–**1h** and eight for **2a**–**2h**) fall very closely to the bisectrix of perfect correlation. The successful decomposition of substituent electronic effects places the discussion of field/inductive and resonance components in numerical terms. Since in our case a_1 and

a_2 have a similar magnitude (Table 6), one might conclude that, as an average, both effects contribute significantly to the reactivity. Now, fluorine derivative **1d** is again less well behaved. It can be seen in Table 4 and Fig. 4 that the field/inductive constant and resonance constant can be very different from each other for every substituent. Fluorine, where these two constants are large, have opposite signs and are almost of the same size, is the exception; in this case the resonance contribution can almost cancel the field/inductive contribution if the reaction under consideration is equally sensitive to both, as has already been discussed by others.[26] However, if in our case the sensitivities concerning the fluorine derivatives are different, these compounds should diverge from the average, which might explain the deviant behaviour.

3. Conclusions

The kinetic results obtained in this investigation show that the reaction rate constants differ sufficiently from compound to compound to allow their interpretation in terms of structure-reactivity considerations. The sensitivity of the measured reaction rates to the nature (electronic contribution) of the substituent at the nitrogen atom of the anilides **3a**–**3e** is larger than that reported[18] for the *N*-acyl group and this may be related to the formation of the C-N double bond required for cyclisation and consequent cleavage of the C-terminal amide bond, as depicted in Scheme 2. *N*-Benzyl derivatives of either α,α-dimethyl- or α,α-dibenzylglycine (**1a**–**1h** and **2a**–**2h**, respectively) exhibit a lesser sensitivity, which is in agreement with the existence of a methylene group between the nitrogen atom and the phenyl ring. Similarly to what we have previously found, α,α-dimethylglycine derivatives react much faster than the corresponding α,α-dibenzylglycines. However, these two sets of compounds show a very similar behaviour in what concerns sensitivity to the electronic contribution of the substituent R^2 to acydolysis and to its main components (resonance and field/inductive effect). Although acidolytic cleavage of the C-terminal amide bond of α,α-dialkylglycine derivatives requires an alkyl/aryl substituent at the amino acid nitrogen atom,[18-22] it occurs independently of the size of the electronic contribution, this contributing only to the rate of acidolysis. This suggests that such requirement is essentially related with steric and not so much with a polar effect, possibly by assisting the molecules to assume a bent

conformation and facilitating internal nucleophilic attack in support of what we had already suggested.[20] Our results showed that the high sensitivity of the acidolysis rate constants of anilides substituted with electron withdrawing groups such *N*-(4-chlorophenyl) and the *N*-(4-cyanophenyl) results in a dramatic decrease of the lability of the C-terminal amide bond of α,α-dialkylglycine amides. This suggests that either of these groups would seem appropriate to impart useful conformational restrictions in combination with α,α-dialkylglycine peptides while preventing unwanted cleavage of the C-terminal peptide bond of the amino acid residue bearing the two side chains. Finally, it is worthwhile noting that while the 4-methoxybenzyl group can be cleaved from the Ugi-Passerini substrate together with the C-terminal amide bond if sufficiently forcing conditions are used (boiling with neat TFA), all the other 4-substityde benzyl groups tested do not. Thus, when cleavage of the *N*-alkyl group from the Ugi-Passerini adducts is required, only 4-methoxybenzyl compounds suit this purpose, the group we have used with success in our previous work.

4. Experimental

4.1. Syntheses

Tri-distilled and de-ionised water was used in HPLC experiments. Methanol and acetone were dried by standard procedures. All other solvents and reagents were used as obtained from commercial sources. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel $60F_{254}$) and spots were visualised under UV light or by exposure to vaporised iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 25 °C in ~5% solutions on a Varian Unity Plus-300 spectrometer; all shifts are given in ppm using $_{H}$ Me_4Si=0, *J*-values are given in Hz, and assignments were made by comparison of chemical shifts, peak multiplicity and *J*-values. ^{13}C NMR spectra were recorded with the same instrument at 75.4 MHz and using the solvent peak as internal reference; assignments were carried out using DEPT 135, HMBC, HMQC and NOE techniques. Elemental analyses were preformed on a Leco CHNS 932

instrument. HPLC measurements were carried out with a Jasco PU-980 intelligent HPLC Pump, a Shimadzu SPD-6AV UV-VIS Spectrophotometric Detector and a Shimadzu C-R6A Chromatopac Printer. A reverse phase LiChrospher 100 RP-18 (5 m) column was used throughout the work. Temperature stability was maintained throughout the kinetic work with a HAAKE Circulator DL30 thermostatic bath, the temperatures being set with the aid of Precision thermometers allowing an accuracy of 0.01 degree.**General method for the synthesis of Ugi-Passerini adducts (1, 2 and 3).**For the preparation of the α,α-dimethylglycine derivatives, a 0.5 M solution of the required amine in dry acetone containing anhydrous sodium sulphate (0.12 g cm^{-3}) was prepared and stirred for 15 min; then, one equivalent of a 2 M solution of phenylacetic acid in dry methanol was added and the mixture stirred for further 15 min. Finally, one equivalent of cyclohexyl isocyanide was also added and the mixture stirred at room temperature for 1-4 weeks in the dark and under nitrogen. To the suspension thus obtained dichloromethane was added to dissolve the product that meanwhile had precipitated and the sodium sulphate filtered off. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography using the following eluent sequence: dichloromethane/*n*-hexane 2:1, dichloromethane, dichloromethane/methanol 200:1, 100:1 and 50:1. For the preparation of the α,α -dibenzylglycine derivatives, to a 1 M solution of 1,3-diphenylpopanone in dry methanol containing anhydrous sodium sulphate (0.12 g cm^{-3}) one equivalent of the required amine was added. After stirring for 45-60 min, one equivalent of cyclohexyl isocyanide was mixed in and the preparation continued as above.***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine cyclohexylamide (1a).** The reaction was carried out on a 0.05-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1a** (19.17 g, 91%) as a white solid, mp 168.9-169.8 ºC (lit.[19] 168.4-169.8 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): 1.08-1.21 (3H, m, C_6H_{11}), 1.42 (6H, s, 2 × CH_3), 1.64-1.73 (5H, m, C_6H_{11}), 1.95 (2H, *m*, C_6H_{11}), 3.68 (2H, s, CH_2CO), 3.71-3.80 (1H, m, C_6H_{11}-*H1*), 3.82 (3H, s, OCH_3), 4.53 (2H, s, NCH_2), 5.50 (1H, d, *J*=8.1 Hz, N*H*), 6.94 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.21-7.31 (5H, m, $COCH_2$*Ph*), 7.38 (2H, d, *J*=9.0 Hz, NCH_2Ph-*H2,6*); ^{13}C NMR (75 MHz, $CDCl_3$): 2 × CH_3), 24.81 (C_6H_{11}-*C3,5*), 25.56 (C_6H_{11}-*C4*), 32.87 (C_6H_{11}-*C2,6*), 42.05 (CH_2CO), 47.06 (CH_2N), 48.25 (C_6H_{11}-*C1*), 55.18 (OCH_3), 62.36 (C^{α}), 114.21 (NCH_2Ph-*C2,6*), 126.71 ($COCH_2$Ph-*C4*), 127.08 (NCH_2Ph-*C3,5*), 128.39 ($COCH_2$Ph-

C2,6), 128.62 ($COCH_2Ph$-*C3,5*), 130.23 (NCH_2Ph-*C4*), 134.86 ($COCH_2Ph$-*C1*), 158.74 (NCH_2Ph-*C4*), 171.74 (*C*OCH_2), 172.65 (*C*ONH). Anal. Calcd. for $C_{26}H_{34}N_2O_3$: C, 73.90; H, 8.11; N, 6.63. Found: C, 73.98; H, 8.08; N, 6.69. ***N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dimethylglycine cyclohexylamide (1b).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1b** (3.68 g, 90%) as a white solid, mp 157.5-158.7 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.03-1.21 (3H, m, C_6H_{11}), 1.29-1.39 (2H, m, C_6H_{11}), 1.42 (6H, s, 2 × CH_3), 1.57-1.72 (3H, m, C_6H_{11}), 1.94 (2H, m, C_6H_{11}), 2.36 (3H, s, Ph-CH_3), 3.67 (2H, s, CH_2CO), 3.70-3.81 (1H, m, C_6H_{11}-*H1*), 4.55 (2H, s, NCH_2), 5.52 (1H, d, *J*=8.1 Hz, N*H*), 7.19-7.44 (9H, m, $COCH_2$*Ph* + NCH_2*Ph*); ^{13}C NMR (75 MHz, $CDCl_3$): Ph-*C*H_3), 2 × *C*H_3), 24.80 (C_6H_{11}-*C3,5*), 25.56 (C_6H_{11}-*C4*), 32.85 (C_6H_{11}-*C2,6*), 42.06 (*C*H_2CO), 47.45 (*C*H_2N), 48.22 (C_6H_{11}-*C1*), 62.40 (C^{α}), 125.84 (NCH_2Ph-*C2,6*), 126.71 ($COCH_2Ph$-*C4*), 128.39 ($COCH_2Ph$-*C2,6*), 128.62 ($COCH_2Ph$-*C3,5*), 129.50 (NCH_2Ph-*C3,5*), 134.82 ($COCH_2Ph$-*C1*), 135.29 (NCH_2Ph-*C1*), 136.88 (NCH_2Ph-*C4*), 171.77 (*C*OCH_2), 173.75 (*C*ONH). Anal. Calcd. for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.98; H, 8.14; N, 7.03. ***N*-Phenylacetyl-*N*-benzyl-α,α-dimethylglycine cyclohexylamide (1c).** The reaction was carried out on a 0.015-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1c** (4.06 g, 71%) as a white solid, mp 161.1-162.0 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.04-1.22 (3H, m, C_6H_{11}), 1.29-1.42 (3H, m, C_6H_{11}), 1.43 (6H, s, 2 × CH_3) 1.67-1.74 (2H, m, C_6H_{11}), 1.96 (2H, m, C_6H_{11}), 3.67 (2H, s, CH_2CO), 3.72-3.82 (1H, m, C_6H_{11}-*H1*), 4.59 (2H, s, NCH_2), 5.52 (1H, d, *J*=7.8 Hz, N*H*), 7.21-7.34 (6H, m, $COCH_2$*Ph* + NCH_2Ph-*H4*), 7.41 (2H, t, *J*=7.5 Hz, NCH_2Ph-*H3,5*), 7.48 (2H, d, *J*=7.5 Hz, NCH_2Ph-*H2,6*); ^{13}C NMR (75 MHz, $CDCl_3$): 24.22 (2 × *C*H_3), 24.84 (C_6H_{11}-*C3,5*), 25.56 (C_6H_{11}-*C4*), 32.90 (C_6H_{11}-*C2,6*), 42.07 (*C*H_2CO), 47.60 (*C*H_2N), 48.29 (C_6H_{11}-*C1*), 62.39 (C^{α}), 125.91 (NCH_2Ph-*C2,6*), 126.76 ($COCH_2Ph$-*C4*), 127.23 (NCH_2Ph-*C4*), 128.39 ($COCH_2Ph$-*C2,6*), 128.67 ($COCH_2Ph$-*C3,5*), 128.86 (NCH_2Ph-*C3,5*), 134.77 ($COCH_2Ph$-*C1*), 138.40 (NCH_2Ph-*C1*), 171.82 (*C*OCH_2), 173.78 (*C*ONH). Anal. Calcd. for $C_{25}H_{32}N_2O_2$: C, 76.50; H, 8.22; N, 7.14. Found: C, 76.44; H, 8.11; N, 7.19. ***N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dimethylglycine cyclohexylamide (1d).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1d** (3.90 g, 95%) as a

white solid, mp 162.5-163.5 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.06-1.22 (3H, m, C_6H_{11}), 1.29-1.40 (2H, m, C_6H_{11}) 1.42 (6H, s, 2 × CH_3) 1.58-1.74 (3H, m, C_6H_{11}), 1.97 (2H, m, C_6H_{11}), 3.61 (2H, s, CH_2CO), 3.71-3.84 (1H, m, C_6H_{11}-*H1*), 4.53 (2H, s, NCH_2), 5.51 (1H, d, *J*=8.1 Hz, N*H*), 7.07 (2H, t, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.18-7.32 (5H, m, $COCH_2Ph$), 7.49 (2H, dd, *J*=5.4, 9.0 Hz, NCH_2Ph-*H2,6*); ^{13}C NMR (75 MHz, $CDCl_3$): 24.17 (2 × CH_3), 24.88 (C_6H_{11}-*C3,5*), 25.57 (C_6H_{11}-*C4*), 32.94 (C_6H_{11}-*C2,6*), 42.06 (CH_2CO), 46.80 (CH_2N), 48.39 (C_6H_{11}-*C1*), 62.29 (C^{α}), 115.70 (d, $J_{C\text{-}F}$=21.3 Hz, NCH_2Ph-*C3,5*), 126.81 ($COCH_2Ph$-*C4*), 127.56 (d, $J_{C\text{-}F}$=8.1 Hz, NCH_2Ph-*C2,6*), 128.33 ($COCH_2Ph$-*C2,6*), 128.32 ($COCH_2Ph$-*C3,5*), 134.13 (d, $J_{C\text{-}F}$=3.2 Hz, NCH_2Ph-*C1*), 134.70 ($COCH_2Ph$-*C1*), 161.93 (d, $J_{C\text{-}F}$=245.6 Hz, NCH_2Ph-*C4*), 171.77 ($COCH_2$), 173.80 (*C*ONH). Anal. Calcd. for $C_{25}FH_{31}N_2O_2$: C, 73.14; H, 7.61; N, 6.82. Found: C, 73.10; H, 7.67; N, 6.86. ***N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dimethylglycine cyclohexylamide (1e).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1e** (3.69 g, 86%) as a white solid, mp 140.4-141.5 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.07-1.22 (3H, m, C_6H_{11}), 1.30-1.39 (2H, m, C_6H_{11}) 1.41 (6H, *s*, 2 × CH_3) 1.59-1.74 (3H, m, C_6H_{11}), 1.96-1.99 (2H, m, C_6H_{11}), 3.60 (2H, s, CH_2CO), 3.75-3.80 (1H, m, C_6H_{11}-*H1*), 4.52 (2H, s, NCH_2), 5.51 (1H, d, *J*=7.8 Hz, N*H*), 7.17-7.29 (5H, m, $COCH_2$-*Ph*), 7.35 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H3,5*), 7.47 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H2,6*); ^{13}C NMR (75 MHz, $CDCl_3$): 24.14 (2 × CH_3), 24.86 (C_6H_{11}-*C3,5*), 25.54 (C_6H_{11}-*C4*), 32.82 (C_6H_{11}-*C2,6*), 42.05 (CH_2CO), 46.87 (CH_2N), 48.39 (C_6H_{11}-*C1*), 62.26 (C^{α}), 126.82 ($COCH_2Ph$-*C4*), 127.36 (NCH_2Ph-*C2,6*), 128.30 ($COCH_2Ph$-*C2,6*), 128.72 ($COCH_2Ph$-*C3,5*), 128.96 (NCH_2Ph-*C3,5*), 132.95 (NCH_2Ph-*C4*), 134.60 ($COCH_2Ph$-*C1*), 137.03 (NCH_2Ph-*C1*), 171.76 ($COCH_2$), 173.73 (*C*ONH). Anal. Calcd. for $C_{25}ClH_{31}N_2O_2$: C, 70.32; H, 7.32; N, 6.52. Found: C, 70.15; H, 7.29; N, 6.66. ***N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dimethylglycine cyclohexylamide (1f).** The reaction was carried out on a 0.006-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1f** (2.61 g, 91%) as a white solid, mp 143.2-144.0 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.08-1.23 (3H, m, C_6H_{11}), 1.32-1.36 (2H, m, C_6H_{11}), 1.43 (6H, s, 2 × CH_3) 1.60-1.74 (3H, m, C_6H_{11}), 1.98 (2H, m, C_6H_{11}), 3.61 (2H, s, CH_2CO), 3.74-3.84 (1H, m, C_6H_{11}-*H1*), 4.56 (2H, s, NCH_2), 5.52 (1H, d, *J*=8.1 Hz, N*H*), 7.17-7.32 (7H, m, $COCH_2Ph$ + NCH_2Ph-*H3,5*), 7.59 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H2,6*); ^{13}C NMR (75

MHz, $CDCl_3$): 24.14 (2 × *C*H_3), 24.86 (C_6H_{11}-*C3,5*), 25.54 (C_6H_{11}-*C4*), 32.93 (C_6H_{11}-*C2,6*), 42.06 (*C*H_2CO), 46.75 (*C*H_2N), 48.42 (C_6H_{11}-*C1*), 62.26 (C^{α}), 120.37 (q, $J_{C\text{-}F}$=257.4 Hz, O*C*F_3), 121.31 (NCH_2Ph-*C3,5*), 126.82 ($COCH_2$Ph-*C4*), 127.35 (NCH_2Ph-*C2,6*), 128.30 ($COCH_2$Ph-*C2,6*), 128.72 ($COCH_2$Ph-*C3,5*), 134.57 ($COCH_2$Ph-*C1*), 137.25 (NCH_2Ph-*C1*), 148.25 (q, $J_{C\text{-}F}$=1.8 Hz, NCH_2Ph-*C4*), 171.76 (*C*OCH_2), 173.77 (*C*ONH). Anal. Calcd. for $C_{26}F_3H_{31}N_2O_3$: C, 65.53; H, 6.56; N, 5.88. Found: C, 65.49; H, 6.42; N, 5.91. ***N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dimethylglycine cyclohexylamide (1g).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1g** (4.51 g, 98%) as a white solid, mp 126.9-128.0 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.09-1.23 (3H, m, C_6H_{11}), 1.31-1.40 (2H, m, C_6H_{11}) 1.43 (6H, *s*, 2 × C*H*$_3$) 1.59-1.75 (3H, m, C_6H_{11}), 1.99 (2H, m, C_6H_{11}), 3.58 (2H, s, C*H*$_2$CO), 3.73-3.85 (1H, m, C_6H_{11}-*H1*), 4.60 (2H, s, NC*H*$_2$), 5.53 (1H, d, *J*=8.1 Hz, N*H*), 7.17-7.32 (5H, m, $COCH_2$*Ph*), 7.67 (4H, dt, *J*=8.4, 14.4 Hz, NCH_2*Ph*); ^{13}C NMR (75 MHz, $CDCl_3$): 24.16 (2 × *C*H_3), 24.90 (C_6H_{11}-*C3,5*), 25.57 (C_6H_{11}-*C4*), 32.97 (C_6H_{11}-*C*2,6), 42.13 (*C*H_2CO), 47.11 (*C*H_2N), 48.48 (C_6H_{11}-*C1*), 62.29 (C^{α}), 124.02 (q, $J_{C\text{-}F}$=272.1 Hz, *C*F_3), 125.81 (q, $J_{C\text{-}F}$=3.7 Hz, NCH_2Ph-*C3,5*), 126.34 (NCH_2Ph-*C2,6*), 126.90 ($COCH_2$Ph-*C4*), 128.30 ($COCH_2$Ph-*C2,6*), 128.79 ($COCH_2$Ph-*C3,5*), 129.55 (q, $J_{C\text{-}F}$=32.5 Hz, NCH_2Ph-*C4*), 134.49 ($COCH_2$Ph-*C1*), 142.79 (NCH_2Ph-*C1*), 171.80 (*C*OCH_2), 173.73 (*C*ONH). Anal. Calcd. for $C_{26}F_3H_{31}N_2O_2$: C, 67.81; H, 6.78; N, 6.08. Found: C, 67.72; H, 6.84; N, 5.92. ***N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dimethylglycine cyclohexylamide (1h).** The reaction was carried out on a 0.005-molar scale, starting with 4-nitrobenzylamine hydrochloride (3 eq., 5.658 g), which was neutralised with triethylamine (2.9 eq., 4.01 ml) in dry diethyl ether (30 ml) at room temperature and under stirring for 90 min. The reaction mixture was filtered and the filtrate concentrated under reduced pressure; the residue was dissolved in freshly distilled acetone (25 ml) and used according to the general procedure described above. The final product was purified by column chromatography and recrystallised from ethyl acetate to yield **1h** (1.09 g, 50%) as a pale yellow solid, mp 141.8-143.0 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10-1.24 (3H, m, C_6H_{11}), 1.31-1.40 (2H, m, C_6H_{11}) 1.42 (6H, s, 2 × C*H*$_3$) 1.60-1.75 (3H, m, C_6H_{11}), 1.99 (2H, m, C_6H_{11}), 3.55 (2H, s, C*H*$_2$CO), 3.77-3.80 (1H, m, C_6H_{11}-*H1*), 4.62 (2H, s, NC*H*$_2$), 5.55 (1H, d, *J*=7.8 Hz, N*H*), 7.14 (2H, d, *J*=6.3 Hz, $COCH_2$Ph-*H2,6*), 7.22-7.28 (3H, m, $COCH_2$Ph-*H3,4,5*), 7.80 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 8.22 (2H, d, *J*=9.0

Hz, NCH_2Ph-*H3,5*); ^{13}C NMR (75 MHz, $CDCl_3$): 24.08 (2 × *C*H_3), 24.88 (C_6H_{11}-*C3,5*), 25.52 (C_6H_{11}-*C4*), 32.94 (C_6H_{11}-*C2,6*), 42.13 (*C*H_2CO), 46.95 (*C*H_2N), 48.54 (C_6H_{11}-*C1*), 62.23 (C^{α}), 124.03 (NCH_2Ph-*C3,5*), 126.91 (NCH_2Ph-*C2,6*), 126.91 ($COCH_2Ph$-*C4*), 128.20 ($COCH_2Ph$-*C2,6*), 128.81 ($COCH_2Ph$-*C3,5*), 134.22 ($COCH_2Ph$-*C1*), 146.32 (NCH_2Ph-*C1*), 147.17 (NCH_2Ph-*C4*), 171.65 (*C*OCH_2), 173.68 (*C*ONH). Anal. Calcd. for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.49; H, 7.07; N, 9.61. ***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine cyclohexylamide (2a).** The reaction was carried out on a 0.05-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2a** (18.78 g, 82%) as a white solid, mp 129.0-130.1 ºC (lit.[19] 87.3-87.9 ºC). ^1H RMN (300 MHz, $CDCl_3$): 0.84-1.07 (3H, m, C_6H_{11}), 1.19-1.29 (2H, m, C_6H_{11}), 1.57-1.61 (5H, m, C_6H_{11}), 2.93 (2H, d, *J*=12.0 Hz, CCH_2Ph), 3.34 (2H, br d, *J*=10.8 Hz, CCH_2Ph), 3.48-3.52 (1H, m, C_6H_{11}-*H1*), 3.55 (2H, s, $COCH_2$), 3.68 (2H, br s, NCH_2), 3.80 (3H, s, OCH_3), 5.05 (1H, d, *J*=7.5 Hz, N*H*), 6.93 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.12-7.25 (10H, m, 2 × CCH_2Ph), 7.32-7.38 (5H, m, $COCH_2Ph$), 7.65 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.86 (C_6H_{11}-*C3,5*), 25.56 (C_6H_{11}-*C4*), 32.57 (C_6H_{11}-*C2,6*), 36.05 (2 × C*C*H_2Ph), 42.08 (*C*H_2CO), 47.25 (*C*H_2N), 48.39 (C_6H_{11}-*C1*), 55.17 (O*C*H_3), 69.15 (C^{α}), 114.17 (NCH_2Ph-*C3,5*), 126.85, 126.88 (2 × CCH_2Ph-*C4* + $COCH_2Ph$-*C4*), 127.07 (NCH_2Ph-*C2,6*), 128.11 (2 × CCH_2Ph-*C3,5*), 128.54 ($COCH_2Ph$-*C3,5*), 129.49 ($COCH_2Ph$-*C2,6*), 130.97 (2 × CCH_2Ph-*C2,6* + NCH_2Ph-*C1*), 134.71 ($COCH_2Ph$-*C1*), 135.33 (2 × CCH_2Ph-*C1*), 158.47 (NCH_2Ph-*C4*), 170.86 (*C*ONH), 172.64 (*C*OCH_2). Anal. Calcd. for $C_{38}H_{42}N_2O_3$: C, 79.41; H, 7.37; N, 4.87. Found: C, 79.07; H, 6.94; N, 4.94. ***N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dibenzylglycine cyclohexylamide (2b).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2b** (3.36 g, 60%) as a white solid, mp 201.8-202.9 ºC. ^1H RMN (300 MHz, $CDCl_3$): 0.86-1.12 (3H, m, C_6H_{11}), 1.27-1.35 (2H, m, C_6H_{11}), 1.54-1.63 (5H, m, C_6H_{11}), 2.35 (3H, s, CH_3Ph), 2.94 (2H, d, *J*=12.0 Hz, CCH_2Ph), 3.35 (2H, br d, *J*=11.7 Hz, CCH_2Ph), 3.52-3.56 (1H, m, C_6H_{11}-*H1*), 3.56 (2H, s, $COCH_2$), 3.72 (2H, br s, NCH_2), 5.07 (1H, d, *J*=7.5 Hz, N*H*), 7.16-7.26 (12H, m, NCH_2Ph-*H3,5* + 2 × CCH_2Ph), 7.33 (5H, m, $COCH_2Ph$), 7.62 (2H, d, *J*=7.8 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 20.99 (*C*H_3Ph), 24.84 (C_6H_{11}-*C3,5*), 25.55 (C_6H_{11}-*C4*), 32.56 (C_6H_{11}-*C2,6*), 36.07 (2 × C*C*H_2Ph), 42.08 (*C*H_2CO), 47.60

(*C*H_2N), 48.35 (C_6H_{11}-*C1*), 69.13 (C^{α}), 125.84 (NCH_2Ph-*C2,6*), 126.85 (2 × CCH_2Ph-*C4* + COCH_2Ph-*C4*), 128.08 (2 × CCH_2Ph-*C3,5*), 128.52 (COCH_2Ph-*C3,5*), 129.48 (COCH_2Ph-*C2,6* + NCH_2Ph-*C3,5*), 130.95 (2 × CCH_2Ph-*C2,6*), 134.68 (COCH_2Ph-*C1*), 135.33 (2 × CCH_2Ph-*C1*), 136.00 (NCH_2Ph-*C1*), 136.37 (NCH_2Ph-*C4*), 170.78 (*C*ONH), 172.63 (*C*OCH_2). Anal. Calcd. for $C_{38}H_{40}N_2O_2$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.84; H, 7.41; N, 5.15.

N*-Phenylacetyl-*N*-benzyl-α,α-dibenzylglycine cyclohexylamide (2c).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2c** (2.40 g, 44%) as a white crystals, mp 206.5-207.4 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 0.66-1.16 (3H, m, C_6H_{11}), 1.21-1.42 (2H, m, C_6H_{11}), 1.50-1.82 (5H, m, C_6H_{11}), 2.94 (2H, d, *J*= 11.7 Hz, CCH_2Ph), 3.34 (2H, br d, *J*= 10.5 Hz, CCH_2Ph), 3.54 (3H, s, COCH_2 + C_6H_{11}-*H1*), 3.74 (2H, br s, NCH_2), 5.05 (1H, d, *J*= 7.5 Hz, N*H*), 7.12-7.23 (11H, m, 2 × CCH_2*Ph* + NCH_2Ph-*H4*), 7.35-7.42 (7H, m, NCH_2Ph-*H3,5* + COCH_2*Ph*), 7.75 (2H, d, *J*= 9.0 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.85 (C_6H_{11}-*C3,5*), 25.54 (C_6H_{11}-*C4*), 32.55 (C_6H_{11}-*C2,6*), 36.12 (2 × C*C*H_2Ph), 42.09 (*C*H_2CO), 47.73 (*C*H_2N), 48.38 (C_6H_{11}-*C1*), 69.10 (C^{α}), 125.92 (NCH_2Ph-*C2,6*), 126.83, 126.89 (2 × CCH_2Ph-*C4* + NCH_2Ph-*C4* + COCH_2Ph-*C4*), 128.12 (2 × CH_2Ph-*C3,5*), 128.56 (NCH_2Ph-*C3,5*), 128.79 (COCH_2Ph-*C3,5*), 129.46 (COCH_2Ph-*C2,6*), 130.94 (2 × CH_2Ph-*C2,6*), 134.58 (COCH_2Ph-*C1*), 135.25 (2 × CCH_2Ph-*C1*), 139.05 (NCH_2Ph-*C1*), 170.79 (*C*ONH), 172.65 (*C*OCH_2). Anal. Calcd. for $C_{37}H_{40}N_2O_2$: C, 81.58; H, 7.40; N, 5.14. Found: C, 81.56; H, 7.27; N, 5.27.N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dibenzylglycine cyclohexylamide (2d).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2d** (4.80 g, 85%) as a white solid, mp 190.9-192.2 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 0.85-1.11 (3H, m, C_6H_{11}), 1.22-1.35 (2H, m, C_6H_{11}), 1.53-1.62 (5H, m, C_6H_{11}), 2.91 (2H, d, *J*=12.0 Hz, CCH_2Ph), 3.34 (2H, br d, *J*=10.8 Hz, CCH_2Ph), 3.51 (2H, s, COCH_2), 3.49-3.58 (1H, m, C_6H_{11}-*H1*), 3.72 (2H, br s, NCH_2), 5.04 (1H, d, *J*=7.5 Hz, N*H*), 7.08 (2H, t, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.13-7.29 (10H, m, 2 × CCH_2*Ph*), 7.33-7.37 (5H, m, COCH_2*Ph*), 7.75 (2H, dd, *J*=5.4, 8.4 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.81 (C_6H_{11}-*C3,5*), 25.52 (C_6H_{11}-*C*4), 32.52 (C_6H_{11}-*C2,6*), 36.00 (2 × C*C*H_2Ph), 42.07 (*C*H_2CO), 47.12 (*C*H_2N), 48.23 (C_6H_{11}-

C1), 69.13 (C^{α}), 115.58 (d, $J_{C\text{-}F}$=21.3 Hz, NCH_2Ph-*C3,5*), 126.90, 126.94 (2 × CCH_2Ph-*C4* + $COCH_2Ph$-*C4*), 127.58 (d, $J_{C\text{-}F}$=7.8 Hz, NCH_2Ph-*C2,6*), 128.14 (2 × CCH_2Ph-*C3,5*), 128.56 ($COCH_2Ph$-*C3,5*), 129.40 ($COCH_2Ph$-*C2,6*), 130.91 (2 × CCH_2Ph-*C2,6*), 134.47 ($COCH_2Ph$-*C1*), 134.70 (d, $J_{C\text{-}F}$=2.9 Hz, NCH_2Ph-*C1*), 135.15 (2 × CCH_2Ph-*C1*), 161.79 (d, $J_{C\text{-}F}$=245.0 Hz, NCH_2Ph-*C4*), 170.84 (*C*ONH), 172.51 (*C*OCH_2). Anal. Calcd. for $C_{37}FH_{39}N_2O_2$: C, 78.97; H, 6.99; N, 4.98. Found: C, 79.11; H, 6.68; N, 4.94.

***N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dibenzylglycine cyclohexylamide (2e).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2e** (4.37 g, 76%) as a beige solid, mp 180.6-181.5 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 0.84-1.07 (3H, m, C_6H_{11}), 1.20-1.30 (2H, m, C_6H_{11}), 1.53-1.62 (5H, m, C_6H_{11}), 2.90 (2H, d, *J*=12.0 Hz, CCH_2Ph), 3.33 (2H, br d, *J*=10.8 Hz, CCH_2Ph), 3.48-3.55 (1H, m, C_6H_{11}-*H1*), 3.50 (2H, s, $COCH_2$), 3.69 (2H, br s, NCH_2), 5.02 (1H, d, *J*=7.5 Hz, N*H*), 7.13-7.26 (10H, m, 2 × CCH_2Ph), 7.30-7.37 (7H, m, $COCH_2Ph$ + NCH_2Ph-*H3,5*), 7.72 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.83 (C_6H_{11}-*C3,5*), 25.52 (C_6H_{11}-*C4*), 32.53 (C_6H_{11}-*C2,6*), 35.97 (2 × CCH_2Ph), 42.11 (CH_2CO), 47.19 (CH_2N), 48.44 (C_6H_{11}-*C1*), 69.11 (C^{α}), 126.95, 127.00 (2 × CCH_2Ph-*C4* + $COCH_2Ph$-*C4*), 127.45 (NCH_2Ph-*C2,6*), 128.17 (2 × CCH_2Ph-*C3,5*), 128.61 (NCH_2Ph-*C3,5*), 128.91 ($COCH_2Ph$-*C3,5*), 129.39 ($COCH_2Ph$-*C2,6*), 130.91 (2 × CCH_2Ph-*C2,6*), 132.66 (NCH_2Ph-*C4*), 134.38 ($COCH_2Ph$-*C1*), 135.08 (2 × CCH_2Ph-*C1*), 137.66 (NCH_2Ph-*C1*), 170.81 (*C*ONH), 172.49 (*C*OCH_2). Anal. Calcd. for $C_{37}ClH_{39}N_2O_2$: C, 76.73; H, 6.79; N, 4.84. Found: C, 76.73; H, 6.73; N, 4.90.

***N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dibenzylglycine cyclohexylamide (2f).** The reaction was carried out on a 0.0056-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2f** (2.23 g, 63%) as a white solid, mp 169.0-170.0 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 0.85-1.11 (3H, m, C_6H_{11}), 1.22-1.35 (2H, m, C_6H_{11}), 1.54-1.63 (5H, m, C_6H_{11}), 2.91 (2H, d, *J*=11.7 Hz, CCH_2Ph), 3.35 (2H, br d, *J*=10.8 Hz, CCH_2Ph), 3.48-3.59 (1H, m, C_6H_{11}-*H1*), 3.51 (2H, s, $COCH_2$), 3.75 (2H, br s, NCH_2), 5.04 (1H, d, *J*=7.5 Hz, N*H*), 7.14-7.27 (12H, m, 2 × CCH_2Ph + NCH_2Ph-*H3,5*), 7.31-7.38 (5H, m, $COCH_2Ph$), 7.81 (2H, d, *J*=9.0 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.84 (C_6H_{11}-*C3,5*), 25.53 (C_6H_{11}-*C4*), 32.53 (C_6H_{11}-*C2,6*), 36.09 (2 × CCH_2Ph), 42.07 (CH_2CO), 47.16 (CH_2N), 48.49 (C_6H_{11}-*C1*), 69.14 (C^{α}), 120.41 (q, $J_{C\text{-}F}$=257.1 Hz, O*C*F_3), 121.21 (NCH_2Ph-

C3,5), 126.98, 127.01 (2 × CCH_2Ph-*C4* + $COCH_2$Ph-*C4*), 128.44 (NCH_2Ph-*C2,6*), 128.19 (2 × CCH_2Ph-*C3,5*), 128.62 ($COCH_2$Ph-*C3,5*), 129.40 ($COCH_2$Ph-*C2,6*), 130.92 (2 × CCH_2Ph-*C2,6*), 134.33 ($COCH_2$Ph-*C1*), 135.07 (2 × CCH_2Ph-*C1*), 137.79 (NCH_2Ph-*C1*), 148.11 (q, $J_{C\text{-}F}$=1.8 Hz, NCH_2Ph-*C4*), 170.86 (*C*ONH), 172.50 (*C*OCH_2). Anal. Calcd. for $C_{38}F_3H_{39}N_2O_3$: C, 72.59; H, 6.25; N, 4.46. Found: C, 72.72; H, 5.89; N, 4.53. ***N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dibenzylglycine cyclohexylamide (2g).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2g** (4.79 g, 78%) as a white solid, mp 213.5-214.5 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 0.87-1.12 (3H, m, C_6H_{11}), 1.24-1.36 (2H, m, C_6H_{11}), 1.59 (5H, m, C_6H_{11}), 2.89 (2H, d, *J*=11.7 Hz, CCH_2Ph), 3.34 (2H, br s, CCH_2Ph), 3.50 (2H, s, $COCH_2$), 3.52-3.60 (1H, m, C_6H_{11}-*H1*), 3.80 (2H, br s, NCH_2), 5.05 (1H, d, *J*=7.5 Hz, N*H*), 7.14-7.30 (10H, m, 2 × $CCCH_2Ph$), 7.31-7.38 (5H, m, $COCH_2Ph$), 7.65 (2H, d, *J*=8.1 Hz, NCH_2Ph-*H3,5*), 7.92 (2H, d, *J*=8.1 Hz, NCH_2Ph-*H2,6*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.81 (C_6H_{11}-*C3,5*), 25.48 (C_6H_{11}-*C4*), 32.49 (C_6H_{11}-*C2,6*), 36.01 (2 × CCH_2Ph), 42.15 (CH_2CO), 47.45 (CH_2N), 48.46 (C_6H_{11}-*C1*), 69.11 (C^{α}), 124.07 (q, $J_{C\text{-}F}$=272.0 Hz, CF_3), 125.68 (q, $J_{C\text{-}F}$=3.8 Hz, NCH_2Ph-*C3,5*), 126.39 (NCH_2Ph-*C2,6*), 126.98, 127.01 (2 × CCH_2Ph-*C4* + $COCH_2$Ph-*C4*), 128.17 (2 × CCH_2Ph-*C3,5*), 128.61 ($COCH_2$Ph-*C3,5*), 129.33 ($COCH_2$Ph-*C2,6*), 129.20 (q, $J_{C\text{-}F}$=32.5 Hz, NCH_2Ph-*C4*), 130.87 (2 × CCH_2Ph-*C2,6*), 134.17 ($COCH_2$Ph-*C1*), 134.96 (2 × CCH_2Ph-*C1*), 143.32 (NCH_2Ph-*C1*), 170.79 (*C*ONH), 172.41 (*C*OCH_2). Anal. Calcd. for $C_{38}F_3H_{39}N_2O_2$: C, 74.49; H, 6.42; N, 4.57. Found: C, 74.46; H, 6.07; N, 4.63. ***N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dibenzylglycine cyclohexylamide (2h)**. The reaction was carried out on a 0.003-molar scale, starting with 4-nitrobenzylamine hydrochloride (1.3 eq., 2.45 g), which was neutralised with triethylamine (1.2 eq., 1.66 ml) in dry diethyl ether (20 ml) at room temperature and under stirring for 90 min. The reaction mixture was filtered and the filtrate concentrated under reduced pressure; the residue was dissolved in dry MeOH (5 ml) and used according to the general procedure described above. The final product was purified by column chromatography and recrystallised from ethyl acetate to yield **2h** (0.84 g, 47%) as a pale yellow solid, mp 211.8-212.8 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 0.88-1.11 (3H, m, C_6H_{11}), 1.24-1.35 (2H, m, C_6H_{11}), 1.53-1.63 (5H, m, C_6H_{11}), 2.87 (2H, d, *J*=11.7 Hz, CCH_2Ph), 3.34 (2H, br s, CCH_2Ph), 3.48 (2H, s, $COCH_2$), 3.52-3.58 (1H, m, C_6H_{11}-*H1*), 3.82 (2H, br s, NCH_2), 5.04 (1H, d, *J*=7.8 Hz, N*H*), 7.17-7.25

(10H, m, 2 × CCH_2*Ph*), 7.30-7.38 (5H, m, $COCH_2$*Ph*), 8.00 (2H, d, *J*=8.1 Hz, NCH_2Ph-*H2,6*), 8.24 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.80 (C_6H_{11}-*C3,5*), 25.49 (C_6H_{11}-*C4*), 32.48 (C_6H_{11}-*C2,6*), 35.93 (2 × C*C*H_2Ph), 42.22 (*C*H_2CO), 47.46 (*C*H_2N), 48.54 (C_6H_{11}-*C1*), 69.15(C^{α}), 124.01 (NCH_2Ph-*C3,5*), 127.02, 127.12 (2 × CCH_2Ph-*C4* + NCH_2Ph-*C2,6* + $COCH_2$Ph-*C4*), 128.25 (2 × CCH_2Ph-*C3,5*), 128.70 ($COCH_2$Ph-*C3,5*), 129.28 ($COCH_2$Ph-*C2,6*), 130.85 (2 × CCH_2Ph-*C2,6*), 133.91 ($COCH_2$Ph-*C1*), 134.80 (2 × CCH_2Ph-*C1*), 146.85 (NCH_2Ph-*C4*), 147.06 (NCH_2Ph-*C1*), 170.78 (*C*ONH), 172.27 (*C*OCH_2). Anal. Calcd. for $C_{37}H_{39}N_3O_4$: C, 75.36; H, 6.67; N, 7.13. Found: C, 75.05; H, 6.60; N, 6.92. ***N*-Phenylacetyl-*N*-(4-methoxyfenyl)-α,α-dimethylglycine cyclohexylamide (3a).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from diethyl ether to yield **3a** (3.77 g, 92%) as a white crystals, mp 105.7-106.8 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.06-1.21 (3H, m, C_6H_{11}), 1.31 (6H, s, 2 × CH_3), 1.37-1.39 (2H, m, C_6H_{11}), 1.58-1.72 (3H, m, C_6H_{11}), 1.93 (2H, m, C_6H_{11}), 3.33 (2H, s, CH_2), 3.69-3.81 (1H, m, C_6H_{11}-*H1*), 3.84 (3H, s, OCH_3), 5.64 (1H, d, *J*=8.1 Hz, N*H*), 6.86 (2H, d, *J*=9.0 Hz, NPh-*H3,5*), 6.99 (2H, m, CH_2Ph-*H2,6*), 7.06 (2H, d, *J*=8.7 Hz, NPh-*H2,6*), 7.20 (3H, m, CH_2Ph-*H3,4,5*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.75 (C_6H_{11}-*C3,5*), 25.29 (2 × *C*H_3), 25.51 (C_6H_{11}-*C4*), 32.75 (C_6H_{11}-*C2,6*), 42.59 (*C*H_2), 48.30 (C_6H_{11}-*C1*), 55.33 (O*C*H_3), 62.61 (C^{α}), 113.99 (NPh-*C3,5*), 126.35 (CH_2Ph-*C4*), 128.11 (CH_2Ph-*C3,5*), 128.83 (CH_2Ph-*C2,6*), 131.27 (NPh-*C2,6*), 132.33 (NPh-*C1*), 135.23 (CH_2Ph-*C1*), 159.21 (NPh-*C4*), 171.23 (*C*ON), 173.71 (*C*ONH). Anal. Calcd. for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.24; H, 7.91; N, 6.97. ***N*-Phenylacetyl-*N*-phenyl-α,α-dimethylglycine cyclohexylamide (3b).** The reaction was carried out on a 0.02-molar scale and the crude product purified by column chromatography as described above and recrystallised from diethyl ether to yield **3b** (6.53 g, 86%) as a white crystals, mp 127.2-128.3 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.03-1.23 (3H, m, C_6H_{11}), 1.34 (6H, s, 2 × CH_3), 1.35-1.40 (2H, m, C_6H_{11}), 1.66-1.71 (3H, m, C_6H_{11}), 1.94 (2H, m, C_6H_{11}), 3.33 (2H, s, CH_2), 3.70-3.83 (1H, m, C_6H_{11}-*H1*), 5.66 (1H, d, *J*=7.5 Hz, N*H*), 6.98 (2H, m, CH_2Ph-*H2,6*), 7.16-7.22 (5H, m, NPh-*H2,6* + CH_2Ph-*H3,4,5*), 7.39 (3H, m, NPh-*H3,4,5*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.78 (C_6H_{11}-*C3,5*), 25.37 (2 × *C*H_3), 25.55 (C_6H_{11}-*C4*), 32.79 (C_6H_{11}-*C2,6*), 42.69 (*C*H_2), 48.36 (C_6H_{11}-*C1*), 62.56 (C^{α}), 126.41 (CH_2Ph-*C4*), 128.16 (CH_2Ph-*C3,5*), 128.46 (NPh-*C4*), 128.84 (CH_2Ph-*C2,6*), 129.03 (NPh-*C3,5*), 130.43 (NPh-*C2,6*), 135.16 (CH_2Ph-*C1*),

139.67 (NPh-*C1*), 170.83 (*C*ON), 173.62 (*C*ONH). Anal. Calcd. for$C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.17; H, 7.90; N, 7.51. ***N*-Phenylacetyl-*N*-(4-chlorofenyl)-α,α-dimethylglycine cyclohexylamide (3c).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **3c** (2.93 g, 71%) as a white crystals, mp 118.9-119.7 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.05-1.22 (3H, m, C_6H_{11}), 1.31 (6H, s, 2 × CH_3), 1.34-1.43 (2H, m, C_6H_{11}), 1.57-1.73 (3H, m, C_6H_{11}), 1.95 (2H, m, C_6H_{11}), 3.32 (2H, s, CH_2), 3.71-3.80 (1H, m, C_6H_{11}-*H1*), 5.63 (1H, d, *J*=7.8 Hz, N*H*), 6.96 (2H, m, CH_2Ph-*H2,6*), 7.11 (2H, d, *J*=8.7 Hz, NPh-*H2,6*), 7.18-7.21 (3H, m, CH_2Ph-*H3,4,5*), 7.31 (2H, d, *J*=8.4 Hz, NPh-*H3,5*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.82 (C_6H_{11}-*C3,5*), 25.48 (2 × *C*H_3), 25.56 (C_6H_{11}-*C4*), 32.85 (C_6H_{11}-*C2,6*), 42.83 (*C*H_2), 48.54 (C_6H_{11}-*C1*), 62.54 (C^{α}), 126.54 (CH_2Ph-*C4*), 128.28 (CH_2Ph-*C3,5*), 128.76 (CH_2Ph-*C2,6*), 129.17 (NPh-*C3,5*), 131.87 (NPh-*C2,6*), 134.42 (NPh-*C4*), 134.93 (CH_2Ph-*C1*), 138.35 (NPh-*C1*), 170.74 (*C*ON), 173.50 (*C*ONH). Anal. Calcd. for $C_{24}ClH_{29}N_2O_2$: C, 69.80; H, 7.08; N, 6.75. Found: C, 69.58; H, 7.07; N, 6.81. ***N*-Phenylacetyl-*N*-(4-cyanofenyl)-α,α-dimethylglycine cyclohexylamide (3d).** The reaction was carried out on a 0.01-molar scale and the crude product purified by column chromatography as described above and recrystallised from ethyl acetate to yield **3d** (0.96 g, 24%) as a white crystals, mp 166.0-167.1 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.08-1.21 (3H, m, C_6H_{11}), 1.32 (6H, s, 2 × CH_3), 1.34-1.42 (2H, m, C_6H_{11}), 1.59-1.74 (3H, m, C_6H_{11}), 1.96 (2H, m, C_6H_{11}), 3.29 (2H, s, CH_2), 3.70-3.82 (1H, m, C_6H_{11}-*H1*), 5.65 (1H, d, *J*=7.8 Hz, N*H*), 6.90 (2H, m, CH_2Ph-*H2,6*), 7.16-7.20 (3H, m, CH_2Ph-*H3,4,5*), 7.34 (2H, d, *J*=8.1 Hz, NPh-*H2,6*), 7.62 (2H, d, *J*=8.4 Hz, NPh-*H3,5*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.79 (C_6H_{11}-*C3,5*), 25.49 (2 × *C*H_3), 25.54 (C_6H_{11}-*C4*), 32.81 (C_6H_{11}-*C2,6*), 43.09 (*C*H_2), 48.68 (C_6H_{11}-*C1*), 62.60 (C^{α}), 112.46 (NPh-*C4*), 117.82 (NPh-*C*N), 126.68 (CH_2Ph-*C4*), 128.37 (CH_2Ph-*C3,5*), 128.55 (CH_2Ph-*C2,6*), 131.77 (NPh-*C2,6*), 132.76 (NPh-*C3,5*), 134.46 (CH_2Ph-*C1*), 143.99 (NPh-*C1*), 170.15 (*C*ON), 173.22 (*C*ONH). Anal. Calcd. for $C_{25}H_{29}N_3O_2$: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.26; H, 7.22; N, 10.38. ***N*-Phenylacetyl-*N*-(4-nitrofenyl)-α,α-dimethylglycine cyclohexylamide (3e).** The reaction was carried out on a 0.04-molar scale and the crude product purified by column chromatography as described above and recrystallised from diethyl ether to yield **3e** (1.47 g, 9%) as a yellow crystals, mp 100.9-101.9 ºC ^{1}H RMN (300 MHz, $CDCl_3$): 1.11-1.24 (3H, m, C_6H_{11}), 1.36 (6H, s, 2 × CH_3), 1.42-1.46 (2H, m,

C_6H_{11}), 1.58-1.76 (3H, m, C_6H_{11}), 2.00 (2H, m, C_6H_{11}), 3.33 (2H, s, CH_2), 3.74-3.85 (1H, m, C_6H_{11}-*H1*), 5.64 (1H, d, *J*=7.8 Hz, N*H*), 6.93 (2H, m, CH_2Ph-*H2,6*), 7.20-7.22 (3H, m, CH_2Ph-*H3,4,5*), 7.41 (2H, d, *J*=9.0 Hz, NPh-*H2,6*), 8.20 (2H, d, *J*=9.0 Hz, NPh-*H3,5*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.86 (C_6H_{11}-*C3,5*), 25.56 (C_6H_{11}-*C4*), 25.64 (2 × CH_3), 32.90 (C_6H_{11}-*C2,6*), 43.19 (CH_2), 48.79 (C_6H_{11}-*C1*), 62.68 (C^{α}), 124.14 (NPh-*C3,5*), 126.80 (CH_2Ph-*C4*), 128.47 (CH_2Ph-*C3,5*), 128.61 (CH_2Ph-*C2,6*), 131.93 (NPh-*C2,6*), 134.45 (CH_2Ph-*C1*), 145.82 (NPh-*C4*), 147.41 (NPh-*C1*), 170.14 (*C*ON), 173.27 (*C*ONH). Anal. Calcd. for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 67.98; H, 6.88; N, 9.85. **General method for the preparative acidolysis of the Ugi-Passerini adducts (4, 5 and 6).**Compounds **1a**–**1h**, **2a**–**2h** and **3a**–**3d** (0.20 or 0.25 g, depending on the solubility) were dissolved in 25 ml of 5% TFA in dry acetonitrile and the solutions kept at room temperature until TLC (dichloromethane/MeOH 25:1) showed no more starting material (2 to 168 hours). The solvent was concentrated under reduced pressure at 30 ºC and the pH of the residue adjusted to 3 by treatment with 2M aqueous NaOH. The mixture was stirred overnight and the resulting suspension extracted into chloroform (3 × 15 ml). The combined organic layers were washed with water (2 × 20 ml) and dried over anhydrous $MgSO_4$; this was filtered off and the filtrate concentrated under reduced pressure. The residue thus obtained was purified by column chromatography and/or recrystallisation; in the former case the desired fraction was evaporated to dryness to give the corresponding compound (**4**, **5** and **6**).***N*-Phenylacetyl-*N*-(4-methoxylbenzyl)-α,α-dimethylglycine (4a).** The reaction was carried out with 0.20 g of compound **1a** and the product purified by recrystallisation from ethyl acetate to yield **4a** (140 mg, 84%), as a white solid, mp 201.1-202.1 °C (lit.[19] 168.6-169.2 ºC). ^{1}H NMR (300 MHz, DMSO-d_6): 1.27 (6H, s, 2 × CH_3), 3.57 (2H, s, CH_2CO), 3.76 (3H, s, OCH_3) 4.59 (2H, s, NCH_2), 6.94 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.11-14 (2H, m, $COCH_2$Ph-*H2,6*), 7.17-7.29 (3H, m, $COCH_2$Ph-*H3,4,5*), 7.36 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 12.02 (1H, br s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 2 × CH_3), 40.34 (CH_2CO), 46.12 (CH_2N), 55.06 (OCH_3), 60.69 (C^{α}), 113.99 (NCH_2Ph-*C3,5*), 126.40 ($COCH_2$Ph-*C4*), 127.03 (NCH_2Ph-*C2,6*), 128.27 ($COCH_2$Ph-*C3,5*), 128.92 ($COCH_2$Ph-*C2,6*), 130.92 (NCH_2Ph-*C1*), 135.58 ($COCH_2$Ph-*C1*), 158.20 (NCH_2Ph-*C4*), 170.78 (*C*OCH_2), 175.20 (*C*OOH). Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.87; H, 6.82; N, 4.21.***N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dimethylglycine (4b).** The reaction was carried out with 0.21 g of

compound **1b** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **4b** (152 mg, 89%), as a white solid, mp 160.7-161.7 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (6H, s, 2 × CH_3), 2.39 (3H, s, Ph-CH_3), 3.70 (2H, s, CH_2CO), 4.57 (2H, s, NCH_2), 7.21-7.35 (9H, m, $COCH_2$*Ph* + NCH_2*Ph*), 9.81 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): Ph-*C*H_3), 2 × *C*H_3), 41.36 (*C*H_2CO), 47.12 (*C*H_2N), 61.40 (C^{α}), 125.76 (NCH_2Ph-*C2,6*), 126.76 ($COCH_2$Ph-*C4*), 128.57 ($COCH_2$Ph-*C2,6*), 128.63 ($COCH_2$Ph-*C3,5*), 129.56 (NCH_2Ph-*C3,5*), 134.54 ($COCH_2$Ph-*C1*), 134.86 (NCH_2Ph-*C1*), 136.92 (NCH_2Ph-*C4*), 172.11 (*C*OCH_2), 179.05 (*C*OOH). Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.64; H, 7.01; N, 4.41. Compound **4b** was also obtained, in a yield of 79%, when 0.25 g of **1b** was submitted to the forcing reaction conditions described below for the preparation of **6e**.

***N*-Phenylacetyl-*N*-benzyl-α,α-dimethylglycine (4c).** The reaction was carried out with 0.20 g of compound **1c** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **4c** (121 mg, 76%), as a white solid, mp 196.9-197.9 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 1.47 (6H, s, 2 × CH_3), 3.69 (2H, s, CH_2CO), 4.61 (2H, s, NCH_2), 7.21-7.31 (6H, m, $COCH_2$*Ph* + NCH_2Ph-*H4*), 7.41-7.45 (4H, m, NCH_2Ph-*H2,3,5,6*), 9.41 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.50 (2 × *C*H_3), 41.36 (*C*H_2CO), 47.31 (*C*H_2N), 61.44 (C^{α}), 125.79 (NCH_2Ph-*C2,6*), 126.78 ($COCH_2$Ph-*C4*), 127.26 (NCH_2Ph-*C4*), 128.56 ($COCH_2$Ph-*C2,6*), 128.63 ($COCH_2$Ph-*C3,5*), 128.88 (NCH_2Ph-*C3,5*), 134.44 ($COCH_2$Ph-*C1*), 137.93 (NCH_2Ph-*C1*), 172.16 (*C*OCH_2), 178.99 (*C*OOH). Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.59; N, 4.61. ***N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dimethylglycine (4d).** The reaction was carried out with 0.25 g of compound **1d** and the product purified by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **4d** (191 mg, 97%), as white crystals, mp 191.4-192.2 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2 × CH_3), 3.67 (2H, s, CH_2CO), 4.56 (2H, s, NCH_2), 7.10 (2H, t, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.18-7.33 (5H, m, $COCH_2$*Ph*), 7.41 (2H, dd, *J*=5.4, 8.4 Hz, NCH_2Ph-*H2,6*), 9.43 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.47 (2 × *C*H_3), 41.41 (*C*H_2CO), 46.68 (*C*H_2N), 61.47 (C^{α}), 115.81 (d, $J_{C\text{-}F}$=21.6 Hz, NCH_2Ph-*C3,5*), 126.90 ($COCH_2$Ph-*C4*), 127.41 (d, $J_{C\text{-}F}$=7.8 Hz, NCH_2Ph-*C2,6*), 128.52 ($COCH_2$Ph-*C2,6*), 128.72 ($COCH_2$Ph-*C3,5*), 133.59 (d, $J_{C\text{-}F}$=3.2 Hz, NCH_2Ph-*C1*), 134.29 ($COCH_2$Ph-*C1*), 162.01 (d, $J_{C\text{-}F}$=245.6 Hz, NCH_2Ph-*C4*),

172.15 (*C*OCH$_2$), 178.83 (*C*OOH). Anal. Calcd. for $C_{19}FH_{20}NO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.14; H, 6.10; N, 4.03. Compound **4d** was also obtained, in a yield of 66%, when 0.25 g of **1d** was submitted to the forcing reaction conditions described below for the preparation of **6e**.

***N*-Phenylacethyl-*N*-(4-chlorobenzyl)-α,α-dimethylglycine** (**4e**)**.** The reaction was carried out with 0.21 g of compound **1e** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **4e** (154 mg, 89%) as a white solid, mp 168.8-169.8 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 1.44 (6H, *s*, 2 × C*H*$_3$), 3.65 (2H, s, C*H*$_2$CO), 4.56 (2H, s, NC*H*$_2$), 7.18-7.38 (9H, m, COCH$_2$-*Ph* + NCH$_2$Ph-*H2,3,5,6*), 10.01 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.43 (2 × *C*H$_3$), 41.40 (*C*H$_2$CO), 46.72 (*C*H$_2$N), 61.45 (C^{α}), 126.90 (COCH$_2$Ph-*C4*), 127.21 (NCH$_2$Ph-*C2,6*), 128.47 (COCH$_2$Ph-*C2,6*), 128.71 (COCH$_2$Ph-*C3,5*), 129.05 (NCH$_2$Ph-*C3,5*), 133.08 (NCH$_2$Ph-*C4*), 134.18 (COCH$_2$Ph-*C1*), 136.49 (NCH$_2$Ph-*C1*), 172.11 (*C*OCH$_2$), 178.81 (*C*OOH). Anal. Calcd. for $C_{19}ClH_{20}NO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.68; H, 5.93; N, 4.01. ***N*-Phenylacetyl-*N*-(4-trifluoromethoxyfbenzyl)-α,α-dimethylglycine (4f).** The reaction was carried out with 0.25 g of compound **1f** and the product purified by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **4f** (153 mg, 90%) as a white solid, mp 149.9-150.7 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2 × C*H*$_3$), 3.66 (2H, s, C*H*$_2$CO), 4.59 (2H, s, NC*H*$_2$), 7.19-7.32 (7H, m, COCH$_2$*Ph* + NCH$_2$Ph-*H3,5*), 7.49 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*), 9.32 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.47 (2 × *C*H$_3$), 41.47 (*C*H$_2$CO), 46.69 (*C*H$_2$N), 61.49 (C^{α}), 120.4 (q, $J_{C\text{-}F}$=257.1 Hz, O*C*F$_3$), 121.45 (NCH$_2$Ph-*C3,5*), 126.96 (COCH$_2$Ph-*C4*), 127.21 (NCH$_2$Ph-*C2,6*), 128.50 (COCH$_2$Ph-*C2,6*), 128.76 (COCH$_2$Ph-*C3,5*), 134.15 (COCH$_2$Ph-*C1*), 136.71 (NCH$_2$Ph-*C1*), 148.39 (q, $J_{C\text{-}F}$=1.9 Hz, NCH$_2$Ph-*C4*), 172.17 (*C*OCH$_2$), 178.80 (*C*OOH). Anal. Calcd. for $C_{20}F_3H_{20}NO_4$: C, 60.76; H, 5.10; N, 3.54. Found: C, 60.67; H, 5.36; N, 3.28. ***N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dimethylglycine** (**4g**)**.** The reaction was carried out with 0.25 g of compound **1g** and the product purified by recrystallisation from ethyl acetate to yield **4g** (161 mg, 92%) as white crystals, mp 180.9-181.8 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (6H, *s*, 2 × C*H*$_3$), 3.65 (2H, s, C*H*$_2$CO), 4.64 (2H, s, NC*H*$_2$), 7.18 (2H, m, COCH$_2$-*H2,6*), 7.24-7.33 (3H, m, COCH$_2$Ph-*H3,4,5*), 7.60 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*), 7.67 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H3,5*), 9.00 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.48 (2 × *C*H$_3$),

41.54 (CH_2CO), 47.03 (CH_2N), 61.54 (C^{α}), 124.03 (q, $J_{C\text{-}F}$=274.0 Hz, CF_3), 125.93 (q, $J_{C\text{-}F}$=3.7 Hz, NCH_2Ph-*C3,5*), 126.20 (NCH_2Ph-*C2,6*), 127.02 ($COCH_2Ph$-*C4*), 128.48 ($COCH_2Ph$-*C2,6*), 128.80 ($COCH_2Ph$-*C3,5*), 129.75 (q, $J_{C\text{-}F}$=32.5 Hz, NCH_2Ph-*C4*), 134.06 ($COCH_2Ph$-*C1*), 142.25 (NCH_2Ph-*C1*), 172.17 ($COCH_2$), 178.67 (COOH). Anal. Calcd. for $C_{20}F_3H_{20}NO_3$: C, 63.32; H, 5.31; N, 3.69. Found: C, 63.38; H, 5.04; N, 3.62. ***N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dimethylglycine (4h).** The reaction was carried out with 0.20 g of compound **1h** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **4h** (146 mg, 89%) as pale yellow crystals, mp 194.7-195.8 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2 × CH_3), 3.64 (2H, s, CH_2CO), 4.68 (2H, s, NCH_2), 7.17 (2H, d, *J*=6.6 Hz, $COCH_2Ph$-*H2,6*), 7.22-7.32 (3H, m, $COCH_2Ph$-*H3,4,5*), 7.66 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 8.26 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 9.03 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 24.44 (2 × CH_3), 41.60 (CH_2CO), 47.00 (CH_2N), 61.59 (C^{α}), 124.19 (NCH_2Ph-*C3,5*), 126.73 (NCH_2Ph-*C2,6*), 127.14 ($COCH_2Ph$-*C4*), 128.41 ($COCH_2Ph$-*C2,6*), 128.87 ($COCH_2Ph$-*C3,5*), 133.75 ($COCH_2Ph$-*C1*), 145.65 (NCH_2Ph-*C1*), 147.32 (NCH_2Ph-*C4*), 172.12 ($COCH_2$), 178.51 (COOH). Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.89; H, 5.65; N, 7.59. ***N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine (5a).** The reaction was carried out with 0.25 g of compound **2a** and the product purified by PLC (dichloromethane/MeOH, 15:1) followed by recrystallisation from ethyl acetate to yield **5a** (81 mg, 38%) as a white solid, mp 208.2-209.3 ºC (lit.[19] 158.2-159.2 ºC). ^{1}H RMN (300 MHz, DMSO-d_6): 2.77 (2H, d, *J*=12.9 Hz, CCH_2Ph), 3.26 (2H, d, *J*=13.2 Hz, CCH_2Ph), 3.44 (2H, s, $COCH_2$), 3.72 (3H, s, OCH_3), 3.80 (2H, s, NCH_2), 6.94 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.13-7.15 (2H, m, $COCH_2Ph$-*H2,6*), 7.19-7.34 (13H, m, 2 × CCH_2Ph + $COCH_2Ph$-*H3,4,5*), 7.44 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 12.34 (1H, br s, OH); ^{13}C RMN (75 MHz, DMSO-d_6): 36.22 (2 × CCH_2Ph), 40.50 (CH_2CO), 47.02 (CH_2N), 55.03 (OCH_3), 68.18 (C^{α}), 114.04 (NCH_2Ph-*C3,5*), 126.54 (2 × CCH_2Ph-*C4*), 126.75 (NCH_2Ph-*C2,6* + $COCH_2Ph$-*C4*), 128.16 (2 × CCH_2Ph-*C3,5*), 128.19 ($COCH_2Ph$-*C3,5*), 129.59 ($COCH_2Ph$-*C2,6*), 130.74 (2 × CCH_2Ph-*C2,6*), 130.96 (NCH_2Ph-*C1*), 135.04 ($COCH_2Ph$-*C1*), 135.68 (2 × CCH_2Ph-*C1*), 158.11 (NCH_2Ph-*C4*), 171.57 ($COCH_2$), 172.29 (COOH). Anal. Calcd. for $C_{32}H_{31}NO_4$: C, 77.87; H, 6.33; N, 2.84. Found: C, 77.44; H, 6.05; N, 2.86. ***N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dibenzylglycine (5b).** The reaction was carried

out with 0.25 g of compound **2b** and the product purified by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **5b** (200 mg, 93%) as a white solid, mp 212.5-213.7ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 2.34 (3H, s, C*H*$_3$Ph), 3.02 (2H, d, *J*=13.2 Hz, CC*H*$_2$Ph), 3.43 (2H, br d, *J*=12.9 Hz, CC*H*$_2$Ph), 3.61 (2H, s, COC*H*$_2$), 3.82 (2H, br s, NC*H*$_2$), 7.17-7.30 (12H, m, 2 × CCH$_2$*Ph* + NCH$_2$Ph-*H3,5*), 7.33-7.44 (7H, m, COCH$_2$*Ph* + NCH$_2$Ph-*H2,6*), 8.45 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 20.98 (*C*H$_3$Ph), 36.13 (2 × C*C*H$_2$Ph), 41.31 (*C*H$_2$CO), 48.11 (*C*H$_2$N), 68.88 (C^{α}), 125.57 (NCH$_2$Ph-*C2,6*), 127.01 (COCH$_2$Ph-*C4*), 127.06 (2 × CCH$_2$Ph-*C4*), 128.40 (2 × CCH$_2$Ph-*C3,5*), 128.58 (COCH$_2$Ph-*C3,5*), 129.62 (NCH$_2$Ph-*C3,5*), 129.72 (COCH$_2$Ph-*C2,6*), 130.87 (2 × CCH$_2$Ph-*C2,6*), 134.42 (COCH$_2$Ph-*C1*), 135.14 (NCH$_2$Ph-*C1*), 135.37 (2 × CCH$_2$Ph-*C1*), 136.68 (NCH$_2$Ph-*C4*), 173.42 (*C*OCH$_2$), 175.66 (*C*OOH). Anal. Calcd. for $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93. Found: C, 80.64; H, 6.64; N, 3.10. ***N*-Phenylacetyl-*N*-benzyl-α,α-dibenzylglycine (5c).** The reaction was carried out with 0.25 g of compound **2c** and the product purified by recrystallisation from ethyl acetate to yield **5c** (207 mg, 98%) as a white solid, mp 228.6-229.7 ºC. ^{1}H RMN (300 MHz, DMSO-d_6): 2.76 (2H, d, *J*=12.9 Hz, CC*H*$_2$Ph), 3.26 (2H, d, *J*=12.9 Hz, CC*H*$_2$Ph), 3.43 (2H, s, COC*H*$_2$), 3.94 (2H, s, NC*H*$_2$), 7.13 (2H, br dd, *J*=1.5, 6.6 Hz, COCH$_2$Ph-*H2,6*), 7.23-7.30 (14H, m, 2 × CCH$_2$*Ph* + NCH$_2$Ph-*H4* + COCH$_2$Ph-*H3,4,5*), 7.37 (2H, t, *J*=7.8 Hz, NCH$_2$Ph-*C3,5*), 7.53 (2H, d, *J*=7.5 Hz, NCH$_2$Ph-*H2,6*), 12.35 (1H, br s, O*H*); ^{13}C RMN (75 MHz, DMSO-d_6): 36.28 (2 × C*C*H$_2$Ph), 40.50 (*C*H$_2$CO), 47.58 (*C*H$_2$N), 68.23 (C^{α}), 125.66 (NCH$_2$Ph-*C2,6*), 126.57 (NCH$_2$Ph-*C4*), 126.78, 126.82 (2 × CCH$_2$Ph-*C4* + COCH$_2$Ph-*C4*), 128.19 (2 × CH$_2$Ph-*C3,5* + COCH$_2$Ph-*C3,5*), 128.63 (NCH$_2$Ph-*C3,5*), 129.60 (COCH$_2$Ph-*C2,6*), 130.75 (2 × CH$_2$Ph-*C2,6*), 134.98 (COCH$_2$Ph-*C1*), 135.67 (2 × CCH$_2$Ph-*C1*), 139.34 (NCH$_2$Ph-*C1*), 171.61 (*C*OCH$_2$), 172.27 (*C*OOH). Anal. Calcd. for $C_{31}H_{29}NO_3$: C, 80.32; H, 6.31; N, 3.02. Found: C, 80.23; H, 6.14; N, 3.14. ***N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dibenzylglycine (5d).** The reaction was carried out with 0.25 g of compound **2d** and the product purified by recrystallisation from ethyl acetate to yield **5d** (190 mg, 88%) as a white solid, mp 193.9-195.0 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 3.01 (2H, d, *J*=13.2 Hz, CC*H*$_2$Ph), 3.45 (2H, br d, *J*=12.6 Hz, CC*H*$_2$Ph), 3.60 (2H, s, COC*H*$_2$), 3.84 (2H, br s, NC*H*$_2$), 7.08 (2H, t, *J*=9.0 Hz, NCH$_2$Ph-*H3,5*), 7.25-7.33 (10H, m, 2 × CCH$_2$*Ph*), 7.35-7.41 (5H, m, COCH$_2$*Ph*), 7.43-7.50 (2H, m, NCH$_2$Ph-*H2,6*), 8.81 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 36.12 (2 × C*C*H$_2$Ph), 41.31 (*C*H$_2$CO), 47.68 (*C*H$_2$N), 68.93 (C^{α}), 115.84

(d, $J_{C\text{-}F}$=21.6 Hz, NCH_2Ph-*C3,5*), 127.16 (2 × CCH_2Ph-*C4* + $COCH_2Ph$-*C4*), 127.28 (d, $J_{C\text{-}F}$=7.8 Hz, NCH_2Ph-*C2,6*), 128.45 (2 × CCH_2Ph-*C3,5*), 128.64 ($COCH_2Ph$-*C3,5*), 129.64 ($COCH_2Ph$-*C2,6*), 130.82 (2 × CCH_2Ph-*C2,6*), 133.82 (d, $J_{C\text{-}F}$=3.2 Hz, NCH_2Ph-*C1*), 134.12 ($COCH_2Ph$-*C1*), 135.17 (2 × CCH_2Ph-*C1*), 161.88 (d, $J_{C\text{-}F}$=245.6 Hz, NCH_2Ph-*C4*), 173.41 (*C*OCH_2), 175.62 (*C*OOH). Anal. Calcd. for $C_{31}FH_{28}NO_3$: C, 77.32; H, 5.86; N, 2.91. Found: C, 76.97; H, 5.79; N, 2.92. ***N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dibenzylglycine (5e).** The reaction was carried out with 0.25 g of compound **2e** and the product purified by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **5e** (186 mg, 85%) as a white solid, mp 207.9-209.1 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 2.98 (2H, d, *J*=13.2 Hz, CCH_2Ph), 3.43 (2H, br d, *J*=12.9 Hz, CCH_2Ph), 3.57 (2H, s, $COCH_2$), 3.81 (2H, br s, NCH_2), 7.26-7.45 (19H, m, 2 × CCH_2Ph + $COCH_2Ph$ + NCH_2Ph), 8.22 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 36.06 (2 × CCH_2Ph), 41.36 (CH_2CO), 47.74 (CH_2N), 68.91 (C^{α}), 127.11 (NCH_2Ph-*C2,6*), 127.17 (2 × CCH_2Ph-*C4* + $COCH_2Ph$-*C4*), 128.47 (2 × CCH_2Ph-*C3,5*), 128.67 (NCH_2Ph-*C3,5*), 129.12 ($COCH_2Ph$-*C3,5*), 129.63 ($COCH_2Ph$-*C2,6*), 130.82 (2 × CCH_2Ph-*C2,6*), 132.99 (NCH_2Ph-*C4*), 134.03 ($COCH_2Ph$-*C1*), 135.13 (2 × CCH_2Ph-*C1*), 136.76 (NCH_2Ph-*C1*), 173.32 (*C*OCH_2), 175.48 (*C*OOH). Anal. Calcd. for $C_{31}ClH_{28}NO_3$: C, 74.76; H, 5.67; N, 2.81. Found: C, 74.48; H, 5.84; N, 2.94. ***N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dibenzylglycine (5f).** The reaction was carried out with 0.25 g of compound **2f** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **5f** (201 mg, 92%) as white crystals, mp 175.4-176.4 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 3.00 (2H, d, *J*=12.9 Hz, CCH_2Ph), 3.45 (2H, br d, *J*=12.9 Hz, CCH_2Ph), 3.59 (2H, s, $COCH_2$), 3.86 (2H, br s, NCH_2), 7.22-7.43 (17H, m, 2 × CCH_2Ph + NCH_2Ph-*H3,5* + $COCH_2Ph$), 7.53 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 8.51 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 36.13 (2 × CCH_2Ph), 41.37 (CH_2CO), 47.71 (CH_2N), 68.96 (C^{α}), 121.46 (NCH_2Ph-*C3,5*), 120.41 (q, $J_{C\text{-}F}$=257.1 Hz, O*C*F_3), 127.12 (NCH_2Ph-*C2,6*), 127.20, 127.22 (2 × CCH_2Ph-*C4* + $COCH_2Ph$-*C4*), 128.49 (2 × CCH_2Ph-*C3,5*), 128.68 ($COCH_2Ph$-*C3,5*), 129.63 ($COCH_2Ph$-*C2,6*), 130.83 (2 × CCH_2Ph-*C2,6*), 133.98 ($COCH_2Ph$-*C1*), 135.09 (2 × CCH_2Ph-*C1*), 136.91 (NCH_2Ph-*C1*), 148.28 (q, $J_{C\text{-}F}$=1.8 Hz, NCH_2Ph-*C4*), 173.41 (*C*OCH_2), 175.61 (*C*OOH). Anal. Calcd. for $C_{32}F_3H_{28}NO_4.{}^1/_3H_2O$: C, 69.43; H, 5.22; N, 2.53. Found: C, 69.53; H, 5.41; N, 2.58. ***N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dibenzylglycine (5g).** The

reaction was carried out with 0.25 g of compound **2g** and the product purified by recrystallisation from ethyl acetate to yield **5g** (207 mg, 95%) as white crystals, mp 201.9-203.0 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 2.99 (2H, d, *J*=12.9 Hz, CC*H*$_2$Ph), 3.45 (2H, br d, *J*=12.6 Hz, CC*H*$_2$Ph), 3.57 (2H, s, COC*H*$_2$), 3.91 (2H, br s, NC*H*$_2$), 7.27-7.42 (15H, m, 2 × CCCH$_2$*Ph* + COCH$_2$*Ph*), 7.64 (4H, s, NCH$_2$Ph-*H2,3,5,6*), 8.44 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 36.21 (2 × C*C*H$_2$Ph), 41.44 (*C*H$_2$CO), 48.01 (*C*H$_2$N), 68.96 (C^{α}), 124,00 (q, $J_{C\text{-}F}$=272.0 Hz, *C*F$_3$), 125.96 (q, $J_{C\text{-}F}$=3.8 Hz, NCH$_2$Ph-*C3,5*), 126.12 (NCH$_2$Ph-*C2,6*), 127.24 (2 × CCH$_2$Ph-*C4* + COCH$_2$Ph-*C4*), 128.51 (2 × CCH$_2$Ph-*C3,5*), 128.71 (COCH$_2$Ph-*C3,5*), 129.59 (q, $J_{C\text{-}F}$=32.5 Hz, NCH$_2$Ph-*C4*), 129.60 (COCH$_2$Ph-*C2,6*), 130.82 (2 × CCH$_2$Ph-*C2,6*), 133.85 (COCH$_2$Ph-*C1*), 135.03 (2 × CCH$_2$Ph-*C1*), 142.45 (NCH$_2$Ph-*C1*), 173.33 (*C*OCH$_2$), 175.40 (*C*OOH). Anal. Calcd. for $C_{32}F_3H_{28}NO_3.{}^1/_3H_2O$: C, 71.50; H, 5.37; N, 2.61. Found: C, 71.33; H, 5.25; N, 2.55.**N-Phenylacetyl-N-(4-nitrobenzyl)-α,α-dibenzylglycine (5h).** The reaction was carried out with 0.20 g of compound **2h** and the product purified by column chromatography (dichloromethane/MeOH, 100:1) followed by recrystallisation from ethyl acetate to yield **5h** (108 mg, 62%) as pale yellow crystals, mp 213.3-214.5 ºC. ^{1}H RMN (300 MHz, DMSO-d_6): 2.73 (2H, d, *J*=12.9 Hz, CC*H*$_2$Ph), 3.29 (2H, d, *J*=13.2 Hz CC*H*$_2$Ph), 3.44 (2H, s, COC*H*$_2$), 4.15 (2H, br s, NC*H*$_2$), 7.13 (2H, dd, *J*=1.5, 9.3 Hz, COCH$_2$Ph-*H2,6*), 7.21-7.29 (13H, m, 2 × CCH$_2$*Ph* + COCH$_2$Ph-*H3,4,5*), 7.78 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H2,6*), 8.21 (2H, d, *J*=9.0 Hz, NCH$_2$Ph-*H3,5*), 12.47 (1H, br s, O*H*); ^{13}C RMN (75 MHz, DMSO-d_6): 36.41 (2 × C*C*H$_2$Ph), 40.49 (*C*H$_2$CO), 47.51 (*C*H$_2$N), 68.39 (C^{α}), 123.63 (NCH$_2$Ph-*C3,*5), 126.57 (COCH$_2$Ph-*C4*), 126.83 (2 × CCH$_2$Ph-*C4*), 127.15 (NCH$_2$Ph-*C2,6*), 128.16 (COCH$_2$Ph-*C3,5*), 128.22 (2 × CCH$_2$Ph-*C3,5*), 129.65 (COCH$_2$Ph-*C2,6*), 130.75 (2 × CCH$_2$Ph-*C2,6*), 134.76 (COCH$_2$Ph-*C1*), 135.54 (2 × CCH$_2$Ph-*C1*), 146.50 (NCH$_2$Ph-*C4*), 147.52 (NCH$_2$Ph-*C1*), 171.68 (*C*OCH$_2$), 172.28 (*C*OOH). Anal. Calcd. for $C_{31}H_{28}N_2O_5$: C, 73.21; H, 5.55; N, 5.51. Found: C, 72.91; H, 5.46; N, 5.52. ***N*-Phenylacetyl-*N*-(4-methoxyfenyl)-α,α-dimethylglycine (6a).** The reaction was carried out with 0.20 g of compound **3a** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **6a** (75 mg, 47%) as white crystals, mp 164.2-165.5 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.36 (6H, s, 2 × C*H*$_3$), 3.40 (2H, s, C*H*$_2$), 3.85 (3H, s, OC*H*$_3$), 6.87 (2H, d, *J*=9.0 Hz, NPh-*H3,5*), 7.04 (2H, m, CH$_2$Ph-*H2,6*), 7.09 (2H, d, *J*=8.7 Hz, NPh-*H2,6*), 7.20 (3H, m, CH$_2$Ph-*H3,4,5*), 8.91 (1H, br s, O*H*);^{13}C RMN (75 MHz,

$CDCl_3$): 24.84 (2 × *C*H_3), 42.08 (*C*H_2), 55.43 (O*C*H_3), 61.69 (C^{α}), 114.17 (NPh-*C3,5*), 126.93 (CH_2Ph-*C4*), 128.14 (CH_2Ph-*C3,5*), 129.03 (CH_2Ph-*C2,6*), 131.26 (NPh-*C2,6*), 131.79 (NPh-*C1*), 135.08 (CH_2Ph-*C1*), 159.47 (NPh-*C4*), 171.60 (*C*ON), 179.08 (*C*OOH). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.52; H, 6.43; N, 4.35. ***N*-Phenylacetyl-*N*-phenyl-α,α-dimethylglycine** (**6b).** The reaction was carried out with 0.25 g of compound **3b** and the product purified by column chromatography (dichloromethane/MeOH, 12:1) followed by recrystallisation from ethyl acetate to yield **6b** (128 mg, 66%) as a white solid, mp 154.8-155.7 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.38 (6H, s, 2 × C*H*$_3$), 3.39 (2H, s, C*H*$_2$), 7.01 (2H, m, CH_2Ph-*H2,6*), 7.19-7.22 (5H, m, NPh-*H2,6* + CH_2Ph-*H3,4,5*), 7.39 (3H, m, NPh-*H3,4,5*), 9.38 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.86 (2 × *C*H_3), 42.13 (*C*H_2), 61.58 (C^{α}), 126.41 (CH_2Ph-*C4*), 128.14 (CH_2Ph-*C3,5*), 128.70 (NPh-*C4*), 128.99 (CH_2Ph-*C2,6*), 129.14 (NPh-*C3,5*), 130.33 (NPh-*C2,6*), 134.94 (CH_2Ph-*C1*), 139.08 (NPh-*C1*), 171.16 (*C*ON), 179.08 (*C*OOH). Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.63; H, 6.48; N, 4.65.***N*-Phenylacetyl-*N*-(4-chlorofenyl)-α,α-dimethylglycine (6c).** The reaction was carried out with 0.21 g of compound **3c** and the product purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40-60 ºC) to yield **6c** (109 mg, 66%), as white crystals, mp 170.4-171.5 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.36 (6H, s, 2 × C*H*$_3$), 3.39 (2H, s, C*H*$_2$), 7.00 (2H, m, CH_2Ph-*H2,6*), 7.11 (2H, d, *J*=8.4 Hz, NPh-*H2,6*), 7.20-7.22 (3H, m, CH_2Ph-*H3,4,5*), 7.35 (2H, d, *J*=8.7 Hz, NPh-*H3,5*), 9.35 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.88 (2 × *C*H_3), 42.29 (*C*H_2), 61.65 (C^{α}), 126.60 (CH_2Ph-*C4*), 128.28 (CH_2Ph-*C3,5*), 128.88 (CH_2Ph-*C2,6*), 129.36 (NPh-*C3,5*), 131.66 (NPh-*C2,6*), 134.58 (CH_2Ph-*C1*), 134.74 (NPh-*C4*), 137.59 (NPh-*C1*), 171.05 (*C*ON), 178.94 (*C*OOH). Anal. Calcd. for $C_{18}ClH_{18}NO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.10; H, 5.59; N, 4.33.***N*-Phenylacetyl-*N*-(4-cyanofenyl)-α,α-dimethylglycine** (**6d).** The reaction was carried out with 0.20 g of compound **3d** and the product purified by column chromatography (dichloromethane/MeOH, 50:1) followed by recrystallisation from ethyl acetate to yield **6d** (90 mg, 56%) as a white solid, mp 167.6-168.7 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.37 (6H, s, 2 × C*H*$_3$), 3.37 (2H, s, C*H*$_2$), 6.93 (2H, m, CH_2Ph-*H2,6*), 7.19-7.21 (3H, m, CH_2Ph-*H3,4,5*), 7.29 (2H, d, *J*=8.1 Hz, NPh-*H2,6*), 7.66 (2H, d, *J*=8.4 Hz, NPh-*H3,5*), 9.56 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.96 (2 × *C*H_3), 42.66 (*C*H_2), 61.91 (C^{α}), 112.89 (NPh-*C4*),

117.75 (NPh-*C*N), 126.83 (CH_2Ph-*C4*), 128.43 (CH_2Ph-*C3,5*), 128.69 (CH_2Ph-*C2,6*), 131.52 (NPh-*C2,6*), 133.01 (NPh-*C3,5*), 134.12 (CH_2Ph-*C1*), 143.20 (NPh-*C1*), 170.50 (*C*ON), 178.85 (*C*OOH). Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.50; H, 5.67; N, 8.65. ***N*-Phenylacetyl-*N*-(4-nitrofenyl)-α,α-dimethylglycine (6e).** Compound **3e** (0.25 g) was dissolved in 5 ml of neat TFA and the solution refluxed for 1 hour. The solvent was concentrated under reduced pressure at 30 ºC and the pH of the residue adjusted to 3 by treatment with 2M aqueous NaOH. The mixture was stirred overnight and the resulting suspension extracted into chloroform (3 × 15 ml). The combined organic layers were washed with water (2 × 20 ml) and dried over anhydrous $MgSO_4$; this was filtered off and the filtrate concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (dichloromethane/MeOH, 50:1) followed by recrystallisation from ethyl acetate to yield **6e** (100 mg, 48%), as a yellow solid, mp 193.5-194.6 ºC. ^{1}H RMN (300 MHz, $CDCl_3$): 1.40 (6H, s, 2 × C*H*$_3$), 3.39 (2H, s, C*H*$_2$), 6.95 (2H, m, CH_2Ph-*H2,6*), 7.20-7.23 (3H, m, CH_2Ph-*H3,4,5*), 7.35 (2H, d, *J*=9.0 Hz, NPh-*H2,6*), 8.23 (2H, d, *J*=8.7 Hz, NPh-*H3,5*), 9.22 (1H, br s, O*H*); ^{13}C RMN (75 MHz, $CDCl_3$): 24.95 (2 × *C*H_3), 42.68 (*C*H_2), 61.89 (*C*$^{\alpha}$), 124.39 (NPh-*C3,5*), 126.90 (CH_2Ph-*C4*), 128.48 (CH_2Ph-*C3,5*), 128.70 (CH_2Ph-*C2,6*), 131.62 (NPh-*C2,6*), 134.01 (CH_2Ph-*C1*), 144.88 (NPh-*C4*), 147.64 (NPh-*C1*), 170.41 (*C*ON), 178.73 (*C*OOH). Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.99; H, 5.36; N, 8.22.

4.2. Kinetic measurements

General method To measure reaction rates with compounds **1a**–**1h** and **3a**–**3e,** 0.02 M solutions in acetonitrile containing 2% of TFA were used; 0.007 M solutions were used for compounds **2a**–**2h**. The reaction mixtures were prepared by dissolving the calculated amount of the Ugi-Passerini adduct in 4.5 ml of acetonitrile contained in a dilution flask; this was followed by addition of 0.4 ml of 25% TFA in acetonitrile and adjustment of the volume to 5 ml with acetonitrile. The above operations were carried out with the reaction vessel and all reagent solutions kept in a thermostatic bath at a temperature stabilised within 0.01 ºC of the required value, the same applying throughout the reaction. At regular intervals of time samples were collected for HPLC monitoring and injected as quickly as possible to minimise errors caused to temperature

fluctuations. A mixture of acetonitrile/water 3:1 (v/v) was used as eluent and in most cases the detection was performed at the wavelength of 260 nm.

Acknowledgements

We wish to acknowledge Miss Elisa Pinto for running the NMR spectra and for the elemental analyses and also the Fundação para a Ciência e Tecnologia (Portugal) for financial support to the Instituto de Biotechnologia e Química Fina (University of Minho and for a socholarship to one of us (F.C.S.C.P.).

References

1. Lombardi, A.; De Simone, G.; Galdiero, S.; Nastri, F.; Di Costanzo, L.; Makihira, K.; Yamada, T.; Pavone, V. *Biopolymers* **2000**, *53*, 150-160.
2. Lombardi, A.; De Simone, G.; Galdiero, S.; Nastri, F.; Di Costanzo, L.; Makihira, K.; Yamada, T.; Pavone, V. *Biopolymers* **2000**, *53*, 182-188.
3. Peggion C.; Crisma, M.; Formaggio, F.; Toniolo, C.; Wright, K.; Wakselman, M.; Mazaleyrat, J.-P. *Biopolymers* **2002**, *63*, 314-324.
4. Rodrigues, L.M.; Fonseca, J.I.; Maia, H.L.S. *Tetrahedron* **2004**, *60*, 8929-8936.
5. Pratt, D.A.; Dilabio, G.A.; Mulder, P.; Ingold, K.U. *Acc. Chem. Res.* **2004**, *37*, 334-340.
6. Mazaleyrat, J.-P.; Wright, K.; Gaucher, A.; Toulemonde, N.; Wakselman, M.; Oancea, S.; Peggion, C.; Formaggio, F.; Setnicka, V.; T.A. Keiderling, T.A.; Toniolo, C. *J. Am. Chem. Soc.* **2004**, *126*, 12874-12879.
7. Kaul, R.; Balaram, P. *Bioorganic & Medicinal Chemistry* **1999**, *7*, 105-117.
8. Preto, M.A.C.; Melo, A.; Costa, S.P.G.; Maia, H.L.S.; Ramos, M.J. *J. Phys. Chem. B* **2003**, *107*, 14556-14562.
9. Preto, M.A.C.; Melo, A.; Maia, H.L.S.; Mavromoustakos, T.; Ramos, M.J. *J. Phys. Chem. B* **2005**, *109*, 17743-17751.
10. Tantry, S.J.; Rao, R.V.R.; Babu, V.V.S. *ARKIVOC* **2006**, *i*, 21-30.
11. Ellis, T.K.; Martin, C.H.; Ueki, H.; Soloshonok, V.A. *Tetrahedron Letters* **2003**, *44*, 1063-1066.

12. Ellis, T.K.; Martin, C.H.; Tsai, G.M.; Ueki, H.; Soloshonok, V.A. *J. Org. Chem.* **2003**, *68*, 6208-6214.

13. Belokon,Y.N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849-1861.

14. Harding, C.I.; Dixon, D.J.; Ley, S.V. *Tetrahedron* **2004**, *60*, 7679-7692.

15. Mazaleyrat, J.-P.; Wright, K.; Gaucher, A.; Wakselman, M.; Oancea, S.; Formaggio, F.; Toniolo, C. Setnicka, V.; Kapita,́ J.; Keiderling, T.A. *Tetrahedron: Asymmetry* **2003**, *14*, 1879-1893.

16. Johnson, T.; Quibell, M.; Owen, D.; Sheppard. R.C. *J. Chem. Soc. Chem. Commun*. **1993**, 369-372.

17. Creighton, C.J.; Romoff, T.T.; Bu, J.H.; Goodman, M. *J. Am. Chem. Soc.* **1999**, *121*, 6786-6791.

18. Costa, S.P.G.; Maia, H.L.S.; Pereira-Lima, S.M.M.A. *Org. Biomol. Chem.* **2003**, *1*, 1475-1479.

19. Jiang, W.-Q.; Costa, S.P.G.; Maia, H.L.S. *Org. Biomol. Chem*. **2003**, *1*, 3804-3810.

20. Jiang, W.-Q.; Ventura, C.; Costa, S.P.G.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H.L.S. *J. Peptide Sci.* **2005**, *11*, 472-480.

21. Jiang, W.-Q.; Pereira-Lima, S.M.M.A.; Ventura, C.; Costa, S.P.G.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H.L.S. *J. Peptide Sci.* **2005**, *11*, 627-632.

22. Ventura, C.; Jiang, W.-Q.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H.L.S. *J. Peptide Sci.* Published Online: 22 Aug **2005** DOI: 10.1002/psc.709.

23. Maia, H.L.; Ridge, B.; Rydon, H.N. *J. Chem. Soc. Perkin Trans. I* **1973**, 98-1973.

24. Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* **1991**, *91*, 165-195.

25. Massart, D.L.; Vandeginste, B.G.M.; Deming, S.N.; Michote, Y.; Kaufman, L.; *Chemometrics: a textbook*; Elsevier: Amsterdam, 1988; pp. 255-270.

26. Schlosser, M. *Angew. Chem. Int. Ed.* **1998**, *110*, 1496-1513

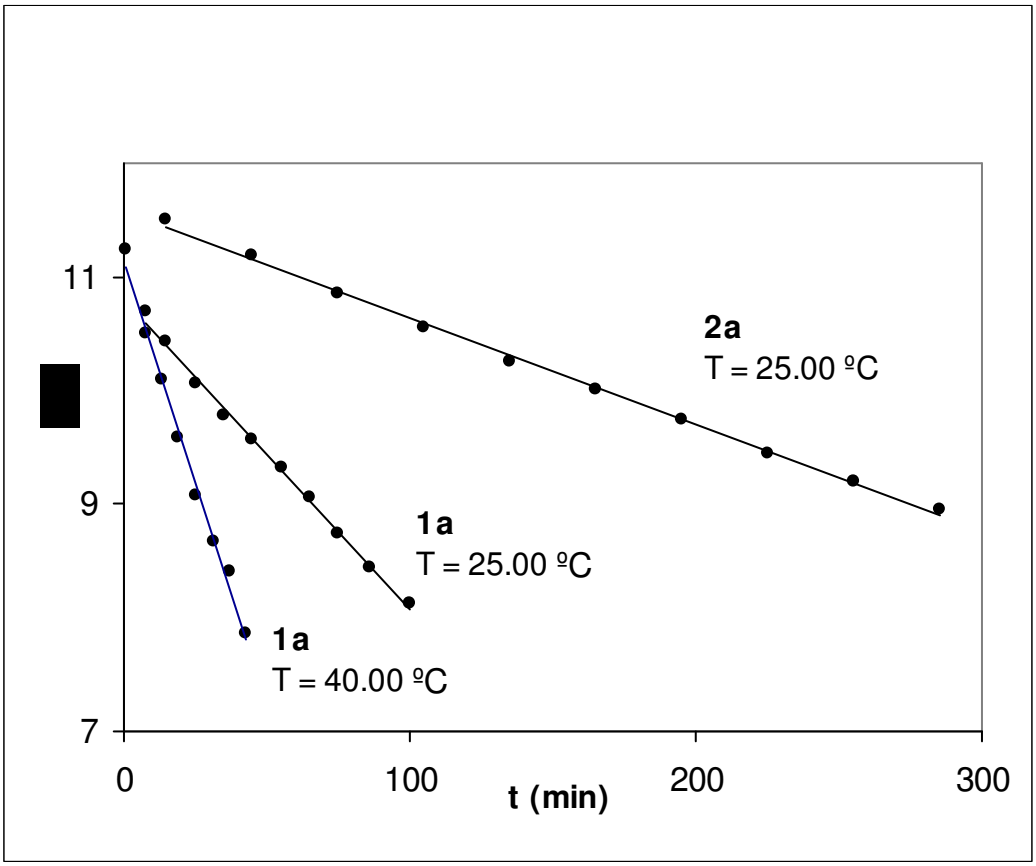


Figure 1. Plots of values of ln *A* vs time for acidolysis of compounds **1a** (25.00 and 40.00 ºC) and **2a** (25.00 ºC).

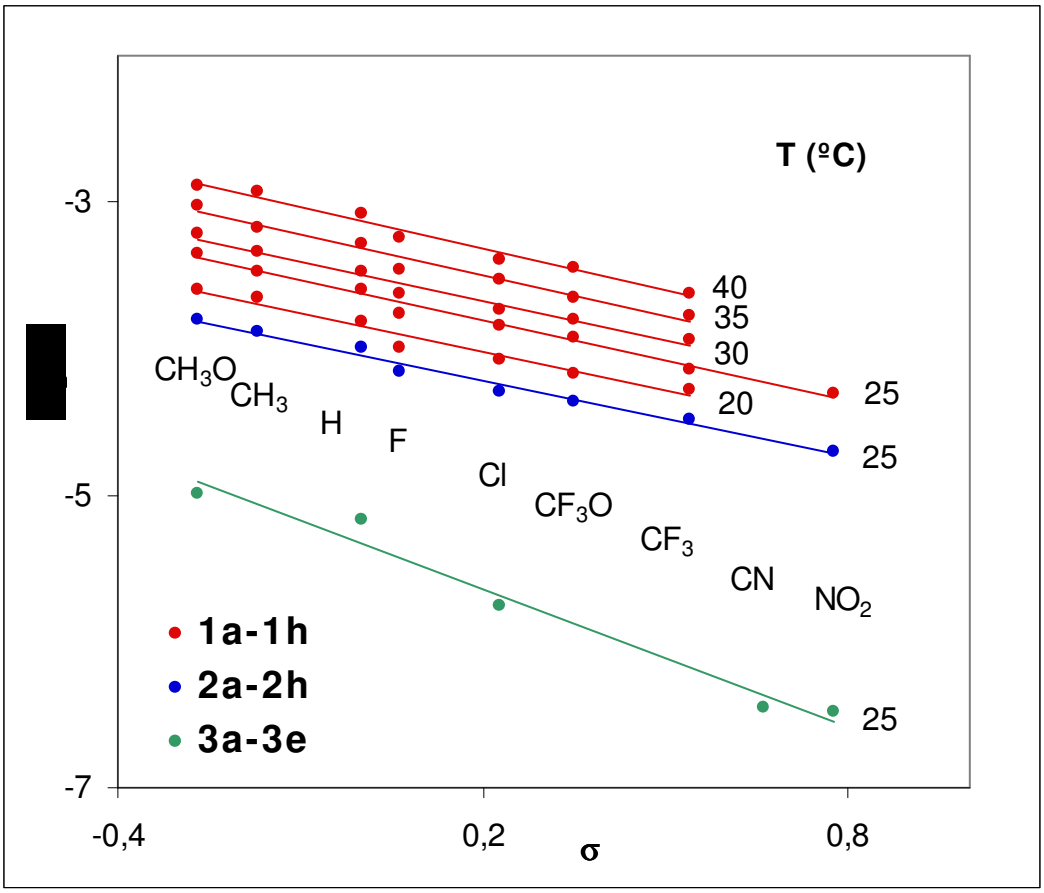


Figure 2. Hammett plots (log *k* vs σ) for compounds **1a**-**1g**, **2a**-**2g** and **3a**-**3e** at 25.00 ºC and **1a**-**1h** at other temperatures.

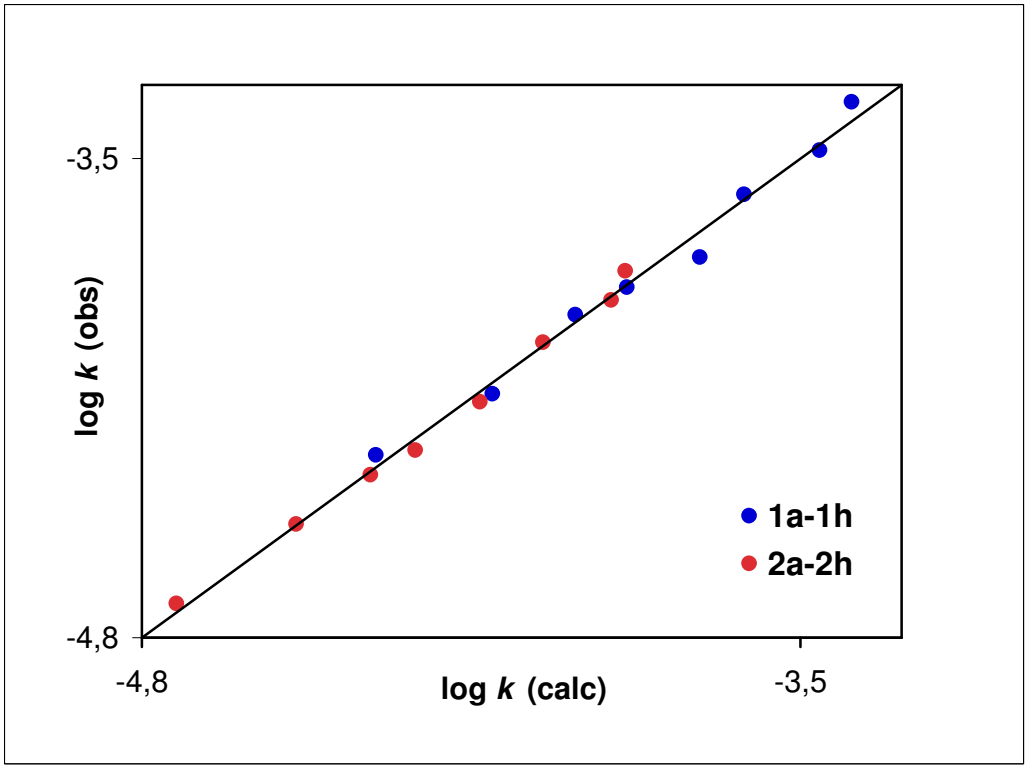


Figure 3. Plot of observed log *k* values for acidolysis of compounds **1a**-**1g** against those calculated with log $k = -3.61 - 0.86\ \sigma_R - 0.95\ \sigma_I$ and of compounds **2a**-**2g** against those calculated with log $k = -4.00 - 0.78\ \sigma_R - 0.96\ \sigma_I$.

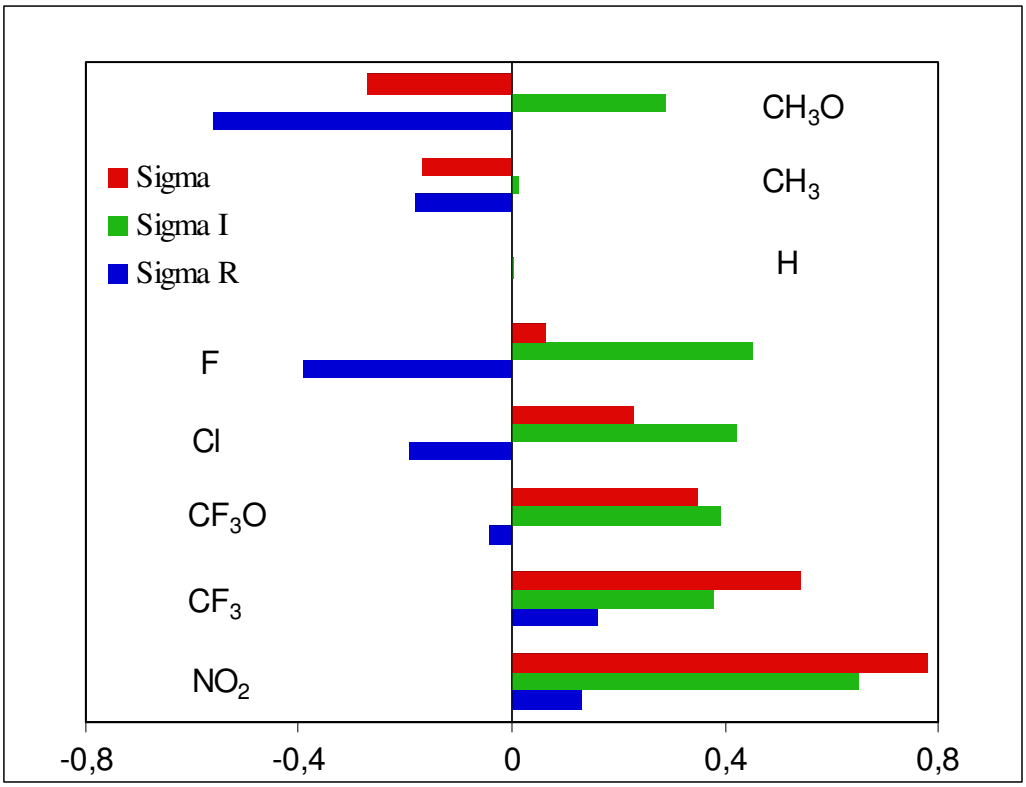
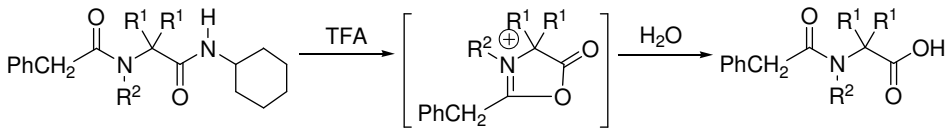


Figure 4. Plot of Hammett constant (Sigma; σ), field/inductive constant (Sigma I; σ_I) and resonance constant (Sigma R; σ_R) for the different substituents.



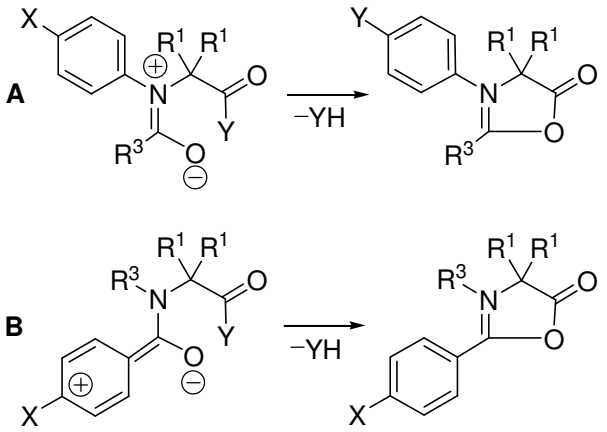
1-3 **4-6**

1a, **4a** R^1 = Me, R^2 = 4-MeO-$C_6H_4CH_2$
1b, **4b** R^1 = Me, R^2 = 4-Me-$C_6H_4CH_2$
1c, **4c** R^1 = Me, R^2 = $C_6H_5CH_2$
1d, **4d** R^1 = Me, R^2 = 4-F-$C_6H_4CH_2$
1e, **4e** R^1 = Me, R^2 = 4-Cl-$C_6H_4CH_2$
1f, **4f** R^1 = Me, R^2 = 4-CF_3O-$C_6H_4CH_2$
1g, **4g** R^1 = Me, R^2 = 4-CF_3-$C_6H_4CH_2$
1h, **4h** R^1 = Me, R^2 =4-NO_2-$C_6H_4CH_2$

2a, **5a** R^1 = Bn, R^2 =4-MeO-$C_6H_4CH_2$
2b, **5b** R^1 = Bn, R^2 = 4-Me-$C_6H_4CH_2$
2c, **5c** R^1 = Bn, R^2 = $C_6H_5CH_2$
2d, **5d** R^1 = Bn, R^2 = 4-F-$C_6H_4CH_2$
2e, **5e** R^1 = Bn, R^2 = 4-Cl-$C_6H_4CH_2$
2f, **5f** R^1 = Bn, R^2 = 4-CF_3O-$C_6H_4CH_2$
2g, **5g** R^1 = Bn, R^2 =4-CF_3-$C_6H_4CH_2$
2h, **5h** R^1 = Bn, R^2 = 4-NO_2-$C_6H_4CH_2$

3a, **6a** R^1 = Me, R^2 = 4-MeO-C_6H_4
3b, **6b** R^1 = Me, R^2 = C_6H_5
3c, **6c** R^1 = Me, R^2 = 4-Cl-C_6H_4
3d, **6d** R^1 = Me, R^2 = 4-CN-C_6H_4
3e, **6e** R^1 = Me, R^2 = 4-NO_2-C_6H_4

(Scheme 1)



Scheme 2

Table 1. Synthesis of Ugi-Passerini adducts $PhCH_2CO$-N(4-X-C_6H_4-CH_2)-C(R^1)$_3$CO-NHC_6H_{11} (**1a**-**1h** and **2a**-**2h**) and $PhCH_2CO$-N(4-X-C_6H_4)-C(CH_3)$_2$CO-NHC_6H_{11} (**3a**-**3e**) and of their cleavage products (**4a**-**4h**, **5a**-**5h** and **6a**-**6e**, respectively)

X	Compound		Yield	Compound		Yield	Compound		Yield	Compound		Yield	Compound		Yield	Compound		Yield
	R^1	No.	(%)	R^1	No.	(%)	R^1	No.	(%)	R^1	No.	(%)	R^1	No.	(%)	R^1	No.	(%)
CH_3O	Me	**1a**	91	Me	**4a**	84	Bn	**2a**	82	Bn	**5a**	32	Me	**3a**	92	Me	**6a**	47
CH_3	Me	**1b**	90	Me	**4b**	89	Bn	**2b**	60	Bn	**5b**	93						
H	Me	**1c**	71	Me	**4c**	76	Bn	**2c**	44	Bn	**5c**	98	Me	**3b**	86	Me	**6b**	66
F	Me	**1d**	95	Me	**4d**	97	Bn	**2d**	85	Bn	**5d**	88						
Cl	Me	**1e**	86	Me	**4e**	89	Bn	**2e**	76	Bn	**5e**	85	Me	**3c**	71	Me	**6c**	66
CF_3O	Me	**1f**	91	Me	**4f**	90	Bn	**2f**	63	Bn	**5f**	92						
CF_3	Me	**1g**	98	Me	**4g**	92	Bn	**2g**	78	Bn	**5g**	95						
CN													Me	**3d**	24	Me	**6d**	56
NO_2	Me	**1h**	50	Me	**4h**	89	Bn	**2h**	47	Bn	**5h**	62	Me	**3e**	9	Me	**6e**	48

Table 2. Rate constants, *k*, and mean deviations, d*k*, at 25.00 ºC for the acidolysis of $PhCH_2CO$-N(4-X-C_6H_4-CH_2)-C(R^1)$_3$CO-NHC_6H_{11} (**1a**-**1h** and **2a**-**2h**) and $PhCH_2CO$-N(4-X-C_6H_4)-C(CH_3)$_2$CO-NHC_6H_{11} (**3a**-**3e**)

X	Compound		$(k\pm dk)\times10^4$	Compound		$(k\pm dk)\times10^4$	Compound		$(k\pm dk)\times10^6$
	R^1	No.	s^{-1}	R^1	No.	s^{-1}	R^1	No.	s^{-1}
CH_3O	Me	**1a**	4.513±0.051	Bn	**2a**	1.567±0.019	Me	**3a**	10.14±0.02
CH_3	Me	**1b**	3.333±0.042	Bn	**2b**	1.306±0.034			
H	Me	**1c**	2.530±0.078	Bn	**2c**	1.005±0.013	Me	**3b**	6.833±0.022
F	Me	**1d**	1.711±0.017	Bn	**2d**	0.692±0.002			
Cl	Me	**1e**	1.417±0.059	Bn	**2e**	0.512±0.002	Me	**3c**	1.729±0.014
CF_3O	Me	**1f**	1.190±0.050	Bn	**2f**	0.439±0.003			
CF_3	Me	**1g**	0.727±0.004	Bn	**2g**	0.322±0.003			
CN							Me	**3d**	0.347±0.018
NO_2	Me	**1h**	0.497±0.010	Bn	**2h**	0.196±0.010	Me	**3e**	0.334±0.017

Table 3. Rate constants, k, and mean deviations, dk, for the acidolysis of $PhCH_2CO\text{-}N(4\text{-}X\text{-}C_6H_4\text{-}CH_2)\text{-}CMe_2CO\text{-}NHC_6H_{11}$ (**1a**-**1g**) at different temperatures

X	Compound no.	$(k\pm dk)\times10^4$ (s^{-1})			
		20.00 ºC	30.00 ºC	35.00 ºC	40.00 ºC
CH_3O	**1a**	2.54±0.05	6.23±0.18	9.44±0.22	12.99±0.48
CH_3	**1b**	2.20±0.06	4.62±0.18	6.68±0.25	11.99±0.45
H	**1c**	1.50±0.06	3.32±0.09	5.13±0.18	8.16±0.40
F	**1d**	1.06±0.03	2.35±0.07	3.45±0.11	5.76±0.23
Cl	**1e**	0.84±0.02	1.84±0.06	2.95±0.10	4.06±0.16
CF_3O	**1f**	0.68±0.01	1.55±0.04	2.20±0.06	3.53±0.18
CF_3	**1g**	0.53±0.02	1.14±0.03	1.68±0.10	2.40±0.08

Table 4. Hammett constants and their constituent contributions (Ref.)

Substituent	σ	σ_R	σ_I
CH_3O	–0.268	–0.56	0.29
CH_3	–0.170	–0.18	0.01
H	0.000	0	0.003
F	0.063	–0.39	0.45
Cl	0.227	–0.19	0.42
CF_3O	0.350	–0.04	0.39
CF_3	0.540	0.16	0.38
CN	0.660	–	–
NO_2	0.778	0.13	0.65

Table 5. Estimated parameters, number of points, N, correlation coefficient, r, and standard deviation, s, of the fit of Hammett plots log $k = a_0 + a_1 \sigma$

Compound	**1a–1h**	**2a–2h**	**3a–1e**	**1a–1g**			
T (ºC)	25.00	25.00	25.00	20.00	30.00	35.00	40.00
a_0	–3.63±0.02	–4.05±0.02	–5.34±0.07	–3.85±0.02	–3.50±0.02	–3.32±0.02	–3.13±0.02
a_1	–0.91±0.05	–0.86±0.04	–1.56±0.15	–0.89±0.08	0.91±0.07	–0.92±0.07	–0.96±0.06
N	8	8	5	7	7	7	7
r	0.993	0.993	0.986	0.981	0.987	0.985	0.990
s	0.04	0.04	0.13	0.05	0.05	0.05	0.04

Table 6. Estimated parameters, correlation coefficient, r, and standard deviation, s, of the fit at 25.00 ºC (N = 8 points) of biparametric Hammett plots log $k = a_0 + a_1 \sigma_R + a_2 \sigma_I$

Compound	a_0	a_1	a_2	r	s
1a-**1h**	–3.61±0.04	–0.86±0.07	–0.95±0.08	0.993	0.05
2a-**2h**	–4.00±0.02	–0.78±0.04	–0.96±0.05	0.996	0.03