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

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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 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 were analysed in terms of structure–reactivity in connection with the sensitivity of the reaction rates to the electronic contributions of the various substituents at 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.

1. Introduction

Conformational rigidity increases potency and selectivity of bioactive peptides, improving their bioavailability and enhancing resistance to peptidases.[1] Consequently, design of conformationally 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-dialkylglycines, conformational rigidity can be obtained by inserting one or more residues 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 the 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 residues 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 one's 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-dialkylglycine unit already incorporated into the peptide chain, a route that is in principal offered by the four-component Ugi-Passerini reaction.[16] This is particularly appropriate when no concern for asymmetric induction is required, such as in the case of symmetric α,α-dialkylglycines, 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 the dialkylated centre be removed and (ii) the unavoidable racemisation of the amino acid residue that follows the

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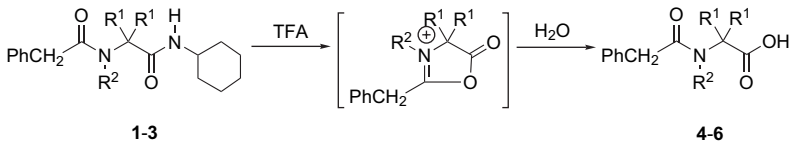


1a, **4a** R^1 = Me, R^2 = 4-MeO-$C_6H_4CH_2$ **2a**, **5a** R^1 = Bn, R^2 = 4-MeO-$C_6H_4CH_2$ **3a**, **6a** R^1 = Me, R^2 = 4-MeO-C_6H_4
1b, **4b** R^1 = Me, R^2 = 4-Me-$C_6H_4CH_2$ **2b**, **5b** R^1 = Bn, R^2 = 4-Me-$C_6H_4CH_2$ **3b**, **6b** R^1 = Me, R^2 = C_6H_5
1c, **4c** R^1 = Me, R^2 = $C_6H_5CH_2$ **2c**, **5c** R^1 = Bn, R^2 = $C_6H_5CH_2$ **3c**, **6c** R^1 = Me, R^2 = 4-Cl-C_6H_4
1d, **4d** R^1 = Me, R^2 = 4-F-$C_6H_4CH_2$ **2d**, **5d** R^1 = Bn, R^2 = 4-F-$C_6H_4CH_2$ **3d**, **6d** R^1 = Me, R^2 = 4-CN-C_6H_4
1e, **4e** R^1 = Me, R^2 = 4-Cl-$C_6H_4CH_2$ **2e**, **5e** R^1 = Bn, R^2 = 4-Cl-$C_6H_4CH_2$ **3e**, **6e** R^1 = Me, R^2 = 4-NO_2-C_6H_4
1f, **4f** R^1 = Me, R^2 = 4-CF_3O-$C_6H_4CH_2$ **2f**, **5f** R^1 = Bn, R^2 = 4-CF_3O-$C_6H_4CH_2$
1g, **4g** R^1 = Me, R^2 = 4-CF_3-$C_6H_4CH_2$ **2g**, **5g** R^1 = Bn, R^2 = 4-CF_3-$C_6H_4CH_2$
1h, **4h** R^1 = Me, R^2 = 4-NO_2-$C_6H_4CH_2$ **2h**, **5h** R^1 = Bn, R^2 = 4-NO_2-$C_6H_4CH_2$

Scheme 1.

newly synthesised unit be overcome. We have shown that the former can be achieved if the unwanted *N*-substituent is methoxybenzyl,[17] 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.[18–20] This allows obtaining the amino acid unit at the peptide C-terminus, ready for further elongation of the chain without any risk of racemisation. The above can be achieved by treatment of 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 C-terminus, and also at the α-carbon atom of the fully substituted amino acid (Scheme 1).[21,23] 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 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.[20] Compounds with methyl group at the side chain reacted faster and behaved better when 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 nonsubstituted 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, substituted or not in position 4 (substrates **3**); in this case only five compounds were envisaged. All the compounds were synthesised by 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).[19,20] As shown previously[18,20] 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. Thus, each of the above substrates was treated at room temperature with 5% TFA in acetonitrile to give three new sets of compounds (**4**, **5** and **6**) homologous to the previous ones (**1**, **2** and **3**, respectively) and the yields are presented also in Table 1.

Table 1. Synthesis of Ugi–Passerini adducts $PhCH_2CO$-N(4-X-C_6H_4-CH_2)-$C(R^1)_2CO$-NHC_6H_{11} (**1a**–**1h** and **2a**–**2h**) and $PhCH_2CO$-N(4-X-C_6H_4)-$C(CH_3)_2CO$-NHC_6H_{11} (**3a**–**3e**) and of their cleavage products (**4a**–**4h**, **5a**–**5h** and **6a**–**6e**, respectively)

X	Compound		Yield (%)	Compound		Yield[a] (%)	Compound		Yield (%)	Compound		Yield[a] (%)	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**	68	Me	**3a**	92	Me	**6a**	98[b]
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**	77[b]
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[a]
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[a]
NO_2	Me	**1h**	50	Me	**4h**	89	Bn	**2h**	47	Bn	**5h**	62	Me	**3e**	9	Me	**6e**	48[c]

[a] Treatment with TFA in acetonitrile (5%) at room temperature.
[b] Treatment with neat TFA at room temperature.
[c] Treatment with boiling neat TFA.

2.2. Acquisition and treatment of kinetic information

As will be discussed below, even in the case of the lower yields obtained in the acidolyses with 5% TFA no signs have been detected for the reagent undergoing any reaction other than acidolytic cleavage of the C-terminal amide bond as depicted in Scheme 1. Thus, each substrate was submitted to acidolysis with 2% TFA under controlled conditions for collection of kinetic data; this was assisted by HPLC to monitor the reagent peak according to the procedure described below in Section 4. As expected,[21–23] 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* versus *t* plots for experiments concerning substrates **1a** at two temperatures (25.00 and 40.00 °C) and **2a** at 25.00 °C 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 °C, 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

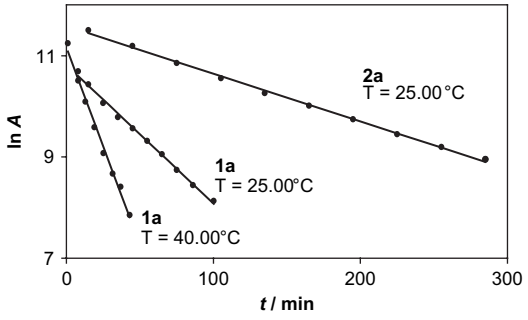


Figure 1. Plots of values of ln *A* versus time for acidolysis of compounds **1a** (25.00 and 40.00 °C) and **2a** (25.00 °C).

Table 3. Rate constants, *k*, and mean deviations, d*k*, 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 °C	30.00 °C	35.00 °C	40.00 °C
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

acidolyses, σ being the Hammett substituent constant and ρ the reaction constant reflecting the sensitivity of the reaction rate to the total electronic effect of the substituents. The values of Hammett constants for *para*-substituents (σ_p) used to fit the observed rate constants (*k*) are listed in Table 4;[25] although the number of substituents used in each set of compounds is not large, it is worthwhile to note that they provide a wide range of electronic effects. Table 5 shows the parameters estimated (a_0 and a_1) for 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[24] 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 leads us to investigate the possibility to quantify field/inductive and resonance contributions. For this purpose, we extended our analysis of rate constants

Table 4. Hammett constants and their constituent contributions[24]

Substituent	σ_P	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 2. Rate constants, *k*, and mean deviations, d*k*, at 25.00 °C for the acidolysis of $PhCH_2CO\text{-}N(4\text{-}X\text{-}C_6H_4\text{-}CH_2)\text{-}C(R^1)_2CO\text{-}NHC_6H_{11}$ (**1a–1h** and **2a–2h**) and $PhCH_2CO\text{-}N(4\text{-}X\text{-}C_6H_4)\text{-}C(CH_3)_2CO\text{–}NHC_6H_{11}$ (**3a–3e**)

X	Compound		$(k\pm dk)\times10^4$ s^{-1}	Compound		$(k\pm dk)\times10^4$ s^{-1}	Compound		$(k\pm dk)\times10^6$ s^{-1}
	R^1	No.		R^1	No.		R^1	No.	
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 5. Application of the Hammett equation[a] $\log k = a_0 + a_1\sigma_p$

Compound	**1a–1h**	**2a–2h**	**3a–3e**	**1a–1g**			
T (°C)	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

[a] Estimated parameters, a_0 and a_1, number of points, N, correlation coefficient, r, and standard deviation, s.

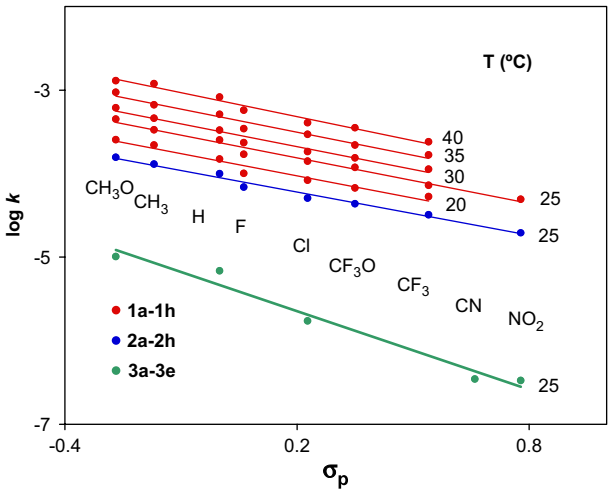


Figure 2. Hammett plots ($\log k$ vs σ_p) for compounds **1a–1h**, **2a–2h** and **3a–3e** at 25.00 °C and **1a–1g** at other temperatures.

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).[25] 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 °C. 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 Ugi–Passerini reaction (Table 1) were usually good to very good, except in the case of nitro derivatives. The behaviour observed with the nitro derivatives is possibly due to the large electron withdrawing effect of the nitro group, which would decrease substantially the nucleophilicity of the amine nitrogen atom when compared with the other substituents. This was so enhanced in the case of nitroanilide **3e** that it could not be obtained in a yield better than 9%. Acidolyses of the dimethylglycine derivatives **1** with 5% TFA were faster than those with the corresponding dibenzylglycine compounds **2** (2.5–4 h for substrates **1a–1g** and 20–27 h for compounds **2a–2e**, respectively). The acidolyses of the nitrobenzyl derivatives were much slower, requiring 26 and 48 h for **1h** and **2h**, respectively. As shown in Table 1, good to very good yields were obtained in the acidolysis of compounds **1b–1g** and **2b–2g**. We have shown[20] that (i) when treated with TFA at low concentration and room temperature the 4-methoxybenzyl group is not cleaved, but (ii) the partial cleavage may occur by prolonged treatment with 5% TFA and (iii) the full cleavage is usually achieved on boiling in neat TFA for 5 min. Thus, full selective cleavage of the amide bond was observed with compound **1a** to give a yield of 91% of the required product. However, as the acidolysis of **2a** was about three times slower than that of **1a**, subsequent partial cleavage of the *N*-methoxybenzyl group took place to allow only 68% of the required product. This did not affect the kinetic measurements not only because these are referred to the disappearance of **2a**, which occurs prior to further cleavage, but also because no secondary peaks were found overlapping with the reagent peak in the chromatograms. When **1b** and **1d** were boiled in neat TFA for 20 min the substituent at R^2 was not eliminated, the corresponding *N*-phenylacetyltrialkylglycine being the only product obtained; this differentiates methoxybenzyl group from the remaining compounds investigated. It was already known[26] 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 h. The reactions of the *N*-phenyl derivatives with 5% TFA at room temperature were so slow (27–168 h for **3a–3d**) that in most cases partial decomposition of the product was observed on completion, thus contributing to lower the final yield. Nevertheless, the acidolysis of compound **3a** was still sufficiently fast to avoid decomposition even when it was treated with neat TFA; so, this gave the best results for compound **3a** and also **3b** (Table 1). However, with the other substrates of this set their reactions with neat TFA were still slow and showed considerable decomposition of the product, the best results being then obtained with 5% TFA at room temperature; in the case of the nitrophenyl derivative (**3e**) boiling in neat TFA for more than 1 h was required for an acceptable progress but a yield of only 48% could be obtained.

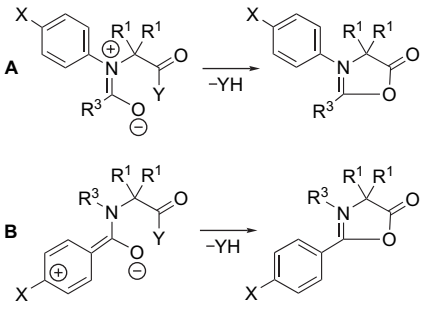
In general, the values of the rate constants for the compounds of *N*-benzyl derivatives of α,α-dimethylglycine **1a–1h** are

Table 6. Application of the biparametric Hammett equation[a] $\log k = a_0 + a_1\sigma_R + a_2\sigma_I$ at 25.00 °C (N=8 points)

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

[a] Estimated parameters, a_0, a_1 and a_2, correlation coefficient, r, and standard deviation, s.

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 °C; 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 40–150 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 above case. 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 onto 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 acidolysis under similar conditions of various *para*-substituted *N*-benzoyl derivatives of *N*,α,α-trimethylglycine, Creighton et al.[18] have found that the value is −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 (Scheme 2A) than that at the *N*-carbonyl carbon atom (Scheme 2B). 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. The results presented in Table 5 and Figure 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 Hammett reaction constant. Fluorine derivatives **1d** and **2d** are the less well behaved compounds; in fact, in the plots obtained at different temperatures they show systematic deviations to the same side of the lines (Fig. 2).



Scheme 2.

The biparametric relationships presented above for compounds **1a**–**1h** and **2a**–**2h** at 25.00 °C 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 16 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.[27] 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.

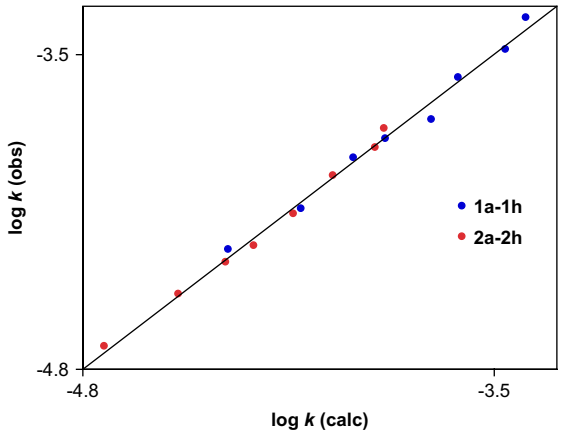


Figure 3. Plot of observed log *k* values for acidolysis of compounds **1a**–**1g** against those calculated with $\log k = -3.61 - 0.86\sigma_R - 0.95\sigma_I$ and of compounds **2a**–**2g** against those calculated with $\log k = -4.00 - 0.78\sigma_R - 0.96\sigma_I$.

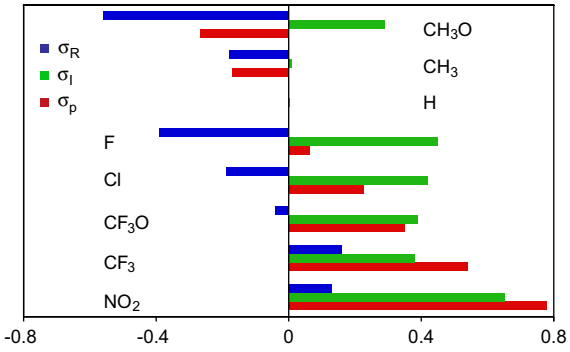


Figure 4. Plot of Hammett constant (σ_p), field/inductive constant (σ_I) and resonance constant (σ_R) for the different substituents.

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[19] for the *N*-acyl group and this may be related to the formation of 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 acidolysis 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,[19–23] it occurs independent of the size of the electronic contribution, which contributes only to the rate of acidolysis. This suggests that such requirement is essentially related to steric effect and not so much to 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.[21] Our results showed that anilides substituted with electron withdrawing groups such as *N*-(4-chlorophenyl) and *N*-(4-cyanophenyl) exhibit a comparatively high resistance of the C-terminal amide bond of α,α-dialkylglycine amides to acidolysis. 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 noteworthy that while the 4-methoxybenzyl group can be cleaved from Ugi–Passerini substrate together with the C-terminal amide bond if sufficient forcing conditions are used (boiling with neat TFA), all the other 4-substituted benzyl groups tested do not. Thus, when cleavage of the *N*-alkyl group from Ugi–Passerini adducts is required, only 4-methoxybenzyl compounds suit this purpose, which was 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 60 F_{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 parts per million using Me_4Si=0; *J*-values are given in hertz, 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 °C.

4.1.1. 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 sulfate (0.12 g cm^{-3}) was prepared and stirred for 15 min; then, 1 equiv of a 2 M solution of phenylacetic acid in dry methanol was added and the mixture was stirred for further 15 min. Finally, 1 equiv of cyclohexyl isocyanide was also added and the mixture was 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 sulfate was filtered off. The filtrate was concentrated under reduced pressure and the residue was 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 α,α-dibenzylglycine derivatives, to a 1 M solution of 1,3-diphenylpropanone in dry methanol containing anhydrous sodium sulfate (0.12 g cm^{-3}) 1 equiv of the required amine was added. After stirring for 45–60 min, 1 equiv of cyclohexyl isocyanide was mixed and the preparation was continued as above.

4.1.1.1. *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 was 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 °C (lit.[20] 168.4–169.8 °C). ^{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}-*H*1), 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-*H*3,5), 7.21–7.31 (5H, m, $COCH_2Ph$), 7.38 (2H, d, *J*=9.0 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.21 (2×CH_3), 24.81 (C_6H_{11}-*C*3,5), 25.56 (C_6H_{11}-*C*4), 32.87 (C_6H_{11}-*C*2,6), 42.05 (*C*H_2CO), 47.06 (*C*H_2N), 48.25 (C_6H_{11}-*C*1), 55.18 (OCH_3), 62.36 (*C*$^\alpha$), 114.21 (NCH_2Ph-*C*2,6), 126.71 ($COCH_2$Ph-*C*4), 127.08 (NCH_2Ph-*C*3,5), 128.39 ($COCH_2$Ph-*C*2,6), 128.62 ($COCH_2$Ph-*C*3,5),

130.23 (NCH_2Ph-*C*4), 134.86 ($COCH_2$Ph-*C*1), 158.74 (NCH_2Ph-*C*4), 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.

4.1.1.2. *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 was 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 °C. ^{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}-*H*1), 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, $CDCl_3$): δ 20.93 (Ph-CH_3), 24.22 (2×CH_3), 24.21 (2×CH_3), 24.80 (C_6H_{11}-*C*3,5), 25.56 (C_6H_{11}-*C*4), 32.85 (C_6H_{11}-*C*2,6), 42.06 (*C*H_2CO), 47.45 (*C*H_2N), 48.22 (C_6H_{11}-*C*1), 62.40 (*C*$^{\alpha}$), 125.84 (NCH_2Ph-*C*2,6), 126.71 ($COCH_2$Ph-*C*4), 128.39 ($COCH_2$Ph-*C*2,6), 128.62 ($COCH_2$Ph-*C*3,5), 129.50 (NCH_2Ph-*C*3,5), 134.82 ($COCH_2$Ph-*C*1), 135.29 (NCH_2Ph-*C*1), 136.88 (NCH_2Ph-*C*4), 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.

4.1.1.3. *N*-Phenylacetyl-*N*-benzyl-α,α-dimethylglycine cyclohexylamide (1c). The reaction was carried out on a 0.015-molar scale and the crude product was 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 °C. ^{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}-*H*1), 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-*H*4), 7.41 (2H, t, *J*=7.5 Hz, NCH_2Ph-*H*3,5), 7.48 (2H, d, *J*=7.5 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.22 (2×*C*H_3), 24.84 (C_6H_{11}-*C*3,5), 25.56 (C_6H_{11}-*C*4), 32.90 (C_6H_{11}-*C*2,6), 42.07 (*C*H_2CO), 47.60 (*C*H_2N), 48.29 (C_6H_{11}-*C*1), 62.39 (*C*$^{\alpha}$), 125.91 (NCH_2Ph-*C*2,6), 126.76 ($COCH_2$Ph-*C*4), 127.23 (NCH_2Ph-*C*4), 128.39 ($COCH_2$Ph-*C*2,6), 128.67 ($COCH_2$Ph-*C*3,5), 128.86 (NCH_2Ph-*C*3,5), 134.77 ($COCH_2$Ph-*C*1), 138.40 (NCH_2Ph-*C*1), 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.

4.1.1.4. *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 was 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 °C. ^{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}-*H*1), 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-*H*3,5), 7.18–7.32 (5H, m, $COCH_2$*Ph*), 7.49 (2H, dd, *J*=5.4, 9.0 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.17 (2×*C*H_3), 24.88 (C_6H_{11}-*C*3,5), 25.57 (C_6H_{11}-*C*4), 32.94 (C_6H_{11}-*C*2,6), 42.06 (*C*H_2CO), 46.80 (*C*H_2N), 48.39 (C_6H_{11}-*C*1), 62.29 (*C*$^{\alpha}$), 115.70 (d, J_{C-F}=21.3 Hz, NCH_2Ph-*C*3,5), 126.81 ($COCH_2$Ph-*C*4), 127.56 (d, J_{C-F}= 8.1 Hz, NCH_2Ph-*C*2,6), 128.33 ($COCH_2$Ph-*C*2,6), 128.32 ($COCH_2$Ph-*C*3,5), 134.13 (d, J_{C-F}=3.2 Hz, NCH_2Ph-*C*1), 134.70 ($COCH_2$Ph-*C*1), 161.93 (d, J_{C-F}=245.6 Hz, NCH_2Ph-*C*4), 171.77 (*C*OCH_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.

4.1.1.5. *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 was 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 °C. ^{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}-*H*1), 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-*H*3,5), 7.47 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14 (2×*C*H_3), 24.86 (C_6H_{11}-*C*3,5), 25.54 (C_6H_{11}-*C*4), 32.82 (C_6H_{11}-*C*2,6), 42.05 (*C*H_2CO), 46.87 (*C*H_2N), 48.39 (C_6H_{11}-*C*1), 62.26 (*C*$^{\alpha}$), 126.82 ($COCH_2$Ph-*C*4), 127.36 (NCH_2Ph-*C*2,6), 128.30 ($COCH_2$Ph-*C*2,6), 128.72 ($COCH_2$Ph-*C*3,5), 128.96 (NCH_2Ph-*C*3,5), 132.95 (NCH_2Ph-*C*4), 134.60 ($COCH_2$Ph-*C*1), 137.03 (NCH_2Ph-*C*1), 171.76 (*C*OCH_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.

4.1.1.6. *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 was 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 °C. ^{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}-*H*1), 4.56 (2H, s, NCH_2), 5.52 (1H, d, *J*=8.1 Hz, N*H*), 7.17–7.32 (7H, m, $COCH_2$*Ph*+NCH_2Ph-*H*3,5), 7.59 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14 (2×*C*H_3), 24.86 (C_6H_{11}-*C*3,5), 25.54 (C_6H_{11}-*C*4), 32.93 (C_6H_{11}-*C*2,6), 42.06 (*C*H_2CO), 46.75 (*C*H_2N), 48.42 (C_6H_{11}-*C*1), 62.26 (*C*$^{\alpha}$), 120.37 (q, J_{C-F}= 257.4 Hz, O*C*F_3), 121.31 (NCH_2Ph-*C*3,5), 126.82 ($COCH_2$Ph-*C*4), 127.35 (NCH_2Ph-*C*2,6), 128.30 ($COCH_2$Ph-*C*2,6), 128.72 ($COCH_2$Ph-*C*3,5), 134.57 ($COCH_2$Ph-*C*1), 137.25 (NCH_2Ph-*C*1), 148.25 (q, J_{C-F}=1.8 Hz, NCH_2Ph-*C*4), 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.

4.1.1.7. *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 was 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 °C. ^{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×CH_3) 1.59–1.75 (3H, m, C_6H_{11}), 1.99 (2H, m, C_6H_{11}), 3.58 (2H, s, CH_2CO), 3.73–3.85 (1H, m, C_6H_{11}-*H*1), 4.60 (2H, s, NCH_2), 5.53 (1H, d, *J*=8.1 Hz, N*H*), 7.17–7.32 (5H, m, $COCH_2Ph$), 7.67 (4H, dt, *J*=8.4, 14.4 Hz, NCH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.16 (2×CH_3), 24.90 (C_6H_{11}-*C*3,5), 25.57 (C_6H_{11}-*C*4), 32.97 (C_6H_{11}-*C*2,6), 42.13 (CH_2CO), 47.11 (CH_2N), 48.48 (C_6H_{11}-*C*1), 62.29 (C^{α}), 124.02 (q, J_{C-F}=272.1 Hz, CF_3), 125.81 (q, J_{C-F}=3.7 Hz, NCH_2Ph-*C*3,5), 126.34 (NCH_2Ph-*C*2,6), 126.90 ($COCH_2Ph$-*C*4), 128.30 ($COCH_2Ph$-*C*2,6), 128.79 ($COCH_2Ph$-*C*3,5), 129.55 (q, J_{C-F}=32.5 Hz, NCH_2Ph-*C*4), 134.49 ($COCH_2Ph$-*C*1), 142.79 (NCH_2Ph-*C*1), 171.80 ($COCH_2$), 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.

4.1.1.8. *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 equiv, 5.658 g), which was neutralised with triethylamine (2.9 equiv, 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 was 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 °C. ^1H 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×CH_3), 1.60–1.75 (3H, m, C_6H_{11}), 1.99 (2H, m, C_6H_{11}), 3.55 (2H, s, CH_2CO), 3.77–3.80 (1H, m, C_6H_{11}-*H*1), 4.62 (2H, s, NCH_2), 5.55 (1H, d, *J*=7.8 Hz, N*H*), 7.14 (2H, d, *J*=6.3 Hz, $COCH_2Ph$-*H*2,6), 7.22–7.28 (3H, m, $COCH_2Ph$-*H*3,4,5), 7.80 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H*2,6), 8.22 (2H, d, *J*=9.0 Hz, NCH_2Ph-*H*3,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.08 (2×CH_3), 24.88 (C_6H_{11}-*C*3,5), 25.52 (C_6H_{11}-*C*4), 32.94 (C_6H_{11}-*C*2,6), 42.13 (CH_2CO), 46.95 (CH_2N), 48.54 (C_6H_{11}-*C*1), 62.23 (C^{α}), 124.03 (NCH_2Ph-*C*3,5), 126.91 (NCH_2Ph-*C*2,6), 126.91 ($COCH_2Ph$-*C*4), 128.20 ($COCH_2Ph$-*C*2,6), 128.81 ($COCH_2Ph$-*C*3,5), 134.22 ($COCH_2Ph$-*C*1), 146.32 (NCH_2Ph-*C*1), 147.17 (NCH_2Ph-*C*4), 171.65 ($COCH_2$), 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.

4.1.1.9. *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 was 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 °C (lit.[20] 87.3–87.9 °C). ^1H NMR (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}-*H*1), 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-*H*3,5), 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-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.86 (C_6H_{11}-*C*3,5), 25.56 (C_6H_{11}-*C*4), 32.57 (C_6H_{11}-*C*2,6), 36.05 (2×CCH_2Ph), 42.08 (CH_2CO), 47.25 (CH_2N), 48.39 (C_6H_{11}-*C*1), 55.17 (OCH_3), 69.15 (C^{α}), 114.17 (NCH_2Ph-*C*3,5), 126.85, 126.88 (2×CCH_2Ph-*C*4+$COCH_2Ph$-*C*4), 127.07 (NCH_2Ph-*C*2,6), 128.11 (2×CCH_2Ph-*C*3,5), 128.54 ($COCH_2Ph$-*C*3,5), 129.49 ($COCH_2Ph$-*C*2,6), 130.97 (2×CCH_2Ph-*C*2,6+NCH_2Ph-*C*1), 134.71 ($COCH_2Ph$-*C*1), 135.33 (2×CCH_2Ph-*C*1), 158.47 (NCH_2Ph-*C*4), 170.86 (*C*ONH), 172.64 ($COCH_2$). 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.

4.1.1.10. *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 was 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 °C. ^1H NMR (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}-*H*1), 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-*H*3,5+2×CCH_2Ph), 7.33 (5H, m, $COCH_2Ph$), 7.62 (2H, d, *J*=7.8 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.99 (CH_3Ph), 24.84 (C_6H_{11}-*C*3,5), 25.55 (C_6H_{11}-*C*4), 32.56 (C_6H_{11}-*C*2,6), 36.07 (2×CCH_2Ph), 42.08 (CH_2CO), 47.60 (CH_2N), 48.35 (C_6H_{11}-*C*1), 69.13 (C^{α}), 125.84 (NCH_2Ph-*C*2,6), 126.85 (2×CCH_2Ph-*C*4+$COCH_2Ph$-*C*4), 128.08 (2×CCH_2Ph-*C*3,5), 128.52 ($COCH_2Ph$-*C*3,5), 129.48 ($COCH_2Ph$-*C*2,6+NCH_2Ph-*C*3,5), 130.95 (2×CCH_2Ph-*C*2,6), 134.68 ($COCH_2Ph$-*C*1), 135.33 (2×CCH_2Ph-*C*1), 136.00 (NCH_2Ph-*C*1), 136.37 (NCH_2Ph-*C*4), 170.78 (*C*ONH), 172.63 ($COCH_2$). 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.

4.1.1.11. *N*-Phenylacetyl-*N*-benzyl-α,α-dibenzylglycine cyclohexylamide (2c). The reaction was carried out on a 0.01-molar scale and the crude product was 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 °C. ^1H NMR (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}-*H*1), 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_2Ph+NCH_2Ph-*H*4), 7.35–7.42 (7H, m, NCH_2Ph-*H*3,5+$COCH_2Ph$), 7.75 (2H, d, *J*=9.0 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.85 (C_6H_{11}-*C*3,5), 25.54 (C_6H_{11}-*C*4), 32.55 (C_6H_{11}-*C*2,6), 36.12 (2×CCH_2Ph), 42.09 (CH_2CO), 47.73 (CH_2N), 48.38 (C_6H_{11}-*C*1), 69.10 (C^{α}), 125.92 (NCH_2Ph-*C*2,6), 126.83, 126.89 (2×CCH_2Ph-*C*4+NCH_2Ph-*C*4+$COCH_2Ph$-*C*4), 128.12 (2×CH_2Ph-*C*3,5), 128.56 (NCH_2Ph-*C*3,5), 128.79 ($COCH_2Ph$-*C*3,5), 129.46 ($COCH_2Ph$-*C*2,6), 130.94 (2×CH_2Ph-*C*2,6), 134.58 ($COCH_2Ph$-*C*1), 135.25 (2×CCH_2Ph-*C*1), 139.05 (NCH_2Ph-*C*1), 170.79 (*C*ONH), 172.65 ($COCH_2$). 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.

4.1.1.12. *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 was 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 °C. ^{1}H NMR (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}-*H*1), 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-*H*3,5), 7.13–7.29 (10H, m, 2×CCH_2Ph), 7.33–7.37 (5H, m, $COCH_2Ph$), 7.75 (2H, dd, J=5.4, 8.4 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.81 (C_6H_{11}-*C*3,5), 25.52 (C_6H_{11}-*C*4), 32.52 (C_6H_{11}-*C*2,6), 36.00 (2×CCH_2Ph), 42.07 (CH_2CO), 47.12 (CH_2N), 48.23 (C_6H_{11}-*C*1), 69.13 (C^{α}), 115.58 (d, J_{C-F}= 21.3 Hz, NCH_2Ph-*C*3,5), 126.90, 126.94 (2×CCH_2Ph-*C*4+ $COCH_2$Ph-*C*4), 127.58 (d, J_{C-F}=7.8 Hz, NCH_2Ph-*C*2,6), 128.14 (2×CCH_2Ph-*C*3,5), 128.56 ($COCH_2$Ph-*C*3,5), 129.40 ($COCH_2$Ph-*C*2,6), 130.91 (2×CCH_2Ph-*C*2,6), 134.47 ($COCH_2$Ph-*C*1), 134.70 (d, J_{C-F}=2.9 Hz, NCH_2Ph-*C*1), 135.15 (2×CCH_2Ph-*C*1), 161.79 (d, J_{C-F}=245.0 Hz, NCH_2Ph-*C*4), 170.84 (*C*ONH), 172.51 ($COCH_2$). 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.

4.1.1.13. *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 was 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 °C. ^{1}H NMR (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}-*H*1), 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-*H*3,5), 7.72 (2H, d, J=8.4 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.83 (C_6H_{11}-*C*3,5), 25.52 (C_6H_{11}-*C*4), 32.53 (C_6H_{11}-*C*2,6), 35.97 (2×CCH_2Ph), 42.11 (CH_2CO), 47.19 (CH_2N), 48.44 (C_6H_{11}-*C*1), 69.11 (C^{α}), 126.95, 127.00 (2×CCH_2Ph-*C*4+$COCH_2$Ph-*C*4), 127.45 (NCH_2Ph-*C*2,6), 128.17 (2×CCH_2Ph-*C*3,5), 128.61 (NCH_2Ph-*C*3,5), 128.91 ($COCH_2$Ph-*C*3,5), 129.39 ($COCH_2$Ph-*C*2,6), 130.91 (2×CCH_2Ph-*C*2,6), 132.66 (NCH_2Ph-*C*4), 134.38 ($COCH_2$Ph-*C*1), 135.08 (2× CCH_2Ph-*C*1), 137.66 (NCH_2Ph-*C*1), 170.81 (*C*ONH), 172.49 ($COCH_2$). 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.

4.1.1.14. *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 was 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 °C. ^{1}H NMR (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}-*H*1), 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-*H*3,5), 7.31–7.38 (5H, m, $COCH_2Ph$), 7.81 (2H, d, J=9.0 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.84 (C_6H_{11}-*C*3,5), 25.53 (C_6H_{11}-*C*4), 32.53 (C_6H_{11}-*C*2,6), 36.09 (2×CCH_2Ph), 42.07 (CH_2CO), 47.16 (CH_2N), 48.49 (C_6H_{11}-*C*1), 69.14 (C^{α}), 120.41 (q, J_{C-F}=257.1 Hz, OCF_3), 121.21 (NCH_2Ph-*C*3,5), 126.98, 127.01 (2×CCH_2Ph-*C*4+$COCH_2$Ph-*C*4), 128.44 (NCH_2Ph-*C*2,6), 128.19 (2× CCH_2Ph-*C*3,5), 128.62 ($COCH_2$Ph-*C*3,5), 129.40 ($COCH_2$Ph-*C*2,6), 130.92 (2×CCH_2Ph-*C*2,6), 134.33 ($COCH_2$Ph-*C*1), 135.07 (2×CCH_2Ph-*C*1), 137.79 (NCH_2Ph-*C*1), 148.11 (q, J_{C-F}=1.8 Hz, NCH_2Ph-*C*4), 170.86 (*C*ONH), 172.50 ($COCH_2$). 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.

4.1.1.15. *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 was 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 °C. ^{1}H NMR (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}-*H*1), 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-*H*3,5), 7.92 (2H, d, J=8.1 Hz, NCH_2Ph-*H*2,6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.81 (C_6H_{11}-*C*3,5), 25.48 (C_6H_{11}-*C*4), 32.49 (C_6H_{11}-*C*2,6), 36.01 (2×CCH_2Ph), 42.15 (CH_2CO), 47.45 (CH_2N), 48.46 (C_6H_{11}-*C*1), 69.11 (C^{α}), 124.07 (q, J_{C-F}=272.0 Hz, CF_3), 125.68 (q, J_{C-F}=3.8 Hz, NCH_2Ph-*C*3,5), 126.39 (NCH_2Ph-*C*2,6), 126.98, 127.01 (2×CCH_2Ph-*C*4+$COCH_2$Ph-*C*4), 128.17 (2×CCH_2Ph-*C*3,5), 128.61 ($COCH_2$Ph-*C*3,5), 129.33 ($COCH_2$Ph-*C*2,6), 129.20 (q, J_{C-F}=32.5 Hz, NCH_2Ph-*C*4), 130.87 (2×CCH_2Ph-*C*2,6), 134.17 ($COCH_2$Ph-*C*1), 134.96 (2×CCH_2Ph-*C*1), 143.32 (NCH_2Ph-*C*1), 170.79 (*C*ONH), 172.41 ($COCH_2$). 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.

4.1.1.16. *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 equiv, 2.45 g), which was neutralised with triethylamine (1.2 equiv, 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 was 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 °C. ^{1}H NMR (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}-*H*1), 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_2Ph), 7.30–7.38 (5H, m, $COCH_2Ph$), 8.00 (2H, d, J=8.1 Hz, NCH_2Ph-*H*2,6), 8.24 (2H, d, J=8.7 Hz, NCH_2Ph-*H*3,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.80 (C_6H_{11}-*C*3,5), 25.49 (C_6H_{11}-*C*4), 32.48 (C_6H_{11}-*C*2,6), 35.93 (2×CCH_2Ph), 42.22 (CH_2CO), 47.46 (CH_2N), 48.54 (C_6H_{11}-*C*1), 69.15(C^{α}), 124.01 (NCH_2Ph-*C*3,5), 127.02, 127.12 (2×CCH_2Ph-*C*4+NCH_2Ph-*C*2,6+$COCH_2$Ph-*C*4), 128.25 (2×CCH_2Ph-*C*3,5), 128.70 ($COCH_2$Ph-*C*3,5), 129.28 ($COCH_2$Ph-*C*2,6), 130.85

(2×CCH_2Ph-*C*2,6), 133.91 ($COCH_2$Ph-*C*1), 134.80 (2×CCH_2Ph-*C*1), 146.85 (NCH_2Ph-*C*4), 147.06 (NCH_2Ph-*C*1), 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.

4.1.1.17. *N*-Phenylacetyl-*N*-(4-methoxyphenyl)-α,α-dimethylglycine cyclohexylamide (3a). The reaction was carried out on a 0.01-molar scale and the crude product was 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 °C. ^{1}H NMR (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}-*H*1), 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-*H*3,5), 6.99 (2H, m, CH_2Ph-*H*2,6), 7.06 (2H, d, *J*=8.7 Hz, NPh-*H*2,6), 7.20 (3H, m, CH_2Ph-*H*3,4,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.75 (C_6H_{11}-*C*3,5), 25.29 (2×CH_3), 25.51 (C_6H_{11}-*C*4), 32.75 (C_6H_{11}-*C*2,6), 42.59 (CH_2), 48.30 (C_6H_{11}-*C*1), 55.33 (OCH_3), 62.61 (C^{α}), 113.99 (NPh-*C*3,5), 126.35 (CH_2Ph-*C*4), 128.11 (CH_2Ph-*C*3,5), 128.83 (CH_2Ph-*C*2,6), 131.27 (NPh-*C*2,6), 132.33 (NPh-*C*1), 135.23 (CH_2Ph-*C*1), 159.21 (NPh-*C*4), 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.

4.1.1.18. *N*-Phenylacetyl-*N*-phenyl-α,α-dimethylglycine cyclohexylamide (3b). The reaction was carried out on a 0.02-molar scale and the crude product was 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 °C. ^{1}H NMR (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}-*H*1), 5.66 (1H, d, *J*=7.5 Hz, N*H*), 6.98 (2H, m, CH_2Ph-*H*2,6), 7.16–7.22 (5H, m, NPh-*H*2,6+CH_2Ph-*H*3,4,5), 7.39 (3H, m, NPh-*H*3,4,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.78 (C_6H_{11}-*C*3,5), 25.37 (2×CH_3), 25.55 (C_6H_{11}-*C*4), 32.79 (C_6H_{11}-*C*2,6), 42.69 (CH_2), 48.36 (C_6H_{11}-*C*1), 62.56 (C^{α}), 126.41 (CH_2Ph-*C*4), 128.16 (CH_2Ph-*C*3,5), 128.46 (NPh-*C*4), 128.84 (CH_2Ph-*C*2,6), 129.03 (NPh-*C*3,5), 130.43 (NPh-*C*2,6), 135.16 (CH_2Ph-*C*1), 139.67 (NPh-*C*1), 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.

4.1.1.19. *N*-Phenylacetyl-*N*-(4-chlorophenyl)-α,α-dimethylglycine cyclohexylamide (3c). The reaction was carried out on a 0.01-molar scale and the crude product was 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 °C. ^{1}H NMR (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}-*H*1), 5.63 (1H, d, *J*=7.8 Hz, N*H*), 6.96 (2H, m, CH_2Ph-*H*2,6), 7.11 (2H, d, *J*=8.7 Hz, NPh-*H*2,6), 7.18–7.21 (3H, m, CH_2Ph-*H*3,4,5), 7.31 (2H, d, *J*=8.4 Hz, NPh-*H*3,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.82 (C_6H_{11}-*C*3,5), 25.48 (2×CH_3), 25.56 (C_6H_{11}-*C*4), 32.85 (C_6H_{11}-*C*2,6), 42.83 (CH_2), 48.54 (C_6H_{11}-*C*1), 62.54 (C^{α}), 126.54 (CH_2Ph-*C*4), 128.28 (CH_2Ph-*C*3,5), 128.76 (CH_2Ph-*C*2,6), 129.17 (NPh-*C*3,5), 131.87 (NPh-*C*2,6), 134.42 (NPh-*C*4), 134.93 (CH_2Ph-*C*1), 138.35 (NPh-*C*1), 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.

4.1.1.20. *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 was 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 °C. ^{1}H NMR (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}-*H*1), 5.65 (1H, d, *J*=7.8 Hz, N*H*), 6.90 (2H, m, CH_2Ph-*H*2,6), 7.16–7.20 (3H, m, CH_2Ph-*H*3,4,5), 7.34 (2H, d, *J*=8.1 Hz, NPh-*H*2,6), 7.62 (2H, d, *J*=8.4 Hz, NPh-*H*3,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.79 (C_6H_{11}-*C*3,5), 25.49 (2×CH_3), 25.54 (C_6H_{11}-*C*4), 32.81 (C_6H_{11}-*C*2,6), 43.09 (CH_2), 48.68 (C_6H_{11}-*C*1), 62.60 (C^{α}), 112.46 (NPh-*C*4), 117.82 (NPh-*C*N), 126.68 (CH_2Ph-*C*4), 128.37 (CH_2Ph-*C*3,5), 128.55 (CH_2Ph-*C*2,6), 131.77 (NPh-*C*2,6), 132.76 (NPh-*C*3,5), 134.46 (CH_2Ph-*C*1), 143.99 (NPh-*C*1), 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.

4.1.1.21. *N*-Phenylacetyl-*N*-(4-nitrophenyl)-α,α-dimethylglycine cyclohexylamide (3e). The reaction was carried out on a 0.04-molar scale and the crude product was 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 °C. ^{1}H NMR (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}-*H*1), 5.64 (1H, d, *J*=7.8 Hz, N*H*), 6.93 (2H, m, CH_2Ph-*H*2,6), 7.20–7.22 (3H, m, CH_2Ph-*H*3,4,5), 7.41 (2H, d, *J*=9.0 Hz, NPh-*H*2,6), 8.20 (2H, d, *J*=9.0 Hz, NPh-*H*3,5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.86 (C_6H_{11}-*C*3,5), 25.56 (C_6H_{11}-*C*4), 25.64 (2×CH_3), 32.90 (C_6H_{11}-*C*2,6), 43.19 (CH_2), 48.79 (C_6H_{11}-*C*1), 62.68 (C^{α}), 124.14 (NPh-*C*3,5), 126.80 (CH_2Ph-*C*4), 128.47 (CH_2Ph-*C*3,5), 128.61 (CH_2Ph-*C*2,6), 131.93 (NPh-*C*2,6), 134.45 (CH_2Ph-*C*1), 145.82 (NPh-*C*4), 147.41 (NPh-*C*1), 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.

4.1.2. General method for the preparative acidolysis of 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 were kept at room temperature until TLC (dichloromethane/MeOH, 25:1) showed no more starting material (2–168 h). The solvent was concentrated under reduced pressure at 30 °C and the pH of the residue was adjusted to 3 by treatment with 2 M aqueous NaOH. The mixture was stirred overnight and the resulting suspension was 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 was 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**).

4.1.2.1. *N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine (4a). The reaction was carried out with compound **1a** (0.20 g) and the product was purified by recrystallisation from ethyl acetate to yield **4a** (140 mg, 84%) as a white solid, mp 201.1–202.1 °C (lit.[20] 168.6–169.2 °C). ^{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$_2$Ph-*H*3,5), 7.11–14 (2H, m, COCH$_2$Ph-*H*2,6), 7.17–7.29 (3H, m, COCH$_2$Ph-*H*3,4,5), 7.36 (2H, d, J=8.7 Hz, NCH$_2$Ph-*H*2,6), 12.02 (1H, br s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.33 (2×CH$_3$), 40.34 (*C*H$_2$CO), 46.12 (*C*H$_2$N), 55.06 (O*C*H$_3$), 60.69 (*C*$^{\alpha}$), 113.99 (NCH$_2$Ph-*C*3,5), 126.40 (COCH$_2$Ph-*C*4), 127.03 (NCH$_2$Ph-*C*2,6), 128.27 (COCH$_2$Ph-*C*3,5), 128.92 (COCH$_2$Ph-*C*2,6), 130.92 (NCH$_2$Ph-*C*1), 135.58 (COCH$_2$Ph-*C*1), 158.20 (NCH$_2$Ph-*C*4), 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.

4.1.2.2. *N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dimethylglycine (4b). The reaction was carried out with compound **1b** (0.21 g) and the product was 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 °C. ^{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, $CDCl_3$): δ 21.01 (Ph-CH$_3$), 23.50 (2×CH$_3$), 41.36 (*C*H$_2$CO), 47.12 (*C*H$_2$N), 61.40 (*C*$^{\alpha}$), 125.76 (NCH$_2$Ph-*C*2,6), 126.76 (COCH$_2$Ph-*C*4), 128.57 (COCH$_2$Ph-*C*2,6), 128.63 (COCH$_2$Ph-*C*3,5), 129.56 (NCH$_2$Ph-*C*3,5), 134.54 (COCH$_2$Ph-*C*1), 134.86 (NCH$_2$Ph-*C*1), 136.92 (NCH$_2$Ph-*C*4), 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 79% yield, when 0.25 g of **1b** was submitted to the forcing reaction conditions described below for the preparation of **6e**.

4.1.2.3. *N*-Phenylacetyl-*N*-benzyl-α,α-dimethylglycine (4c). The reaction was carried out with compound **1c** (0.20 g) and the product was 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 °C. ^{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$_2$Ph-*H*4), 7.41–7.45 (4H, m, NCH$_2$Ph-*H*2,3,5,6), 9.41 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.50 (2×*C*H$_3$), 41.36 (*C*H$_2$CO), 47.31 (*C*H$_2$N), 61.44 (*C*$^{\alpha}$), 125.79 (NCH$_2$Ph-*C*2,6), 126.78 (COCH$_2$Ph-*C*4), 127.26 (NCH$_2$Ph-*C*4), 128.56 (COCH$_2$Ph-*C*2,6), 128.63 (COCH$_2$Ph-*C*3,5), 128.88 (NCH$_2$Ph-*C*3,5), 134.44 (COCH$_2$Ph-*C*1), 137.93 (NCH$_2$Ph-*C*1), 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.

4.1.2.4. *N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dimethylglycine (4d). The reaction was carried out with compound **1d** (0.25 g) and the product was purified by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4d** (191 mg, 97%) as white crystals, mp 191.4–192.2 °C. ^{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$_2$Ph-*H*3,5), 7.18–7.33 (5H, m, COCH$_2$*Ph*), 7.41 (2H, dd, J=5.4, 8.4 Hz, NCH$_2$Ph-*H*2,6), 9.43 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.47 (2×*C*H$_3$), 41.41 (*C*H$_2$CO), 46.68 (*C*H$_2$N), 61.47 (*C*$^{\alpha}$), 115.81 (d, J_{C-F}=21.6 Hz, NCH$_2$Ph-*C*3,5), 126.90 (COCH$_2$Ph-*C*4), 127.41 (d, J_{C-F}=7.8 Hz, NCH$_2$Ph-*C*2,6), 128.52 (COCH$_2$Ph-*C*2,6), 128.72 (COCH$_2$Ph-*C*3,5), 133.59 (d, J_{C-F}=3.2 Hz, NCH$_2$Ph-*C*1), 134.29 (COCH$_2$Ph-*C*1), 162.01 (d, J_{C-F}=245.6 Hz, NCH$_2$Ph-*C*4), 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 66% yield, when 0.25 g of **1d** was submitted to the forcing reaction conditions described below for the preparation of **6e**.

4.1.2.5. *N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dimethylglycine (4e). The reaction was carried out with compound **1e** (0.21 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4e** (154 mg, 89%) as a white solid, mp 168.8–169.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.44 (6H, s, 2×CH_3), 3.65 (2H, s, CH_2CO), 4.56 (2H, s, NCH_2), 7.18–7.38 (9H, m, COCH$_2$-*Ph*+NCH$_2$Ph-*H*2,3,5,6), 10.01 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.43 (2×*C*H$_3$), 41.40 (*C*H$_2$CO), 46.72 (*C*H$_2$N), 61.45 (*C*$^{\alpha}$), 126.90 (COCH$_2$Ph-*C*4), 127.21 (NCH$_2$Ph-*C*2,6), 128.47 (COCH$_2$Ph-*C*2,6), 128.71 (COCH$_2$Ph-*C*3,5), 129.05 (NCH$_2$Ph-*C*3,5), 133.08 (NCH$_2$Ph-*C*4), 134.18 (COCH$_2$Ph-*C*1), 136.49 (NCH$_2$Ph-*C*1), 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.

4.1.2.6. *N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dimethylglycine (4f). The reaction was carried out with compound **1f** (0.25 g) and the product was purified by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4f** (153 mg, 90%) as a white solid, mp 149.9–150.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2×CH_3), 3.66 (2H, s, CH_2CO), 4.59 (2H, s, NCH_2), 7.19–7.32 (7H, m, COCH$_2$*Ph*+NCH$_2$Ph-*H*3,5), 7.49 (2H, d, J=8.4 Hz, NCH$_2$Ph-*H*2,6), 9.32 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.47 (2×*C*H$_3$), 41.47 (*C*H$_2$CO), 46.69 (*C*H$_2$N), 61.49 (*C*$^{\alpha}$), 120.4 (q, J_{C-F}=257.1 Hz, O*C*F$_3$), 121.45 (NCH$_2$Ph-*C*3,5), 126.96 (COCH$_2$Ph-*C*4), 127.21 (NCH$_2$Ph-*C*2,6), 128.50 (COCH$_2$Ph-*C*2,6), 128.76 (COCH$_2$Ph-*C*3,5), 134.15 (COCH$_2$Ph-*C*1), 136.71 (NCH$_2$Ph-*C*1), 148.39 (q, J_{C-F}=1.9 Hz, NCH$_2$Ph-*C*4), 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.

4.1.2.7. *N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dimethylglycine (4g). The reaction was carried out with compound **1g** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **4g** (161 mg,

92%) as white crystals, mp 180.9–181.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (6H, s, 2×CH_3), 3.65 (2H, s, CH_2CO), 4.64 (2H, s, NCH_2), 7.18 (2H, m, $COCH_2$-*H*2,6), 7.24–7.33 (3H, m, $COCH_2$Ph-*H*3,4,5), 7.60 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H*2,6), 7.67 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H*3,5), 9.00 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.48 (2×*C*H_3), 41.54 (*C*H_2CO), 47.03 (*C*H_2N), 61.54 (C^{α}), 124.03 (q, J_{C-F}=274.0 Hz, *C*F_3), 125.93 (q, J_{C-F}=3.7 Hz, NCH_2Ph-*C*3,5), 126.20 (NCH_2Ph-*C*2,6), 127.02 ($COCH_2$Ph-*C*4), 128.48 ($COCH_2$Ph-*C*2,6), 128.80 ($COCH_2$Ph-*C*3,5), 129.75 (q, J_{C-F}=32.5 Hz, NCH_2Ph-*C*4), 134.06 ($COCH_2$Ph-*C*1), 142.25 (NCH_2Ph-*C*1), 172.17 (*C*OCH_2), 178.67 (*C*OOH). 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.

4.1.2.8. *N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dimethylglycine (4h). The reaction was carried out with compound **1h** (0.20 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4h** (146 mg, 89%) as pale yellow crystals, mp 194.7–195.8 °C. ^{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, $COCH_2$Ph-*H*2,6), 7.22–7.32 (3H, m, $COCH_2$Ph-*H*3,4,5), 7.66 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H*2,6), 8.26 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H*3,5), 9.03 (1H, br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.44 (2×*C*H_3), 41.60 (*C*H_2CO), 47.00 (*C*H_2N), 61.59 (C^{α}), 124.19 (NCH_2Ph-*C*3,5), 126.73 (NCH_2Ph-*C*2,6), 127.14 ($COCH_2$Ph-*C*4), 128.41 ($COCH_2$Ph-*C*2,6), 128.87 ($COCH_2$Ph-*C*3,5), 133.75 ($COCH_2$Ph-*C*1), 145.65 (NCH_2Ph-*C*1), 147.32 (NCH_2Ph-*C*4), 172.12 (*C*OCH_2), 178.51 (*C*OOH). 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.

4.1.2.9. *N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine (5a). The reaction was carried out with compound **2a** (0.14 g) and the product was purified by PLC (dichloromethane/MeOH, 15:1) followed by recrystallisation from ethyl acetate to yield **5a** (81 mg, 68%) as a white solid, mp 208.2–209.3 °C (lit.[20] 158.2–159.2 °C). ^{1}H NMR (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-*H*3,5), 7.13–7.15 (2H, m, $COCH_2$Ph-*H*2,6), 7.19–7.34 (13H, m, 2×CCH_2*Ph*+$COCH_2$Ph-*H*3,4,5), 7.44 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H*2,6), 12.34 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.22 (2×*C*CH_2Ph), 40.50 (*C*H_2CO), 47.02 (*C*H_2N), 55.03 (O*C*H_3), 68.18 (C^{α}), 114.04 (NCH_2Ph-*C*3,5), 126.54 (2×CCH_2Ph-*C*4), 126.75 (NCH_2Ph-*C*2,6+$COCH_2$Ph-*C*4), 128.16 (2×CCH_2Ph-*C*3,5), 128.19 ($COCH_2$Ph-*C*3,5), 129.59 ($COCH_2$Ph-*C*2,6), 130.74 (2×CCH_2Ph-*C*2,6), 130.96 (NCH_2Ph-*C*1), 135.04 ($COCH_2$Ph-*C*1), 135.68 (2×CCH_2Ph-*C*1), 158.11 (NCH_2Ph-*C*4), 171.57 (*C*OCH_2), 172.29 (*C*OOH). 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.

4.1.2.10. *N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dibenzylglycine (5b). The reaction was carried out with compound **2b** (0.25 g) and the product was purified by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **5b** (200 mg, 93%) as a white solid, mp 212.5–213.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.34 (3H, s, CH_3Ph), 3.02 (2H, d, *J*=13.2 Hz, CCH_2Ph), 3.43 (2H, br d, *J*=12.9 Hz, CCH_2Ph), 3.61 (2H, s, COCH_2), 3.82 (2H, br s, NCH_2), 7.17–7.30 (12H, m, 2×CCH_2*Ph*+NCH_2Ph-*H*3,5), 7.33–7.44 (7H, m, $COCH_2$*Ph*+NCH_2Ph-*H*2,6), 8.45 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.98 (*C*H_3Ph), 36.13 (2×*C*CH_2Ph), 41.31 (*C*H_2CO), 48.11 (*C*H_2N), 68.88 (C^{α}), 125.57 (NCH_2Ph-*C*2,6), 127.01 ($COCH_2$Ph-*C*4), 127.06 (2×CCH_2Ph-*C*4), 128.40 (2×CCH_2Ph-*C*3,5), 128.58 ($COCH_2$Ph-*C*3,5), 129.62 (NCH_2Ph-*C*3,5), 129.72 ($COCH_2$Ph-*C*2,6), 130.87 (2×CCH_2Ph-*C*2,6), 134.42 ($COCH_2$Ph-*C*1), 135.14 (NCH_2Ph-*C*1), 135.37 (2×CCH_2Ph-*C*1), 136.68 (NCH_2Ph-*C*4), 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.

4.1.2.11. *N*-Phenylacetyl-*N*-benzyl-α,α-dibenzylglycine (5c). The reaction was carried out with compound **2c** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **5c** (207 mg, 98%) as a white solid, mp 228.6–229.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 2.76 (2H, d, *J*=12.9 Hz, CCH_2Ph), 3.26 (2H, d, *J*=12.9 Hz, CCH_2Ph), 3.43 (2H, s, COCH_2), 3.94 (2H, s, NCH_2), 7.13 (2H, br dd, *J*=1.5, 6.6 Hz, $COCH_2$Ph-*H*2,6), 7.23–7.30 (14H, m, 2×CCH_2*Ph*+NCH_2Ph-*H*4+$COCH_2$Ph-*H*3,4,5), 7.37 (2H, t, *J*=7.8 Hz, NCH_2Ph-*C*3,5), 7.53 (2H, d, *J*=7.5 Hz, NCH_2Ph-*H*2,6), 12.35 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.28 (2×*C*CH_2Ph), 40.50 (*C*H_2CO), 47.58 (*C*H_2N), 68.23 (C^{α}), 125.66 (NCH_2Ph-*C*2,6), 126.57 (NCH_2Ph-*C*4), 126.78, 126.82 (2×CCH_2Ph-*C*4+$COCH_2$Ph-*C*4), 128.19 (2×CH_2Ph-*C*3,5+$COCH_2$Ph-*C*3,5), 128.63 (NCH_2Ph-*C*3,5), 129.60 ($COCH_2$Ph-*C*2,6), 130.75 (2×CH_2Ph-*C*2,6), 134.98 ($COCH_2$Ph-*C*1), 135.67 (2×CCH_2Ph-*C*1), 139.34 (NCH_2Ph-*C*1), 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.

4.1.2.12. *N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dibenzylglycine (5d). The reaction was carried out with compound **2d** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **5d** (190 mg, 88%) as a white solid, mp 193.9–195.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.01 (2H, d, *J*=13.2 Hz, CCH_2Ph), 3.45 (2H, br d, *J*=12.6 Hz, CCH_2Ph), 3.60 (2H, s, COCH_2), 3.84 (2H, br s, NCH_2), 7.08 (2H, t, *J*=9.0 Hz, NCH_2Ph-*H*3,5), 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_2Ph-*H*2,6), 8.81 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.12 (2×*C*CH_2Ph), 41.31 (*C*H_2CO), 47.68 (*C*H_2N), 68.93 (C^{α}), 115.84 (d, J_{C-F}=21.6 Hz, NCH_2Ph-*C*3,5), 127.16 (2×CCH_2Ph-*C*4+$COCH_2$Ph-*C*4), 127.28 (d, J_{C-F}=7.8 Hz, NCH_2Ph-*C*2,6), 128.45 (2×CCH_2Ph-*C*3,5), 128.64 ($COCH_2$Ph-*C*3,5), 129.64 ($COCH_2$Ph-*C*2,6), 130.82 (2×CCH_2Ph-*C*2,6), 133.82 (d, J_{C-F}=3.2 Hz, NCH_2Ph-*C*1), 134.12 ($COCH_2$Ph-*C*1), 135.17 (2×CCH_2Ph-*C*1), 161.88 (d, J_{C-F}=245.6 Hz, NCH_2Ph-*C*4), 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.

4.1.2.13. *N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dibenzylglycine (5e). The reaction was carried out with compound **2e** (0.25 g) and the product was purified by

recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **5e** (186 mg, 85%) as a white solid, mp 207.9–209.1 °C. ^{1}H NMR (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$_2$*Ph*+COCH$_2$*Ph*+NCH$_2$*Ph*), 8.22 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.06 (2×C*C*H$_2$Ph), 41.36 (*C*H$_2$CO), 47.74 (*C*H$_2$N), 68.91 (C^{α}), 127.11 (NCH$_2$Ph-*C*2,6), 127.17 (2×CCH$_2$Ph-*C*4+COCH$_2$Ph-*C*4), 128.47 (2×CCH$_2$Ph-*C*3,5), 128.67 (NCH$_2$Ph-*C*3,5), 129.12 (COCH$_2$Ph-*C*3,5), 129.63 (COCH$_2$Ph-*C*2,6), 130.82 (2×CCH$_2$Ph-*C*2,6), 132.99 (NCH$_2$Ph-*C*4), 134.03 (COCH$_2$Ph-*C*1), 135.13 (2×CCH$_2$Ph-*C*1), 136.76 (NCH$_2$Ph-*C*1), 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.

4.1.2.14. *N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dibenzylglycine (5f). The reaction was carried out with compound **2f** (0.25 g) and the product was 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 °C. ^{1}H NMR (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$_2$*Ph*+NCH$_2$Ph-*H*3,5+COCH$_2$*Ph*), 7.53 (2H, d, J=8.7 Hz, NCH$_2$Ph-*H*2,6), 8.51 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.13 (2×C*C*H$_2$Ph), 41.37 (*C*H$_2$CO), 47.71 (*C*H$_2$N), 68.96 (C^{α}), 121.46 (NCH$_2$Ph-*C*3,5), 120.41 (q, J_{C-F}=257.1 Hz, O*C*F$_3$), 127.12 (NCH$_2$Ph-*C*2,6), 127.20, 127.22 (2×CCH$_2$Ph-*C*4+COCH$_2$Ph-*C*4), 128.49 (2×CCH$_2$Ph-*C*3,5), 128.68 (COCH$_2$Ph-*C*3,5), 129.63 (COCH$_2$Ph-*C*2,6), 130.83 (2×CCH$_2$Ph-*C*2,6), 133.98 (COCH$_2$Ph-*C*1), 135.09 (2×CCH$_2$Ph-*C*1), 136.91 (NCH$_2$Ph-*C*1), 148.28 (q, J_{C-F}=1.8 Hz, NCH$_2$Ph-*C*4), 173.41 (*C*OCH$_2$), 175.61 (*C*OOH). Anal. Calcd for $C_{32}F_3H_{28}NO_4\cdot 1/3H_2O$: C, 69.43; H, 5.22; N, 2.53. Found: C, 69.53; H, 5.41; N, 2.58.

4.1.2.15. *N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dibenzylglycine (5g). The reaction was carried out with compound **2g** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **5g** (207 mg, 95%) as white crystals, mp 201.9–203.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 2.99 (2H, d, J=12.9 Hz, CCH_2Ph), 3.45 (2H, br d, J=12.6 Hz, CCH_2Ph), 3.57 (2H, s, COCH_2), 3.91 (2H, br s, NCH_2), 7.27–7.42 (15H, m, 2×CCCH$_2$*Ph*+COCH$_2$*Ph*), 7.64 (4H, s, NCH$_2$Ph-*H*2,3,5,6), 8.44 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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-F}=272.0 Hz, *C*F$_3$), 125.96 (q, J_{C-F}=3.8 Hz, NCH$_2$Ph-*C*3,5), 126.12 (NCH$_2$Ph-*C*2,6), 127.24 (2×CCH$_2$Ph-*C*4+COCH$_2$Ph-*C*4), 128.51 (2×CCH$_2$Ph-*C*3,5), 128.71 (COCH$_2$Ph-*C*3,5), 129.59 (q, J_{C-F}=32.5 Hz, NCH$_2$Ph-*C*4), 129.60 (COCH$_2$Ph-*C*2,6), 130.82 (2×CCH$_2$Ph-*C*2,6), 133.85 (COCH$_2$Ph-*C*1), 135.03 (2×CCH$_2$Ph-*C*1), 142.45 (NCH$_2$Ph-*C*1), 173.33 (*C*OCH$_2$), 175.40 (*C*OOH). Anal. Calcd for $C_{32}F_3H_{28}NO_3\cdot 1/3H_2O$: C, 71.50; H, 5.37; N, 2.61. Found: C, 71.33; H, 5.25; N, 2.55.

4.1.2.16. *N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dibenzylglycine (5h). The reaction was carried out with compound **2h** (0.20 g) and the product was 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 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 2.73 (2H, d, J=12.9 Hz, CCH_2Ph), 3.29 (2H, d, J=13.2 Hz, CCH_2Ph), 3.44 (2H, s, COCH_2), 4.15 (2H, br s, NCH_2), 7.13 (2H, dd, J=1.5, 9.3 Hz, COCH$_2$Ph-*H*2,6), 7.21–7.29 (13H, m, 2×CCH$_2$*Ph*+COCH$_2$Ph-*H*3,4,5), 7.78 (2H, d, J=8.7 Hz, NCH$_2$Ph-*H*2,6), 8.21 (2H, d, J=9.0 Hz, NCH$_2$Ph-*H*3,5), 12.47 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 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-*C*3,5), 126.57 (COCH$_2$Ph-*C*4), 126.83 (2×CCH$_2$Ph-*C*4), 127.15 (NCH$_2$Ph-*C*2,6), 128.16 (COCH$_2$Ph-*C*3,5), 128.22 (2×CCH$_2$Ph-*C*3,5), 129.65 (COCH$_2$Ph-*C*2,6), 130.75 (2×CCH$_2$Ph-*C*2,6), 134.76 (COCH$_2$Ph-*C*1), 135.54 (2×CCH$_2$Ph-*C*1), 146.50 (NCH$_2$Ph-*C*4), 147.52 (NCH$_2$Ph-*C*1), 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.

4.1.2.17. *N*-Phenylacetyl-*N*-(4-methoxyphenyl)-α,α-dimethylglycine (6a). The reaction was carried out with compound **3a** (0.38 g) in neat TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **6a** (0.30 g, 98%) as white crystals, mp 164.2–165.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (6H, s, 2×CH_3), 3.40 (2H, s, CH_2), 3.85 (3H, s, OCH_3), 6.87 (2H, d, J=9.0 Hz, NPh-*H*3,5), 7.04 (2H, m, CH$_2$Ph-*H*2,6), 7.09 (2H, d, J=8.7 Hz, NPh-*H*2,6), 7.20 (3H, m, CH$_2$Ph-*H*3,4,5), 8.91 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.84 (2×*C*H$_3$), 42.08 (*C*H$_2$), 55.43 (O*C*H$_3$), 61.69 (C^{α}), 114.17 (NPh-*C*3,5), 126.93 (CH$_2$Ph-*C*4), 128.14 (CH$_2$Ph-*C*3,5), 129.03 (CH$_2$Ph-*C*2,6), 131.26 (NPh-*C*2,6), 131.79 (NPh-*C*1), 135.08 (CH$_2$Ph-*C*1), 159.47 (NPh-*C*4), 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.

4.1.2.18. *N*-Phenylacetyl-*N*-phenyl-α,α-dimethylglycine (6b). The reaction was carried out with compound **3b** (0.25 g) in neat TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 12:1) followed by recrystallisation from ethyl acetate to yield **6b** (72 mg, 77%) as a white solid, mp 154.8–155.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.38 (6H, s, 2×CH_3), 3.39 (2H, s, CH_2), 7.01 (2H, m, CH$_2$Ph-*H*2,6), 7.19–7.22 (5H, m, NPh-*H*2,6+CH$_2$Ph-*H*3,4,5), 7.39 (3H, m, NPh-*H*3,4,5), 9.38 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.86 (2×*C*H$_3$), 42.13 (*C*H$_2$), 61.58 (C^{α}), 126.41 (CH$_2$Ph-*C*4), 128.14 (CH$_2$Ph-*C*3,5), 128.70 (NPh-*C*4), 128.99 (CH$_2$Ph-*C*2,6), 129.14 (NPh-*C*3,5), 130.33 (NPh-*C*2,6), 134.94 (CH$_2$Ph-*C*1), 139.08 (NPh-*C*1), 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.

4.1.2.19. *N*-Phenylacetyl-*N*-(4-chlorophenyl)-α,α-dimethylglycine (6c). The reaction was carried out with compound **3c** (0.21 g) in 5% TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **6c** (109 mg, 66%) as white crystals, mp 170.4–171.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (6H, s, 2×CH_3), 3.39 (2H, s,

CH_2), 7.00 (2H, m, CH_2Ph-*H*2,6), 7.11 (2H, d, *J*=8.4 Hz, NPh-*H*2,6), 7.20–7.22 (3H, m, CH_2Ph-*H*3,4,5), 7.35 (2H, d, *J*=8.7 Hz, NPh-*H*3,5), 9.35 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.88 (2×CH_3), 42.29 (CH_2), 61.65 (C^{α}), 126.60 (CH_2Ph-*C*4), 128.28 (CH_2Ph-*C*3,5), 128.88 (CH_2Ph-*C*2,6), 129.36 (NPh-*C*3,5), 131.66 (NPh-*C*2,6), 134.58 (CH_2Ph-*C*1), 134.74 (NPh-*C*4), 137.59 (NPh-*C*1), 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.

4.1.2.20. *N*-Phenylacetyl-*N*-(4-cyanophenyl)-α,α-dimethylglycine (6d). The reaction was carried out with compound **3d** (0.20 g) in 5% TFA at room temperature and the product was 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 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.37 (6H, s, 2×CH_3), 3.37 (2H, s, CH_2), 6.93 (2H, m, CH_2Ph-*H*2,6), 7.19–7.21 (3H, m, CH_2Ph-*H*3,4,5), 7.29 (2H, d, *J*=8.1 Hz, NPh-*H*2,6), 7.66 (2H, d, *J*=8.4 Hz, NPh-*H*3,5), 9.56 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.96 (2×CH_3), 42.66 (CH_2), 61.91 (C^{α}), 112.89 (NPh-*C*4), 117.75 (NPh-*C*N), 126.83 (CH_2Ph-*C*4), 128.43 (CH_2Ph-*C*3,5), 128.69 (CH_2Ph-*C*2,6), 131.52 (NPh-*C*2,6), 133.01 (NPh-*C*3,5), 134.12 (CH_2Ph-*C*1), 143.20 (NPh-*C*1), 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.

4.1.2.21. *N*-Phenylacetyl-*N*-(4-nitrophenyl)-α,α-dimethylglycine (6e). Compound **3e** (0.25 g) was dissolved in 5 ml of neat TFA and the solution was refluxed for 1 h. The solvent was concentrated under reduced pressure at 30 °C and the pH of the residue was adjusted to 3 by treatment with 2 M aqueous NaOH. The mixture was stirred overnight and the resulting suspension was 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 was 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 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.40 (6H, s, 2×CH_3), 3.39 (2H, s, CH_2), 6.95 (2H, m, CH_2Ph-*H*2,6), 7.20–7.23 (3H, m, CH_2Ph-*H*3,4,5), 7.35 (2H, d, *J*=9.0 Hz, NPh-*H*2,6), 8.23 (2H, d, *J*=8.7 Hz, NPh-*H*3,5), 9.22 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.95 (2×CH_3), 42.68 (CH_2), 61.89 (C^{α}), 124.39 (NPh-*C*3,5), 126.90 (CH_2Ph-*C*4), 128.48 (CH_2Ph-*C*3,5), 128.70 (CH_2Ph-*C*2,6), 131.62 (NPh-*C*2,6), 134.01 (CH_2Ph-*C*1), 144.88 (NPh-*C*4), 147.64 (NPh-*C*1), 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

4.2.1. 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 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 were kept in a thermostatic bath at a temperature stabilised within 0.01 °C of the required value, the same was applied throughout the reaction. At regular intervals of time samples were collected for HPLC monitoring and injected as quickly as possible to minimise errors caused due 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.

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