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One-pot synthesis of 5-oxopyrrolidine-2-carboxamides via a tandem Ugi 4CC/S_N cyclization starting from Baylis–Hillman bromides

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ABSTRACT

A one-pot base-mediated synthesis of 5-oxopyrrolidine-2-carboxamides was developed. The reaction of Baylis–Hillman bromides **1**, primary amines **2**, isocyanides **3** and arylglyoxals **4** produced the 5-oxopyrrolidine-2-carboxamides **6** in good yields via a tandem Ugi condensation and intramolecular substitution at room temperature in the presence of Cs_2CO_3.

1. Introduction

Multicomponent reactions (MCRs) constitute a superior tool for diversity-oriented and complexity-generating synthesis of various heterocycles, which are particularly well-represented among natural products and pharmaceuticals.[1] The Ugi reaction is one of the two main isocyanide-based multicomponent reactions (I-MCRs) (the Ugi reaction and the Passerini reaction) and is a powerful, atom-economical reaction of isonitrile, amino, aldehyde (or ketone) with carboxylic acid. It generates a significantly more complex α-acylamino-carboxamide adduct that have received increased attention in view of its utility in the synthesis of nitrogen heterocyclic compounds.[2]

The derivatives of heterocycles containing the pyrrolidinone moiety are of great importance because they have wide application in pharmaceutical, chemical and other fields. They proved to show significant antimuscarinic,[3] antiepileptic,[4] anti-AIDS,[5] and antiviral activities.[6] The classic synthetic methodology for the construction of a pyrrolidinone scaffold have been focused primarily on cyclization of the dialkyl itaconate with different primary amines.[7] For example, some chemists utilized the method of combinatorial chemistry following this strategy to prepare various pyrrolidinone derivatives.[8] Kenda et al. also described the synthesis of pyrrolidinone based on a sequential alkylation or reductive amination followed by cyclization.[4] In addition, pyrrolidinones have been prepared by other methods, such as rearrangement of β-lactam,[9] the radical addition–cyclization reaction,[10] cycloaddition reaction,[11] and transition-metal-catalyzed intramolecular allylic alkylation reaction.[12] However, these strategies typically require lengthy reaction steps or are compatible with few functional groups.

The Baylis–Hillman (B–H) reaction has become a powerful synthetic tool for the preparation of densely functionalized molecules through construction of C–C bonds in an operationally simple one-pot procedure.[13] The densely functionalized products, which are usually known as Baylis–Hillman adducts, have been employed recently in further preparations of various heterocyclic compounds, such as 4(3*H*)-pyrimidinones, quinolines, pyrroles, 1,3-thiazin-4-ones, and pyrrolo[1,2-*a*]pyrazines.[14] We envisioned that the Baylis–Hillman acid may be used as one reactant of the Ugi reaction, which might produce various multisubstituted heterocycles in one-pot fashion. Continuing our interest in I-MCR mediated synthesis of heterocycles,[15] herein we report a direct synthesis of 5-oxopyrrolidine-2-carboxamides by Ugi reaction of Baylis–Hillman acid, primary amines, arylglyoxals and isocyanides.

2. Results and discussion

Initially, we selected the Baylis–Hillman bromide **1a**, 4-bromophenylglyoxal **2a**, *n*-propylamine **3a** and *tert*-butylisocyanide **4a** as the reactants (Scheme 1). When the Baylis–Hillman bromide **1a**, 4-bromophenylglyoxal **2a**, *n*-propylamine **3a** and *tert*-butylisocyanide **4a** was stirred in methanol at room temperature for 24 h, the 5-oxopyrrolidine-2-carboxamide derivative **6a** was directly obtained albeit in low yield (34%). The expected Ugi product **5a** might produced but cyclized directly to give 5-oxopyrrolidine-2-carboxamide **6a** under the reaction condition. Further study of the reaction time revealed that nearly the same yields (32–34%) of the product **6a** were obtained as the reactions were carried out for 2–48 h (Table 1, entry 2–5) whereas relative lower yield (12%) was reached when the reaction time was reduced to 1 h (Table 1, entry 1). The detection of reaction mixture also

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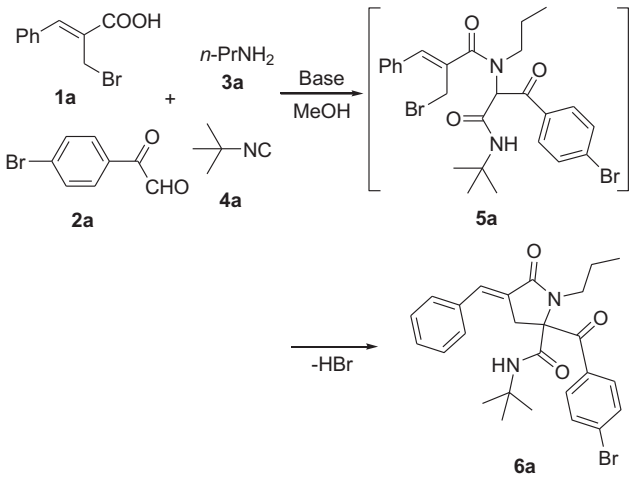


Scheme 1. Preparation of compound **6a**.

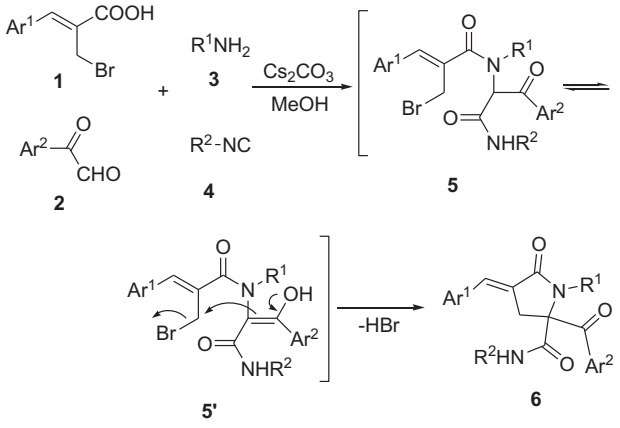
Table 1
Optimization of the reaction conditions about **6a**

Entry	Base	Condition	Yield (%)[a]
1	—	rt/1 h	12
2	—	rt/2 h	32
3	—	rt/12 h	34
4	—	rt/24 h	34
5	—	rt/48 h	33
6	NEt_3	rt/12 h	64
7	K_2CO_3	rt/12 h	71
8	$NaHCO_3$	rt/12 h	75
9	Cs_2CO_3	rt/12 h	83

[a] Isolated yields based on Baylis–Hillman bromide **1a**.

revealed that the pH of the solution decreased from 7 to 4 during the reaction process and reached the minimum in 2 h, after which the reaction took place slowly accompanying side reactions. This evidence implies that the intramolecular substitution reaction of intermediate **5a** occurs even under acidic condition and is pH dependant. So it's understandable that good yields of **6a** were obtained (Table 1, entry 6–9) when a base was added to adjust the pH of the solution to 6 during the reaction process. The best result was reached as Cs_2CO_3 was utilized as a base (Table 1, entry 9) probably due to its good solubility in the solvent. In the 4-bromophenylglyoxal **2a**, there were two carbonyl groups, which might both involve into the reaction. But we didn't isolate the byproduct resulted from the ketone carbonyl group. This is probably due to the higher reactivity of the aldehyde carbonyl group compared with the ketone carbonyl one.

With the optimized condition, various Baylis–Hillman bromides **1**, arylglyoxal **2**, amine **3** and isocyanide **4** were employed for the reaction with Cs_2CO_3 as a base to adjust the pH of the solution to 6 during the reaction process (Scheme 2). All reactions proceeded smoothly to give the corresponding 5-oxopyrrolidine-2-carboxamides **6** (Table 2) in 65–91% yields. As shown in Table 2, the yields of the products were related to the R^1 group of amine **3**. When various aliphatic amines were used, the reaction produced 5-oxopyrrolidine-2-carboxamides **6** in good to high yields (71–91%, Table 2, compounds **6a**–**r**). However, as the aromatic amine was utilized, moderate yields of the products **6s** and **t** were obtained (65–68%, Table 2). The electron-donating ability of the R^1 group might be an important influencing factor for the yields of the products. The formation of the 5-oxopyrrolidine-2-carboxamides **6** can be rationalized in terms of an initial Ugi reaction to give the adduct **5**, which directly undergoes intramolecular nucleophilic substitution to give **6** through the enol form of intermediate **5′** under the acidic condition. Although the Ugi intermediates **5** or **5′** were not isolated from the reaction mixture, some similar Ugi adducts from arylglyoxals **2**, primary amines, isocyanides and carboxylic acid were reported to exist exclusively as the enol forms.[16]



Scheme 2. Preparation of compounds **6**.

Table 2
Preparation of compounds **6**

	Ar^1	Ar^2	R^1	R^2	Yield (%)[a]
6a	Ph	4-BrC_6H_4	*n*-Pr	*t*-Bu	83
6b	Ph	4-ClC_6H_4	$PhCH_2$	*t*-Bu	86
6c	Ph	4-ClC_6H_4	*n*-Pr	*c*-C_6H_{11}	84
6d	Ph	4-ClC_6H_4	*n*-Pr	*t*-Bu	82
6e	Ph	4-ClC_6H_4	$PhCH_2$	*n*-Bu	82
6f	Ph	4-ClC_6H_4	*n*-Pr	*n*-Bu	71
6g	Ph	4-ClC_6H_4	*i*-Pr	*c*-C_6H_{11}	81
6h	Ph	4-ClC_6H_4	*i*-Pr	*t*-Bu	79
6i	Ph	4-ClC_6H_4	*n*-Bu	*t*-Bu	73
6j	Ph	4-ClC_6H_4	Me	*t*-Bu	71
6k	Ph	4-ClC_6H_4	Me	*c*-C_6H_{11}	75
6l	Ph	4-ClC_6H_4	Et	*t*-Bu	73
6m	Ph	4-ClC_6H_4	Et	*c*-C_6H_{11}	75
6n	Ph	4-ClC_6H_4	$PhCH_2$	*c*-C_6H_{11}	89
6o	4-ClC_6H_4	4-BrC_6H_4	*n*-Pr	*t*-Bu	85
6p	Ph	4-BrC_6H_4	$PhCH_2$	*t*-Bu	86
6q	4-ClC_6H_4	4-BrC_6H_4	$PhCH_2$	*t*-Bu	91
6r	4-ClC_6H_4	4-BrC_6H_4	*i*-Pr	*t*-Bu	87
6s	4-ClC_6H_4	4-BrC_6H_4	4-ClC_6H_4	*t*-Bu	68
6t	Ph	4-ClC_6H_4	4-ClC_6H_4	*t*-Bu	65

[a] Isolated yields based on Baylis–Hillman bromide **1**.

The compounds **6a**–**t** was confirmed by their spectrum data. For example, the ^1H NMR spectrum of **6a** shows two doublets at 3.78 and 3.32 ppm due to the CH_2 of the pyrrolidine ring. The signals of CONH are found at 6.15 ppm as singlet. The signals of NCH_2 appear at 3.62–3.57 and 3.19–3.14 ppm as two multiplets. The signals of CH_2 and CH_3 appear at 1.74–1.46, 1.35 and 0.87 ppm as multiplets, singlet and triplets, respectively. The signals attributable to the Ar–Hs and vinyl–H are found at 7.72–7.32 ppm as multiplets and singlet. The ^{13}C NMR spectrum data in **6a** showed the signals of C=O and CON carbon at 196.0, 169.8 and 167.5 ppm. The quaternary carbon of the pyrrolidine ring absorbs at 74.8 ppm. The MS spectrum of **6a** shows molecular ion peak and M^+–CONHBu-*t* at *m*/*z* 496 and 397 with 2% and 21% abundance. Furthermore a single crystal of 5-oxopyrrolidine-2-carboxamide **6c** was obtained from the CH_2Cl_2/ethanol solution of **6c**, and X-ray structure analysis verified the proposed structure (Fig. 1). In the solid state, the five-membered ring of the pyrrolidinone system adopts a planar conformation and the configuration of the product **6c** is *E* form.

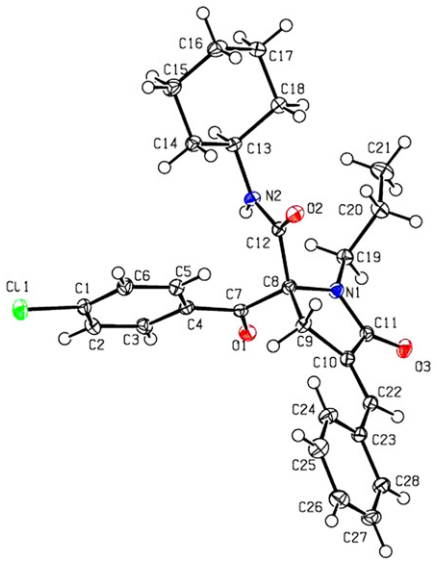


Fig. 1. ORTEP drawing of **6c** with 50% probability thermal ellipsoids (with only one enantiomer shown).

3. Conclusion

We have developed an efficient synthesis of 5-oxopyrrolidine-2-carboxamides via a new one-pot Ugi 4CC/S_N cyclization reaction. Due to the mild reaction condition, good yields and easily accessible starting material, we think that this new synthetic approach discussed here has the potential in synthesis of various 5-oxopyrrolidine-2-carboxamides, which are of considerable interest as potential biological active compounds or pharmaceuticals.

4. Experimental

4.1. General

Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 600 spectrometer and resonances relative to TMS. Elementary analyzes were taken on a Vario EL III elementary analysis instrument. The X-ray diffraction data were collected on a *Bruker SMART AXS CCD* diffractometer, MoKα, 2θ=1.86–27.50°.

4.2. One-pot synthesis of 5-oxopyrrolidine-2-carboxamide 6

*4.2.1. (E)-4-Benzylidene-2-(4-bromobenzoyl)-N-(tert-butyl)-5-oxo-1-propylpyrrolidine-2-carboxamide (**6a**).* A mixture of the 2-(bromomethyl)-3-phenyl-2-propenoic acid[17] **1a** (Ar^1=Ph, 0.24 g, 1 mmol) and *n*-propylamine **3a** (R^1=*n*-Pr, 0.06 g, 1 mmol) was stirred in methanol (5 mL) at room temperature for 10 min, then *tert*-butylisocyanide **3a** (R^2=*t*-Bu, 0.08 g, 1 mmol) and the 4-bromophenylglyoxal **4a** (Ar^2=4-BrC_6H_4, 0.21 g, 1 mmol) were added consecutively to the solution. The mixture was stirred at room temperature and the pH value of the solution was adjusted to 6 using Cs_2CO_3 during the reaction process. After stirring for 12 h, the mixture was chilled and the resulted solid were then filtered, recrystallized from ether to give product **6a** as white solid (0.41 g, 83%). Mp: 196–197 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.72 (d, *J*=7.8 Hz, 2H, Ar–H), 7.61 (d, *J*=7.8 Hz, 2H, Ar–H), 7.43 (s, 1H, =CH), 7.41–7.32 (m, 5H, Ar–H), 6.15 (s, 1H, NH), 3.78 (d, *J*=18.0 Hz, 1H, CH_2^a), 3.62–3.57 (m, 1H, NCH_2^a), 3.32 (d, *J*=18.0 Hz, 1H, CH_2^b), 3.19–3.14 (m, 1H, NCH_2^b), 1.74–1.46 (m, 2H, CH_2), 1.35 (s, 9H, $3CH_3$), 0.87 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 196.0, 169.8, 167.5, 134.9, 132.5, 132.1, 132.0, 131.9, 130.6, 129.7, 129.6, 129.1, 128.8, 128.7, 126.5, 74.8, 52.6, 46.0, 35.5, 28.3, 21.3, 11.7. MS *m*/*z* (%): 496 (M^+, 2), 397 (21), 313 (89), 214 (43), 185 (100), 115 (72). Anal. Calcd for $C_{26}H_{29}BrN_2O_3$: C, 62.78; H, 5.88; N, 5.63. Found: C, 62.94; H, 6.03; N, 5.44.

*4.2.2. (E)-1-Benzyl-4-benzylidene-N-(tert-butyl)-2-(4-chlorobenzoyl)-5-oxopyrrolidine-2-carboxamide (**6b**).* Operation as above with benzylamine (0.11 g, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6b** (0.43 g, 86%) was also isolated as white solid. Mp: 194–195 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.73 (d, *J*=8.4 Hz, 2H, Ar–H), 7.53 (s, 1H, =CH), 7.44 (d, *J*=7.2 Hz, 2H, Ar–H), 7.40–7.14 (m, 10H, Ar–H), 6.01 (s, 1H, NH), 5.12 (d, *J*=16.2 Hz, 1H, NCH_2^a), 4.49 (d, *J*=16.2 Hz, 1H, NCH_2^b), 3.95 (d, *J*=18.0 Hz, 1H, CH_2^a), 3.41 (d, *J*=18.0 Hz, 1H, CH_2^b), 0.99 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 194.2, 170.3, 165.8, 139.9, 136.6, 134.5, 132.4, 132.1, 131.4, 130.5, 130.4, 129.7, 129.4, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 126.8, 126.7, 126.6, 126.0, 75.0, 52.3, 46.7, 34.8, 27.5. MS *m*/*z* (%): 500 (M^+, 2), 400 (24), 361 (37), 262 (18), 139 (35), 91 (100). Anal. Calcd for $C_{30}H_{29}ClN_2O_3$: C, 71.92; H, 5.83; N, 5.59. Found: C, 71.91; H, 5.97; N, 5.46.

*4.2.3. (E)-4-Benzylidene-2-(4-chlorobenzoyl)-N-cyclohexyl-1-propyl-5-oxopyrrolidine-2-carboxamide (**6c**).* Operation as above with cyclohexylisocyanide (0.11 g, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6c** (0.40 g, 84%) was also isolated as white solid. Mp: 205–206 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.80 (d, *J*=7.8 Hz, 2H, Ar–H), 7.41 (d, *J*=8.4 Hz, 2H, Ar–H), 7.34–7.28 (m, 6H, Ar–H and =CH), 6.64 (d, *J*=7.2 Hz, 1H, NH), 3.88–3.85 (m, 2H, NCH and CH_2^a), 3.63–3.60 (m, 1H, NCH_2^a), 3.33 (d, *J*=17.2 Hz, 1H, CH_2^b), 3.26–3.22 (m, 1H, NCH_2^b), 1.92–1.11 (m, 12H, $6CH_2$), 0.85 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 194.9, 169.6, 167.4, 140.1, 134.7, 131.8, 131.4, 130.6, 130.5, 129.6, 129.4, 129.0, 128.8, 128.5, 126.5, 74.5, 49.5, 45.7, 35.2, 32.1, 24.8, 21.3, 11.6, 11.2. MS *m*/*z* (%): 478 (M^+, 2), 353 (17), 339 (100), 214 (22), 139 (34). Anal. Calcd for $C_{28}H_{31}ClN_2O_3$: C, 70.21; H, 6.52; N, 5.85. Found: C, 70.34; H, 6.58; N, 5.79.

*4.2.4. (E)-4-Benzylidene-N-(tert-butyl)-2-(4-chlorobenzoyl)-1-propyl-5-oxopyrrolidine-2-carboxamide (**6d**).* Operation as above with 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6d** (0.37 g, 82%) was also isolated as white solid. Mp: 186–187 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.81 (d, *J*=7.8 Hz, 2H, Ar–H), 7.43 (d, *J*=7.8 Hz, 2H, Ar–H), 7.37–7.30 (m, 6H, Ar–H and =CH), 6.32 (s, 1H, NH), 3.83 (d, *J*=18.0 Hz, 1H, CH_2^a), 3.65–3.60 (m, 1H, NCH_2^a), 3.32 (d, *J*=18.0 Hz, 1H, CH_2^b), 3.22–3.17 (m, 1H, NCH_2^b), 1.74–1.52 (m, 2H, CH_2), 1.36 (s, 9H, $3CH_3$), 0.87 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.4, 169.6, 167.4, 140.2, 134.8, 131.9, 131.6, 130.5, 129.5, 128.9, 128.8, 128.6, 126.5, 74.8, 52.5, 45.9, 35.4, 28.2, 21.2, 11.4. MS *m*/*z* (%): 452 (M^+, 2), 352 (74), 313 (100), 139 (79). Anal. Calcd for $C_{26}H_{29}ClN_2O_3$: C, 68.94; H, 6.45; N, 6.18. Found: C, 68.67; H, 6.60; N, 6.33.

*4.2.5. (E)-1-Benzyl-4-benzylidene-N-butyl-2-(4-chlorobenzoyl)-5-oxopyrrolidine-2-carboxamide (**6e**).* Operation as above with benzylamine (0.11 g, 1 mmol), 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol) and *n*-butylisocyanide (0.08 g, 1 mmol), compound **6e** (0.41 g, 82%) was also isolated as white solid. Mp: 135–136 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.71 (d, *J*=7.8 Hz, 2H, Ar–H), 7.41–7.10 (m, 13H, Ar–H and =CH), 6.74 (s, 1H, NH), 5.14 (d, *J*=16.2 Hz, 1H, NCH_2^a), 4.55 (d, *J*=16.2 Hz, 1H, NCH_2^b), 4.05 (d, *J*=18.0 Hz, 1H, CH_2^a), 3.34 (d, *J*=18.0 Hz, 1H, CH_2^b), 2.81–2.69 (m, 2H, NCH_2), 1.11–0.85 (m, 4H, CH_2), 0.74 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 194.4, 170.3, 167.4, 140.1, 136.4, 134.7, 132.7, 131.6, 130.5, 129.7, 129.0, 128.8, 128.7, 128.2, 127.3, 127.0, 126.0, 74.1, 46.7, 40.0, 35.1, 30.4, 19.9, 13.5. MS *m*/*z* (%): 500 (M^+, 3), 400 (8), 361

(52), 262 (51), 91 (100). Anal. Calcd for $C_{30}H_{29}ClN_2O_3$: C, 71.92; H, 5.83; N, 5.59. Found: C, 71.64; H, 5.99; N, 5.56.

*4.2.6. (E)-4-Benzylidene-N-butyl-2-(4-chlorobenzoyl)-1-propyl-5-oxopyrrolidine-2-carboxamide (**6f**).* Operation as above with 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol) and *n*-butylisocyanide (0.08 g, 1 mmol), compound **6f** (0.32 g, 71%) was also isolated as white solid. Mp: 199–200 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.79 (d, J=7.8 Hz, 2H, Ar–H), 7.41 (d, J=7.8 Hz, 2H, Ar–H), 7.33–7.30 (m, 6H, Ar–H and =CH), 7.11 (s, 1H, NH), 3.84 (d, J=18.0 Hz, 1H, CH_2^a), 3.57–3.53 (m, 1H, NCH_2^a), 3.37–3.27 (m, 4H, CH_2^b, NCH_2^b and NCH_2), 1.59–1.24 (m, 6H, $3CH_2$), 0.90 (t, J=7.2 Hz, 3H, CH_3), 0.82 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.1, 169.8, 168.7, 140.1, 134.7, 132.0, 131.8, 131.7, 130.5, 129.6, 129.0, 128.7, 126.5, 74.3, 45.9, 40.2, 35.5, 31.0, 21.1, 20.1, 13.6, 11.5. MS m/z (%): 452 (M^+, 2), 352 (17), 313 (100), 214 (27), 139 (39). Anal. Calcd for $C_{26}H_{29}ClN_2O_3$: C, 68.94; H, 6.45; N, 6.18. Found: C, 68.89; H, 6.42; N, 5.97.

*4.2.7. (E)-4-Benzylidene-2-(4-chlorobenzoyl)-N-cyclohexyl-1-isopropyl-5-oxopyrrolidine-2-carboxamide (**6g**).* Operation as above with *i*-propylamine (0.06 g, 1 mmol), 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol) and cyclohexylisocyanide (0.11 g, 1 mmol), compound **6g** (0.39 g, 81%) was also isolated as white solid. Mp: 166–167 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.80 (d, J=8.4 Hz, 2H, Ar–H), 7.43 (d, J=8.4 Hz, 2H, Ar–H), 7.36–7.29 (m, 6H, Ar–H and =CH), 6.54 (s, 1H, NH), 3.81–3.78 (m, 2H, CH_2^a and NCH), 3.72–3.68 (m, 1H, NCH), 3.21 (d, J=18.0 Hz, 1H, CH_2^b), 1.93–1.65 (m, 4H, $2CH_2$), 1.60 (d, J=6.6 Hz, 3H, CH_3), 1.37 (d, J=6.6 Hz, 3H, CH_3), 1.33–1.09 (m, 6H, $3CH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.2, 169.0, 167.7, 140.1, 134.8, 132.0, 130.9, 130.4, 129.4, 128.9, 128.7, 128.6, 127.6, 74.7, 49.1, 35.6, 32.4, 32.0, 25.1, 24.6, 19.6. MS m/z (%): 478 (M^+, 4), 352 (32), 339 (100), 297 (32), 172 (38), 139 (61). Anal. Calcd for $C_{28}H_{31}ClN_2O_3$: C, 70.21; H, 6.52; N, 5.85. Found: C, 69.98; H, 6.67; N, 5.71.

*4.2.8. (E)-4-Benzylidene-N-(tert-butyl)-2-(4-chlorobenzoyl)-1-isopropyl-5-oxopyrrolidine-2-carboxamide (**6h**).* Operation as above with *iso*-propylamine (0.06 g, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6h** (0.36 g, 79%) was also isolated as white solid. Mp: 121–122 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.81 (d, J=8.4 Hz, 2H, Ar–H), 7.45 (d, J=8.4 Hz, 2H, Ar–H), 7.40–7.32 (m, 6H, Ar–H and =CH), 6.29 (s, 1H, NH), 3.72 (d, J=18.0 Hz, 1H, CH_2^a), 3.68–3.66 (m, 1H, NCH), 3.25 (d, J=18.0 Hz, 1H, CH_2^b), 1.59 (d, J=6.6 Hz, 3H, CH_3), 1.41 (d, J=6.6 Hz, 3H, CH_3), 1.35 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.7, 169.3, 167.8, 140.2, 134.8, 132.1, 131.2, 130.5, 129.6, 129.0, 128.8, 128.7, 127.5, 75.1, 52.4, 49.1, 35.9, 28.3, 19.7. MS m/z (%): 452 (M^+, 6), 352 (50), 313 (100), 172 (42), 139 (91). Anal. Calcd for $C_{26}H_{29}ClN_2O_3$: C, 68.94; H, 6.45; N, 6.18. Found: C, 68.79; H, 6.61; N, 6.35.

*4.2.9. (E)-4-Benzylidene-N-(tert-butyl)-1-butyl-2-(4-chlorobenzoyl)-5-oxopyrrolidine-2-carboxamide (**6i**).* Operation as above with butylamine (0.07 g, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6i** (0.34 g, 73%) was also isolated as white solid. Mp: 174–175 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.82 (d, J=8.4 Hz, 2H, Ar–H), 7.44–7.30 (m, 8H, Ar–H and =CH), 6.49 (br, 1H, NH), 3.87 (d, J=18.0 Hz, 1H, CH_2^a), 3.72–3.67 (m, 1H, NCH_2^a), 3.32 (d, J=18.0 Hz, 1H, CH_2^b), 3.28–3.23 (m, 1H, NCH_2^b), 1.70–1.47 (m, 2H, CH_2), 1.38 (s, 9H, $3CH_3$), 1.30–1.22 (m, 2H, CH_2), 0.88 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.2, 169.5, 167.4, 140.1, 134.7, 131.8, 131.4, 130.5, 129.6, 129.0, 128.7, 128.5, 126.5, 74.8, 52.5, 44.1, 38.8, 35.3, 28.1, 20.4, 13.8. MS m/z (%): 466 (M^+, 2), 366 (32), 327 (60), 228 (26), 139 (100). Anal. Calcd for $C_{27}H_{31}ClN_2O_3$: C, 69.44; H, 6.69; N, 6.00. Found: C, 69.67; H, 6.84; N, 5.75.

*4.2.10. (E)-4-Benzylidene-N-(tert-butyl)-2-(4-chlorobenzoyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (**6j**).* Operation as above with methylamine (0.08 g, 40%, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6j** (0.30 g, 71%) was also isolated as white solid. Mp: 237–238 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.81 (d, J=8.4 Hz, 2H, Ar–H), 7.45 (d, J=8.4 Hz, 2H, Ar–H), 7.43–7.34 (m, 6H, Ar–H and =CH), 6.08 (s, 1H, NH), 3.77 (d, J=18.0 Hz, 1H, CH_2^a), 3.34 (d, J=18.0 Hz, 1H, CH_2^b), 3.05 (s, 3H, CH_3), 1.36 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.6, 169.6, 167.0, 140.3, 134.8, 132.3, 130.5, 129.8, 129.6, 129.1, 129.0, 128.9, 126.2, 74.9, 52.6, 35.3, 29.1, 28.4. MS m/z (%): 424 (M^+, 2), 325 (38), 285 (71), 186 (50), 139 (100). Anal. Calcd for $C_{24}H_{25}ClN_2O_3$: C, 67.84; H, 5.93; N, 6.59. Found: C, 67.56; H, 6.07; N, 6.54.

*4.2.11. (E)-4-Benzylidene-2-(4-chlorobenzoyl)-N-cyclohexyl-1-methyl-5-oxopyrrolidine-2-carboxamide (**6k**).* Operation as above with methylamine (0.08 g, 40%, 1 mmol), cyclohexylisocyanide (0.11 g, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6k** (0.34 g, 75%) was also isolated as white solid. Mp: 246–248 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.81 (d, J=6.0 Hz, 2H, Ar–H), 7.43 (d, J=6.6 Hz, 2H, Ar–H), 7.35–7.27 (m, 6H, Ar–H and =CH), 6.77 (s, 1H, NH), 3.88–3.84 (m, 1H, NCH), 3.75 (d, J=16.8 Hz, 1H, CH_2^a), 3.42 (d, J=16.2 Hz, 1H, CH_2^b), 3.04 (s, 3H, CH_3), 1.96–1.18 (m, 10H, $5CH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.3, 169.7, 167.3, 140.1, 134.5, 132.2, 131.9, 130.6, 129.5, 129.1, 128.8, 128.6, 126.1, 74.3, 49.3, 35.4, 32.9, 29.2, 24.8, 21.7. MS m/z (%): 450 (M^+, 2), 325 (24), 311 (100), 186 (84), 139 (93). Anal. Calcd for $C_{26}H_{27}ClN_2O_3$: C, 69.25; H, 6.03; N, 6.21. Found: C, 69.03; H, 6.20; N, 5.98.

*4.2.12. (E)-4-Benzylidene-N-(tert-butyl)-2-(4-chlorobenzoyl)-1-ethyl-5-oxopyrrolidine-2-carboxamide (**6l**).* Operation as above with ethylamine (0.11 g, 40%, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6l** (0.32 g, 73%) was also isolated as white solid. Mp: 183–184 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.81 (d, J=8.4 Hz, 2H, Ar–H), 7.43 (d, J=8.4 Hz, 2H, Ar–H), 7.37–7.30 (m, 6H, Ar–H and =CH), 6.43 (br, 1H, NH), 3.81 (d, J=18.0 Hz, 1H, CH_2^a), 3.74–3.71 (m, 1H, NCH_2^a), 3.40–3.37 (m, 1H, NCH_2^b), 3.32 (d, J=18.0 Hz, 1H, CH_2^b), 1.38 (s, 9H, $3CH_3$), 1.22 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.4, 169.6, 167.6, 140.1, 134.7, 131.9, 131.5, 130.5, 129.7, 129.4, 129.1, 129.0, 128.8, 128.5, 126.5, 74.82, 52.49, 38.91, 35.48, 28.25, 13.33. MS m/z (%): 438 (M^+, 1), 339 (41), 299 (74), 200 (43), 139 (100). Anal. Calcd for $C_{25}H_{27}ClN_2O_3$: C, 68.41; H, 6.20; N, 6.38. Found: C, 68.23; H, 6.35; N, 6.34.

*4.2.13. (E)-4-Benzylidene-2-(4-chlorobenzoyl)-N-cyclohexyl-1-ethyl-5-oxopyrrolidine-2-carboxamide (**6m**).* Operation as above with ethylamine (0.11 g, 40%, 1 mmol), cyclohexylisocyanide (0.11 g, 1 mmol) and 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol), compound **6m** (0.35 g, 75%) was also isolated as white solid. Mp: 183–184 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.80 (d, J=7.8 Hz, 2H, Ar–H), 7.41 (d, J=8.4 Hz, 2H, Ar–H), 7.33–7.29 (m, 6H, Ar–H and =CH), 6.93 (br, 1H, NH), 3.90–3.72 (m, 3H, CH, CH_2^a and NCH_2^a), 3.45–3.41 (m, 1H, NCH_2^b), 3.31 (d, J=18.0 Hz, 1H, CH_2^b), 1.95–1.11 (m, 13H, $5CH_2$ and CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 194.9, 169.5, 167.6, 140.0, 134.7, 131.9, 131.4, 130.5, 129.6, 129.4, 128.9, 128.8, 128.7, 128.5, 126.6, 74.4, 60.3, 49.6, 38.9, 35.2, 32.1, 24.7, 13.3. MS m/z (%): 464 (M^+, 2), 339 (22), 325 (100), 200 (58), 139 (94). Anal. Calcd for $C_{27}H_{29}ClN_2O_3$: C, 69.74; H, 6.29; N, 6.02. Found: C, 69.52; H, 6.46; N, 5.76.

*4.2.14. (E)-1-Benzyl-4-benzylidene-2-(4-chlorobenzoyl)-N-cyclohexyl-5-oxopyrrolidine-2-carboxamide (**6n**).* Operation as above with benzylamine (0.11 g, 1 mmol), 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol) and cyclohexylisocyanide (0.11 g, 1 mmol), compound **6n** (0.47 g, 89%) was also isolated as white solid. Mp: 125–126 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.69 (d, J=8.4 Hz, 2H, Ar–H), 7.54 (s, 1H, =CH), 7.43 (d, J=7.8 Hz, 2H, Ar–H),

7.40–7.34 (m, 10H, Ar–H), 6.22 (s, 1H, NH), 5.02 (d, J=15.6 Hz, 1H, NCH_2^a), 4.51 (d, J=15.6 Hz, 1H, NCH_2^b), 3.84 (d, J=18.6 Hz, 1H, CH_2^a), 3.50–3.40 (m, 2H, NCH_2^b and CH_2^b), 1.53–0.78 (m, 10H, $5CH_2$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.0, 170.4, 166.9, 140.1, 136.4, 134.7, 132.8, 131.9, 130.5, 129.7, 128.9, 128.7, 128.4, 128.2, 127.8, 127.6, 125.9, 74.0, 49.3, 35.6, 32.0, 31.7, 25.2, 24.6. MS m/z (%): 526 (M^+, 4), 400 (12), 387 (39), 262 (25), 91 (100). Anal. Calcd for $C_{32}H_{31}ClN_2O_3$: C, 72.92; H, 5.93; N, 5.32. Found: C, 72.83; H, 6.07; N, 5.19.

*4.2.15. (E)-2-(4-Bromobenzoyl)-N-(tert-butyl)-4-(4-chlorobenzylidene) -1-propyl-5-oxo-pyrrolidine-2-carboxamide (**6o**).* Operation as above with 2-(bromomethyl)-3-(4-chlorophenyl)-2-propenoic acid **1b** (Ar^1=4-ClC_6H_4, 0.27 g, 1 mmol), compound **6o** (0.45 g, 85%) was also isolated as white solid. Mp: 201–202 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.72 (d, J=8.4 Hz, 2H, Ar–H), 7.61 (d, J=8.4 Hz, 2H, Ar–H), 7.38–7.33 (m, 5H, Ar–H and =CH), 6.11 (s, 1H, NH), 3.76 (d, J=18.0 Hz, 1H, CH_2^a), 3.61–3.57 (m, 1H, NCH_2^a), 3.26 (d, J=16.2 Hz, 1H, CH_2^b), 3.17–3.12 (m, 1H, NCH_2^b), 1.74–1.49 (m, 2H, CH_2), 1.35 (s, 9H, $3CH_3$), 0.87 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.7, 169.4, 167.2, 134.7, 133.2, 132.3, 131.9, 130.5, 130.5, 129.1, 128.9, 128.8, 127.1, 74.7, 52.5, 45.9, 35.2, 28.2, 21.2, 11.6. MS m/z (%): 530 (M^+, 4), 430 (25), 347 (51), 248 (52), 183 (100). Anal. Calcd for $C_{26}H_{28}BrClN_2O_3$: C, 58.71; H, 5.31; N, 5.27. Found: C, 58.42; H, 5.48; N, 5.05.

*4.2.16. (E)-1-Benzyl-4-benzylidene-2-(4-bromobenzoyl)-N-(tert-butyl)-5-oxopyrrolidine-2-carboxamide (**6p**).* Operation as above with benzylamine (0.11 g, 1 mmol), compound **6p** (0.47 g, 86%) was also isolated as white solid. Mp: 183–184 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.65 (d, J=8.4 Hz, 2H, Ar–H), 7.52 (d, J=9.0 Hz, 2H, Ar–H), 7.44–7.14 (m, 11H, Ar–H and =CH), 6.06 (s, 1H, NH), 5.11 (d, J=16.2 Hz, 1H, NCH_2^a), 4.51 (d, J=16.2 Hz, 1H, NCH_2^b), 3.96 (d, J=18.0 Hz, 1H, CH_2^a), 3.41 (d, J=18.0 Hz, 1H, CH_2^b), 0.99 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.5, 170.6, 166.5, 136.6, 134.8, 132.9, 132.3, 131.9, 131.8, 130.5, 129.7, 129.0, 128.7, 128.6, 128.4, 127.5, 127.3, 125.9, 74.6, 52.3, 41.0, 35.4, 27.7. MS m/z (%): 544 (M^+, 4), 448 (3), 361 (11), 183 (17), 91 (100). Anal. Calcd for $C_{30}H_{29}BrN_2O_3$: C, 66.06; H, 5.36; N, 5.14. Found: C, 66.18; H, 5.62; N, 4.93.

*4.2.17. (E)-1-Benzyl-2-(4-bromobenzoyl)-N-(tert-butyl)-4-(4-chlorobenzylidene)-5-oxopyrrolidine-2-carboxamide (**6q**).* Operation as above with 2-(bromomethyl)-3-(4-chlorophenyl)-2-propenoic acid **1b** (Ar^1=4-ClC_6H_4, 0.27 g, 1 mmol) and benzylamine (0.11 g, 1 mmol), compound **6q** (0.53 g, 91%) was also isolated as white solid. Mp: 183–184 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.65 (d, J=8.4 Hz, 2H, Ar–H), 7.54 (d, J=8.4 Hz, 2H, Ar–H), 7.45 (s, 1H, =CH), 7.36–7.12 (m, 9H, Ar–H), 6.03 (s, 1H, NH), 5.13 (d, J=16.2 Hz, 1H, NCH_2^a), 4.54 (d, J=16.8 Hz, 1H, NCH_2^b), 3.96 (d, J=18.0 Hz, 1H, CH_2^a), 3.34 (d, J=18.0 Hz, 1H, CH_2^b), 0.98 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.4, 170.4, 166.2, 136.5, 135.0, 133.3, 132.2, 131.9, 131.4, 131.0, 130.6, 129.2, 129.0, 128.5, 127.4, 127.2, 126.5, 74.6, 52.5, 47.2, 35.2, 27.6. MS m/z (%): 578 (M^+, 1), 480 (2), 395 (4), 183 (15), 91 (100). Anal. Calcd for $C_{30}H_{28}BrClN_2O_3$: C, 62.13; H, 4.87; N, 4.83. Found: C, 62.35; H, 4.71; N, 4.57.

*4.2.18. (E)-2-(4-Bromobenzoyl)-N-(tert-butyl)-4-(4-chlorobenzylidene)-1-isopropyl-5-oxopyrrolidine-2-carboxamide (**6r**).* Operation as above with 2-(bromomethyl)-3-(4-chlorophenyl)-2-propenoic acid **1b** (Ar^1=4-ClC_6H_4, 0.27 g, 1 mmol) and *iso*-propylamine (0.06 g, 1 mmol), compound **6r** (0.46 g, 87%) was also isolated as white solid. Mp: 135–136 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.73 (d, J=8.4 Hz, 2H, Ar–H), 7.63 (d, J=8.4 Hz, 2H, Ar–H), 7.35–7.29 (m, 5H, Ar–H and =CH), 6.26 (s, 1H, NH), 3.71–3.65 (m, 2H, CH_2^a and NCH), 3.20 (d, J=18 Hz, 1H, CH_2^b), 1.58 (d, J=6.6 Hz, 3H, CH_3), 1.40 (d, J=6.6 Hz, 3H, CH_3), 1.35 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.9, 168.9, 167.6, 134.6, 133.4, 132.4, 132.1, 131.9, 130.7, 129.6, 129.1, 128.9, 128.2, 75.1, 52.5, 49.4, 35.5, 28.5, 19.8. MS m/z (%): 530 (M^+, 2), 430 (15), 347 (50), 206 (47), 183 (100). Anal. Calcd for $C_{26}H_{28}BrClN_2O_3$: C, 58.71; H, 5.31; N, 5.27. Found: C, 58.65; H, 5.54; N, 5.47.

*4.2.19. (E)-2-(4-Bromobenzoyl)-N-(tert-butyl)-4-(4-chlorobenzylidene)-1-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxamide (**6s**).* Operation as above with 4-chlorophenylamine (0.13 g, 1 mmol) and 2-(bromomethyl)-3-(4-chlorophenyl)-2-propenoic acid **1b** (Ar^1=4-ClC_6H_4, 0.27 g, 1 mmol), compound **6s** (0.41 g, 68%) was also isolated as white solid. Mp: 247–248 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.70 (d, J=8.4 Hz, 2H, Ar–H), 7.55 (d, J=8.4 Hz, 2H, Ar–H), 7.53 (s, 1H, =CH), 7.37–7.31 (m, 8H, Ar–H), 6.18 (s, 1H, NH), 4.05 (d, J=17.4 Hz, 1H, CH_2^a), 3.35 (d, J=18.0 Hz, 1H, CH_2^b), 1.16 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 196.7, 169.3, 165.5, 135.7, 135.2, 133.2, 133.1, 132.1, 132.0, 131.0, 130.9, 130.4, 13.6, 129.3, 129.1, 129.0, 126.3, 75.6, 52.4, 28.1. MS m/z (%): 600 (M^+, 2), 500 (16), 415 (27), 185 (100), 57 (40). Anal. Calcd for $C_{29}H_{25}BrCl_2N_2O_3$: C, 58.02; H, 4.20; N, 4.67. Found: C, 58.17; H, 4.39; N, 4.43.

*4.2.20. (E)-4-Benzylidene-N-(tert-butyl)-2-(4-chlorobenzoyl)-1-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxamide (**6t**).* Operation as above with 4-chlorophenylglyoxal **4b** (Ar^2=4-ClC_6H_4, 0.17 g, 1 mmol) and 4-chlorophenylamine (0.13 g, 1 mmol), compound **6t** (0.34 g, 65%) was also isolated as white solid. Mp: 264–265 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, J=9.0 Hz, 2H, Ar–H), 7.60 (s, 1H, =CH), 7.46 (d, J=7.2 Hz, 2H, Ar–H), 7.41–7.30 (m, 9H, Ar–H), 6.26 (s, 1H, NH), 4.06 (d, J=17.4 Hz, 1H, CH_2^a), 3.41 (d, J=18.0 Hz, 1H, CH_2^b), 1.17 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 196.8, 169.5, 165.8, 140.6, 135.9, 134.7, 134.0, 133.0, 131.8, 130.4, 129.8, 129.1, 128.8, 127.9, 125.8, 75.6, 52.3, 35.8, 27.9. MS m/z (%): 520 (M^+, 3), 420 (52), 381 (100), 282 (59), 139 (98), 57 (14). Anal. Calcd for $C_{29}H_{26}Cl_2N_2O_3$: C, 66.80; H, 5.03; N, 5.37. Found: C, 66.83; H, 5.21; N, 5.21.

5. Crystallographic material

Compound **6c**: formula $C_{28}H_{31}ClN_2O_3$, colourless crystal. The crystal is of triclinic, space group P21/c with a=10.5450(11) Å, b=12.3170(12) Å, c=20.5162(17) Å, β=116.566(4)°, V=2383.4(4) Å^3, Z=4, D_c=1.335 g/cm^3, $F(000)$=1016, μ=0.194 mm^{-1}, R=0.0395 and wR=0.1184 for 6880 observed reflections with $I>2\sigma(I_0)$. Crystallographic data for **6c** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 917576. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.058. These data include MOL files and InChiKeys of the most important compounds described in this article.

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