The Ugi reaction in a polyethylene glycol medium: a mild, protocol for the production of compound libraries

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A mild, efficient, and eco-friendly method for the Ugi reaction between a carboxylic acid, an amine, a carbonyl compound and an isocyanide to give a bisamide is described using PEG–H_2O as a solvent. Reactants of poor water-solubility could be used in an aqueous medium without significant decrease in the yield. No side products were observed. The advantages of this protocol are short reaction time and easy isolation of the precipitated product when compared to reactions carried out in methanol.

Keywords: green chemistry, multicomponent reaction, Ugi reaction, PEG–H_2O medium, isocyanides, poor water-solubility reactants

In modern organic chemistry, environmental friendly chemical synthesis is gaining considerable interest in both academic and industrial research. Multicomponent reactions[1,2] (MCRs) are used in "green chemistry". Since their atom economy, facile execution and high efficiency allow a wide range of components to be subjected to one pot reactions making it possible to prepare numerous products within a few steps. One of the most commonly used MCRs is the Ugi four-component reaction, in which a carboxylic acid, an amine, a carbonyl compound, and an isocyanide are reacted to form amide derivatives.[3,4] Recently, the Ugi reaction has been developed to generate natural products and drugs in high yields and high diastereoselectivities.[5–9] Recent examples include pyrazinones,[10] β-turn mimics,[11] carfentanil,[12] remifentanil,[12] and the anti-schistosomal drug praziquantel (PZQ).[13]

"Green chemistry" involves a reduction in pollutants such as organic solvents whose recovery is regulated by evermore strict laws. In order to fulfill this, it is better to use water as solvent, which can be advantageous as a medium for reaction and workup relative to flammable, volatile, or toxic organic solvents.[14] Moreover, the recognition of biomolecules by receptors usually takes place in water at room temperature under close to neutral pH. Water as a solvent has been wildly accepted for organic transformation.[15–18] However, most Ugi reactions have been performed in organic solvents such as MeOH, CH_2Cl_2.

Since the discovery by Pirrung and coworkers[19] that multicomponent reactions can be accelerated in aqueous medium compared to organic solvents, some Ugi reactions have been performed in water. For example, Kanizsai *et al.*,[20,22] Pirrung *et al.*[21] and Szakonyi *et al.*[23] have reported that β-lactam derivatives were synthesised successfully in aqueous medium with high yields and high diastereoselectivities as compared with that in MeOH. Abbas *et al.* reported that an acetal was used in an Ugi-MCR to furnish selenocysteine peptides in one step as model compounds for selenocysteine peptides and proteins.[24] An Ugi-Smiles type reaction has also been performed in water instead of methanol or toluene by Kaïm and coworkers.[25] However, water has not enjoyed extensive use in the Ugi reaction, due to the poor solubility of the reactants which reduce the yield. For example, β-amino acid needed to be completely dissolved in water,[20,22] but in some examples a concentration of only 0.1M could be achieved.[19,26] Raising the reaction temperature can be effective. Recently, Kaïm *et al.* reported an Ugi-Smiles coupling reaction in water at 90°C, while methanol required 40°C.[25] Thus it was urgent to develop a mild methodology which could increase the solubility of the reactants in water efficiently. Herein, we describe an efficient, mild and high concentration method for the Ugi reaction using PEG–H_2O as solvent.

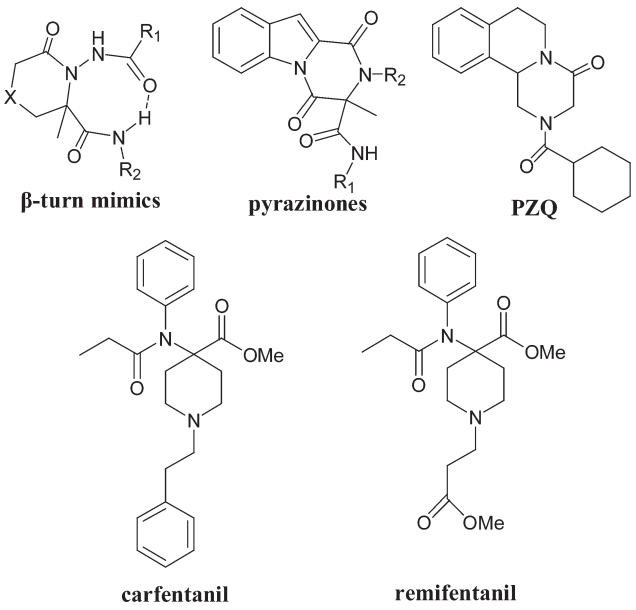

Fig. 1 Some natural products and drugs synthesised through the Ugi reaction.

Results and discussion

To improve the poor solubility of reactants in water and avoid possible side reactions, we focused our research on finding a "green" medium which can disperse organic molecules in water efficiently. Some surfactants and phase transfer catalysts have been tested by a prototype Ugi reaction of aniline, benzaldehyde, phenylformic acid and ethyl isocyanoacetate (Table 1). The starting materials were selected using one criterion: poor solubility in water. We found that the reaction was completed within 3h in pure water and a medium yield was obtained (Table 1, entry 1). However, the starting materials were found to adhere to the vessel. The reactants were not dispersed in water efficiently if no additives were added. However, phase transfer catalysts, such as TEBA (benzyl trimethylammonium chloride) and TBAB (tetra-*n*-butylammonium bromide), did not efficiently increase the water solubility of reactants, and only a slight increase in the yield was observed (Table 1, entries 2, 4). SDS (sodium dodecylsulfate) worked better than TBAB and TEBA, but was still undesirable (Table 1, entry 6). Adding more PTC did not work, either (Table 1, entries 3, 5, 7). Mironov *et al.* found surfactants such as cetylpyridinium chloride and bovine serum albumin could increase

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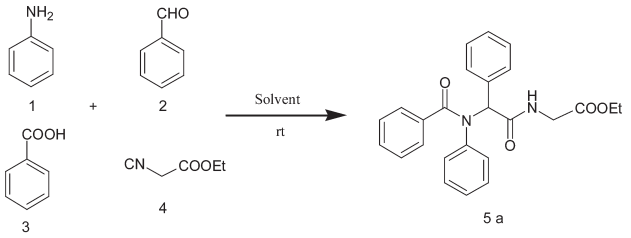
Table 1 Selected Ugi reactions under various reaction conditions[a]



Entry	Solvent	Time/h	Yield/%
1	Pure water	3	46
2	TBAB-H_2O (0.1M)	4	48
3	TBAB-H_2O (0.2M)	4	48
4	TEBA-H_2O (0.1M)	4	51
5	TEBA-H_2O (0.2M)	4	50
6	SDS-H_2O (0.1M)	4	57
7	SDS-H_2O (0.2M)	4	59[b]
8	PEG–H_2O (1:1)	4	73[b]
9	TX10-H_2O (1:9)	4.5	68[b]
10	TX10-H_2O (1:4)	6	65[b]

[a] Reaction condition: **1**, 3mmol; **2**, 3mmol; **3**, 3mmol; **4**, 3mmol, solvent 3mL, mechanical stirring, rt.
[b] Reaction condition: **1**, 3mmol; **2**, 3mmol; **3**, 3mmol; **4**, 3mmol, solvent 3mL, magnetic stirring, rt.

the water solubility of reactants, but a long reaction time was needed.[27] The yield was significantly increased in PEG–H_2O (Table 1, entry 8). No side reactions have been found. It is important to notice that PEG is also non-toxic, cheap and eco-friendly, fulfilling the principles of "green chemistry".[28–32]

We optimised the volume ratio of PEG and water; the results are summarised in Table 2. Obviously, the amount of water played a key role in the reaction. No product was obtained in pure PEG (Table 2, entry 1). The reaction proceeded slowly to afford a medium yield when 25% water was utilised after 24 h (Table 2, entry 2). By increasing the H_2O/PEG ratio, a higher yield was obtained and the product precipitated from the solvent when the reaction was complete (Table 2, entry 4). However, long reaction times were needed when the ratio came to 1:5 (Table 2, entry 8). This is easily explained by a decrease in the dispersal of the reactants. In dilute PEG–H_2O solution, the organic molecules were not dispersed efficiently and reactants associated together, causing a long reaction time. When the volume ratio of PEG and water came to 1:9 (Table 2, entry 9), the starting materials soon associated and adhered to the vessel, as in pure water (Table 1, entry 1). It is found that 25% ratio of PEG and water (Table 2, entry 6) was the best choice. The product was insoluble in PEG–H_2O medium which facilitated its isolation.

It is well known that the Ugi reactions are often performed in organic solvents like MeOH, MeCN, THF *et al.* To compare

Table 2 Influence of volume ratio of PEG and water[a]

Entry	Solvent	Time/h	Yield/%
1	Pure PEG	24	0
2	PEG–H_2O (3:1)	24	37[b]
3	PEG–H_2O (2:1)	24	58[b]
4	PEG–H_2O (1:1)	4	73
5	PEG–H_2O (1:2)	4	74
6	PEG–H_2O (1:3)	3	74
7	PEG–H_2O (1:4)	5	72
8	PEG–H_2O (1:5)	12	73
9	PEG–H_2O (1:9)	3	51

[a] Reaction condition: **1**, 3mmol; **2**, 3mmol; **3**, 3mmol; **4**, 3mmol, solvent 3mL, rt. [b] no precipitate was found.

Table 3 Selected Ugi reaction in different organic solvents[a]

Entry	Solvent	Time/h	Yield/%
1	MeOH	8	76
2	EtOH	8	72
3	MeCN	12	63
4	CH_2Cl_2	12	58
5	THF	12	56

[a] Reaction condition: **1**, 3mmol; **2**, 3mmol; **3**, 3mmol; **4**, 3 mmol, solvent 3 mL, rt. Reactions were detected by TLC.

with that in PEG–H_2O (1:3) medium, the selected Ugi reaction was studied under various conditions summarised in Table 3. This reaction gave the highest yield in methanol in a reasonable reaction time (Table 3, entry 1). The result can be compared with the 74% yield obtained by using PEG–H_2O (1:3) for 3 hours (Table 2, entry 6). Other solvents such as MeCN, CH_2Cl_2 resulted in mild yield and long reaction time (Table 3, entries 2, 3, 4, and 5). Obviously the PEG–H_2O (1:3) medium can accelerate the reaction efficiently without significant decrease of the yield. This might be attributed to the hydrophobic effect and enhanced hydrogen bonding.[20]

With the optimal conditions in hand, we examined a series of reactions in PEG–H_2O and MeOH (Table 4). We found that the reactions were finished when the precipitates did not increase and the solution became clear. With the exceptions of products **5b**, **5f**, **5h**, **and 5k**, the other compounds precipitated from the PEG–H_2O medium and were isolated by filtration. The results revealed that the reaction proceeded successfully in PEG–H_2O and provided about a 3-fold acceleration over MeOH. In PEG–H_2O, most of the yields were similar to those in MeOH. However, in some cases the results decreased significantly, such as (Table 4, entries 8, 11). HPLC test showed that the precipitated products contained some starting reactants. We attributed the incomplete reaction to the high reaction rates which produced short reaction times. Starting materials were inevitably co-precipitated when the products precipitated from the PEG–H_2O medium in the short reaction times, which reduced the yield. The precipitation depends greatly on the solubility and concentration of the starting materials (Table 4, entries 8, 11). In dilute solutions, the reactants did not precipitate, and the yields were similar to those in MeOH.[20]

In conclusion, we report an efficient, mild and eco-friendly method for the Ugi reaction in PEG–H_2O medium. In this protocol, reactants with a poor water solubility could be utilized in an aqueous medium in high concentration and no side products were found. The unique solvating properties of PEG–H_2OH medium has a stimulating effect on the Ugi reaction with respect to the high yield and the short reaction time. The precipitation process was efficient and most of the products were easily isolated by simple filtration.

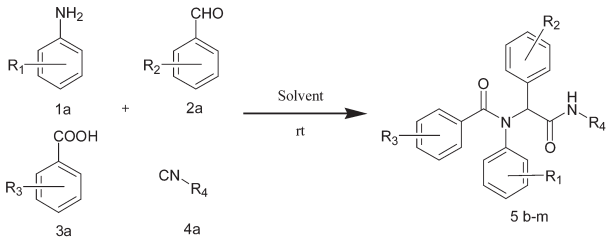
Experimental

Melting points were determined uncorrected. Analytical TLC was performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm). The plates were visualised by exposure to UV light. ^{1}H NMR spectra were recorded on Bruker DRX500 (500 MHz) and ^{13}C NMR spectra on Bruker DRX500 (125 MHz) spectrometer. Mass spectra were taken on a Finnigan TSQ Quantum–MS instrument in the electrospray ionisation (ESI) mode. Elemental analyses were performed on a Vario EL III recorder. PEG 400 was purchased from the petrochemical plant of Jiangsu Haian. All other chemicals (AR grade) were commercially available and used without further purification.

General procedure

A suspension of the amine (3 mmol) and aldehyde (3 mmol) in 3 mL PEG–H_2O was stirred at room temperature for 30–45 minutes. Isonitrile (3 mmol) and acid (3 mmol) were then added to the reaction

Table 4 Ugi reaction in MeOH and PEG–H_2O[a]



Entry	R_1	R_2	R_3	R_4	Product	Method A[a]		Method B[b]	
						t/h	Yield/%[c]	t/h	Yield/%[c]
1	4-NO_2	H	H	CH_2CO_2Et	**5b**	48	37	12	41
2	4-Br	H	H	CH_2CO_2Et	**5c**	3	87	1	84
3	4-Me	H	H	CH_2CO_2Et	**5d**	4	77	1.5	75
4	2-Me	H	H	CH_2CO_2Et	**5e**	8	70	3	72
5	H	4-NO_2	H	CH_2CO_2Et	**5f**	24	42	12	40
6	H	4-Cl	H	CH_2CO_2Et	**5g**	4	74	1	73
7	H	4-MeO	H	CH_2CO_2Et	**5h**	24	50	6	51
8	H	H	4-NO_2	CH_2CO_2Et	**5i**	1.5	75	0.5	64/73[d]/78[e]
9	H	H	4-Cl	CH_2CO_2Et	**5j**	4	86	1	83
10	H	H	4-Me	CH_2CO_2Et	**5k**	8	34	3	36
11	H	H	H	Cy	**5l**	1	91	0.5	77/85[d]/88[e]
12	H	H	H	$PhCH_2$	**5m**	2	85	1	80

[a] Reaction condition: **1a**, 3mmol; **2a**, 3mmol; **3a**, 3mmol; **4a**, 3mmol; MeOH 3mL; rt. Reactions were detected by TLC. [b] Reaction condition: **1a**, 3mmol; **2a**, 3mmol; **3a**, 3mmol; **4a**, 3mmol; PEG–H_2O 3mL, rt. [c] Isolated yield. [d] For another 3 hours reaction at 60°C. [e] 0.1M of reactants.

mixture and stirring was continued for 0.5–12 hours. For solids, the products were isolated by filtration and purified by column chromatography with n-hexane/EtOAc (v:v=2:1). For oily products, 2 mL of dichloromethane was added to the reaction mixtures. The aqueous layer was separated, and concentrated under reduced pressure to give the crude products and purified by column chromatography with n-hexane/EtOAc (v:v=2:1) to afford the desired product .

[2-(Benzoyl-phenyl-amino)-2-phenyl-acetylamino]-acetic acid ethyl ester (**5a**): White solid, 74% yield, M.p. 146–148°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.33 (m, 4H, aromatic), 7.29–7.28 (m, 3H, aromatic), 7.20 (t, J = 7.5 Hz, 1H, aromatic), 7.15 (t, J = 7.5 Hz, 2H, aromatic), 7.03 (t, J = 2.5 Hz,, 5H, aromatic), 6.56 (s, 1H, CH), 6.26 (m, 1H, NH), 4.25–4.20 (q, J = 7.0 Hz, 2H, CH_2), 4.15 (d, J = 5.0 Hz, 2H, CH_2 of Et), 1.35 (t, J = 7.0 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C=O), 169.7 (C=O), 169.6 (C=O), 141.3, 135.8, 134.3, 130.1, 129.6, 128.6, 128.5, 127.6 and 127.2 (C aromatic), 66.8 (CH), 61.5 (CH_2 of Et), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: m/z = 417 $[M+1]^+$. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73; O, 15.37. Found: C, 72.12; H, 5.80; N, 6.77; O, 15.33%.

{2-[Benzoyl-(4-nitro-phenyl)-amino]-2-phenyl-acetylamino}-acetic acid ethyl ester (**5b**): Yellow solid, yield 41%, M.p. 150–152°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2H, aromatic), 7.33–7.28 (m, 2H, aromatic), 7.26–7.25 (m, 5H, aromatic), 7.20–7.20 (m, 1H, aromatic), 7.17–7.15 (m, 4H, aromatic), 6.49 (s, 1H, CH), 6.43 (t, J = 5.0 Hz, 1H, NH), 4.25–4.2 (q, J = 7.0 Hz, 2H, CH_2), 4.17–4.10 (q, J = 5 Hz, 2H, CH_2 of Et), 1.35 (t, J = 7.0 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C=O), 169.5 (C=O), 147.0, 146.0, 135.1, 133.5, 131.1, 130.3, 130.3, 129.2, 128.9, 128.6, 128.1, 123.5 and 112.4 (C aromatic), 65.5 (CH), 61.6 (CH_2 of Et), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: m/z = 462 $[M+1]^+$. Anal. Calcd for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11; O, 20.80. Found: C, 65.03; H, 5.00; N, 9.09; O, 20.77%.

{2-[Benzoyl-(4-bromo-phenyl)-amino]-2-phenyl-acetylamino}-acetic acid ethyl ester (**5c**): White solid, 84% yield, M.p. 166–168°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 7H, aromatic), 7.25 (t, J = 7.5 Hz, 1H, aromatic), 7.19–7.14 (m, 4H, aromatic), 6.87 (d, J = 7.5 Hz, 2H, aromatic), 6.43 (t, J = 5.0 Hz, 1H, NH), 6.34 (s, 1H, CH), 4.24–4.20 (q, J = 7.0 Hz, 2H, CH_2), 4.14–4.11 (q, J = 5.0 Hz, 2H, CH_2 of Et), 1.30–1.27 (t, J = 7.0 Hz, 3H, , CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C=O), 169.6 (C=O), 169.6 (C=O), 140.1, 135.6, 133.9, 132.0, 131.6, 130.4, 129.8, 128.9, 128.7, 128.5, 127.8 and 121.2 (C aromatic), 65.8 (CH), 61.5 (CH_2 of Et), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: m/z = 496 $[M+1]^+$. Anal. Calcd for $C_{25}H_{23}BrN_2O_4$: C, 60.62; H, 4.68; N, 5.66; O, 12.92 . Found: C, 60.59; H, 4.65; N, 5.68; O, 12.91%.

[2-(Benzoyl-p-tolyl-amino)-2-phenyl-acetylamino]-acetic acid ethyl ester (**5d**): White solid, 75% yield, M.p. 142-145°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2H, aromatic), 7.29 (t, J = 2.5 Hz, 3H, aromatic), 7.23–7.20 (m, 1H, aromatic), 7.16–7.13 (q, J = 7.5 Hz, 2H, aromatic), 6.89–6.83 (q, J = 8.0 Hz, 4H, aromatic), 6.60 (t, J = 4.5 Hz, 1H, NH), 6.22 (s, 1H, CH), 4.24–4.20 (q, J = 7.0 Hz, 2H, CH_2), 4.14–4.13 (q, J = 2.5 Hz, CH_2 of Et), 2.18 (s, 3H, CH_3), 1.29 (t, J = 7.0 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C=O), 169.8 (C=O), 169.7 (C=O), 138.8, 137.0, 136.0, 134.4, 130.2, 129.7, 129.5, 129.2, 128.6, 128.5, 128.5 and 127.6 (C aromatic), 66.9 (CH), 61.5 (CH_2 of Et), 41.7 (CH_2), 20.9 (CH_3), 14.1 (CH_3 of Et); ESI-MS: m/z = 428 $[M+1]^+$. Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51; O, 14.87. Found: C, 72.52; H, 6.08; N, 6.53; O, 14.88 %.

[2-(Benzoyl-o-tolyl-amino)-2-phenyl-acetylamino]-acetic acid ethyl ester (**5e**): Yellow solid, 72% yield, M.p. 142–144°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.22 (m, 2H, aromatic), 7.20 (t, J = 7.5 Hz, 3H, aromatic), 7.14 (t, J = 7.5 Hz, 2H, aromatic), 7.06–7.04 (m, 3H, aromatic), 7.00–6.99 (m, 2H, aromatic), 6.79 (d, J = 8.5 Hz, 2H, aromatic), 6.51 (t, J = 5.0 Hz, 1H, NH), 6.25 (s, 1H, CH), 4.24–4.20 (q, J = 7.0 Hz, 2H, CH_2), 4.14 (d, J = 5.5 Hz, 2H, CH_2 of Et), 3.78 (s, 3H, CH_3), 1.29 (t, J = 7.5 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C=O), 170.0 (C=O), 169.7 (C=O), 159.7, 141.2, 136.0, 131.7, 130.3, 129.5, 128.6, 128.5, 127.6, 127.2, 126.3 and 113.9 (C aromatic), 65.8 (CH), 61.5 (CH_2 of Et), 55.2 (CH_3), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: m/z = 428 $[M+1]^+$. Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51; O, 14.87. Found: C, 72.52; H, 6.08; N, 6.53; O, 14.88 %.

[2-(Benzoyl-phenyl-amino)-2-(4-nitro-phenyl)-acetylamino]-acetic acid ethyl ester (**5f**): Yellow solid, 40% yield, M.p. 100–102°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 4.0 Hz, 2H, aromatic), 7.55

(d, *J* = 8.5 Hz, 2H, aromatic), 7.35 (d, *J* = 7.5 Hz, 2H, aromatic), 7.28–7.23 (m, 1H, aromatic), 7.17 (t, *J* = 8 Hz, 2H, aromatic), 7.10–7.09 (m, 4H, aromatic), 7.02 (s, 2H, aromatic, NH), 6.41 (s, 1H, CH), 4.26–4.22 (q, *J* = 7.0 Hz, 2H, CH_2), 4,21–4.09 (m, 2H, CH_2 of Et), 1.30 (t, *J* = 7 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (C=O), 169.6 (C=O), 168.9 (C=O), 147.7, 141.5, 140.8, 135.1, 131.1, 129.7, 129.0, 128.6, 127.8 and 123.4 (C aromatic), 65.7 (CH), 61.7 (CH_2 of Et), 41.6 (CH_2), 14.2 (CH_3 of Et); ESI-MS: *m/z* = 462 $[M+1]^+$. Anal. Calcd for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11; O, 20.80. Found: C, 65.00; H, 5.01; N, 9.08; O, 20.76%.

[2-(Benzoyl-phenyl-amino)-2-(4-chloro-phenyl)-acetylamino]-acetic acid ethyl ester (**5g**): Yellow solid, 73% yield, M.p. 156–158°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 5 Hz, 2H, aromatic), 7.25–7.20 (m, 5H, aromatic), 7.14 (t, *J* = 7.5 Hz, 2H, aromatic), 7.08 (t, *J* = 3.5 Hz, 3H, aromatic), 7.01 (t, *J* = 2.5 Hz, 2H, aromatic), 6.71 (t, *J* = 5.0 Hz, 1H, NH), 6.27 (s, 1H, CH), 4.25–4.21 (q, *J* = 7.0 Hz, 2H, CH_2), 4.15–4.13 (q, *J* = 3.0 Hz, 2H, CH_2 of Et), 1.30 (t, *J* = 7.0 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C=O), 169.7 (C=O), 169.5 (C=O), 141.0, 135.6, 134.6, 132.8, 131.7, 130.1, 129.7, 128.7, 128.7, 128.6, 127.7 and 127.5 (C aromatic), 65.6 (CH), 61.6 (CH_2 of Et), 41.6 (CH_2), 14.2 (CH_3 of Et); ESI-MS: *m/z* = 452 $[M+1]^+$. Anal. Calcd for $C_{25}H_{23}ClN_2O_4$: C, 66.59; H, 5.14; N, 6.21; O, 14.19. Found: C, 66.56; H, 5.13; N, 6.20; O, 14.17 %.

[2-(Benzoyl-phenyl-amino)-2-(4-methoxy-phenyl)-acetylamino]-acetic acid ethyl ester (**5h**): Yellow solid, 51% yield, M.p. 127–130°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H, aromatic), 7.22–7.18 (m, 3H, aromatic), 7.14 (t, *J* = 7.5 Hz, 2H, aromatic), 7.05 (t, *J* = 3 Hz, 3H, aromatic), 6.99 (d, *J* = 2.5 Hz, 2H, aromatic), 6.79 (d, *J* = 7.5 Hz, 2H, aromatic), 6.51 (t, *J* = 5.0 Hz, 1H, NH), 6.25 (s, 1H, CH), 4.24–4.20 (q, *J* = 7.0 Hz, 2H, CH_2), 4.14 (d, *J* = 5.5 Hz, 2H, CH_2 of Et), 3.78 (s, 3H, OCH_3), 1.29 (t, *J* = 7.0 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C=O), 170.0 (C=O), 169.7 (C=O), 159.7, 141.2, 136.0, 131.7, 130.3, 129.5, 128.6, 128.5, 127.6, 127.2, 126.3 and 113.9 (C aromatic), 65.8 (CH), 61.5 (CH_2 of Et), 55.2 (OCH_3), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: *m/z* = 444 $[M+1]^+$. Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27; O, 17.92. Found: C, 69.92; H, 5.85; N, 6.29; O, 17.91%.

{2-[(4-Nitro-benzoyl)-phenyl-amino]-2-phenyl-acetylamino}-acetic acid ethyl ester (**5i**): Bronze solid, 64% yield, M.p. 167–180°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H, aromatic), 7.49 (d, *J* = 8.5 Hz, 2H, aromatic), 7.29–7.26 (m ,5H, aromatic), 7.05–6.99 (q, *J* = 6 Hz, 5H, aromatic), 6.33 (t, *J* = 5.0 Hz, 1H, NH), 6.32 (s, 1H, CH), 4.23–4.19 (q, *J* = 7.0 Hz, 2H, CH_2), 4.18–4.13 (m, 2H, CH_2 of Et), 1.29 (t, *J* = 7.5 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5 (C=O), 169.3 (C=O), 169.2 (C=O), 147.8, 142.3, 139.9, 133.5, 130.5, 130.4, 130.1, 129.3, 129.0, 128.8, 128.7, 128.6, 128.5, 128.0, 127.6 and 122.9 (C aromatic), 66.2 (CH), 61.6 (CH_2 of Et), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: *m/z* = 462 $[M+1]^+$. Anal. Calcd for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11; O, 20.80. Found: C, 65.05; H, 5.03; N, 9.09; O, 20.76%.

{2-[(4-Chloro-benzoyl)-phenyl-amino]-2-phenyl-acetylamino}-acetic acid ethyl ester (**5j**): White solid, 83% yield, M.p. 142–145°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 4H, aromatic), 7.28–7.26 (m, 3H, aromatic), 7.14–7.11 (m, 2H, aromatic), 7.08–7.04 (m, 3, aromatic), 7.00 (s, 2H, aromatic), 6.46 (t, *J* = 5.0 Hz, 1H, NH), 6.25 (s, 1H, CH), 4.24–4.2 (q, *J* = 7.5 Hz, 2H, CH_2), 4.14 (d, *J* = 5.5 Hz, 2H, CH_2 of Et), 1.29 (t, *J* = 7.5 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C=O), 169.6 (C=O), 141.0, 135.7, 134.3, 134.1, 130.3, 130.2, 130.1, 128.7, 128.7, 128.6, 128.5, 127.9 and 127.5 (C aromatic), 66.7 (CH), 61.5 (CH_2 of Et), 41.7 (CH_2), 14.1 (CH_3 of Et); ESI-MS: *m/z* = 452 $[M+1]^+$. Anal. Calcd for $C_{25}H_{23}ClN_2O_4$: C, 66.59; H, 5.14; N, 6.21; O, 14.19. Found: C, 66.58; H, 5.11; N, 6.19; O, 14.17 %.

{2-[(4-Methyl-benzoyl)-phenyl-amino]-2-phenyl-acetylamino}-acetic acid ethyl ester (**5k**): Yellow solid, 36% yield, M.p. 128–130°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.33 (q, *J* = 4 Hz, 2H, aromatic), 7.29–7.24 (m, 6H, aromatic), 7.71–76 (m, 3H, aromatic), 7.04–7.02 (m, 2H, aromatic), 6.95 (d, *J* = 8.5 Hz, 2H, aromatic), 6.62 (t, *J* = 8.0 Hz, 1H, NH), 6.26 (s, 1H, CH), 4.24–4.20 (q, *J* = 7.5 Hz, 2H, CH_2), 4.15-4.13 (m, 2H, CH_2 of Et), 2.24 (s,3H, CH_3), 1.29 (t, *J* = 7.0 Hz, 3H, CH_3 of Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C=O), 169.8 (C=O), 169.7 (C=O), 141.7, 139.9, 134.4, 132.8, 130.2, 120.0, 128.8, 128.6, 128.5, 128.3, 127.6 and 127.1 (C aromatic), 67.0 (CH), 61.5 (CH_2 of Et), 41.7 (CH_2), 21.3 (CH_3), 14.1 (CH_3 of Et); ESI-MS: *m/z* = 428 $[M+1]^+$. Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51; O, 14.87. Found: C, 72.51; H, 6.07; N, 6.53; O, 14.85%.

N-(Cyclohexylcarbamoyl-phenyl-methyl)-N-phenyl-benzamide (**5l**): White solid, 77% yield, M.p. 164–167°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9.5 Hz, 2H, aromatic), 7.29 (t, *J* = 3.5 Hz, 2H, aromatic), 7.26 (d, *J* = 2.5 Hz, 3H, aromatic), 7.19 (d, *J* = 7.5 Hz, 1H, aromatic), 7.13 (t, *J* = 7.5 Hz, 2H, aromatic), 7.02 (s, 5H, aromatic), 6.18 (s, 1H, CH), 5.85 (d, *J* = 7.5 Hz, 1H, NH), 3.91 (m, 1H, CH of Cy), 1.99–1.90 (dd, *J* = 1.0 Hz, 2H, CH_2 of Cy), 1.70–1.68 (m, 2H, CH_2 of Cy), 1.65–1.59 (m, 1H, CH_2 of Cy), 1.40–1.35 (m, H, CH_2 of Cy), 1.23–1.11 (m, 3H, CH_2 of Cy); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.37 (C=O), 168.6 (C=O), 141.4, 136.1, 134.9, 130.2, 130.1, 129.4, 128.5, 128.4, 127.6 and 127.1 (C aromatic), 66.9 (CH), 48.8 (CH of Cy), 32.8, 25.5, 24.8, 24.7 (CH_2 of Cy); ESI-MS: *m/z* = 413 $[M+1]^+$. Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79; O, 7.76. Found: C, 78.58; H, 6.82; N, 6.77; O, 7.78%.

N-(Benzylcarbamoyl-phenyl-methyl)-N-phenyl-benzamide (**5m**): White solid, 80% yield, M.p. 172–175°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 7H, aromatic), 7.28–7.22 (m, 5H, aromatic), 7.20 (d, *J* = 7 Hz, 1H, aromatic), 7.14 (t, *J* = 7.5 Hz, 2H, aromatic), 7.10–7.03 (m, 5H, aromatic), 6.34 (s, 1H, NH), 6.21 (s, 1H, CH), 4.61–4.56 (q, *J* = 6.0 Hz, 2H, CH_2), ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C=O), 169.6 (C=O), 141.4, 138.1, 136.0, 134.6, 130.2, 129.5, 128.6, 128.6, 128.6, 128.4, 127.6, 127.4 and 127.2 (C aromatic), 67.0 (CH), 43.8 (CH_2); ESI-MS: *m/z* = 421 $[M+1]^+$. Anal. Calcd for: $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66; O, 7.61. Found: C, 79.96; H, 5.74; N, 6.63; O, 7.58%.

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