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Regio- and chemo-selective cyclization of allenic-Ugi products for the synthesis of 3-pyrroline skeletons†‡

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A highly efficient and stable novel class of allenic-Ugi products through a Crabbé homologation reaction is successfully demonstrated. Then, a regio- and chemo-selective cyclization of allenic-Ugi derivatives in a 5-*exo*-dig fashion to access 3-pyrroline skeletons is developed. Also, computational studies were performed and explained to provide insights into the reaction mechanism. This approach displays high bond-forming efficiency and atom economy with high yields.

Introduction

Over the past few years, allenes have emerged as powerful and versatile building blocks in organic synthesis. Allene moieties have been identified in several natural products, molecular materials and bioactive compounds.[1] Synthesis of compounds containing allene moieties and their corresponding cyclization reactions are useful approaches for the synthesis of extended heterocyclic skeletons.[2] Thus, numerous synthetic protocols have been reported for the preparation of allenes from readily available organic compounds.[3] One method is the allenylation of terminal alkynes (ATA) *via* homologation which was originally reported by Crabbé and coworkers.[4] This framework was applied for a broad spectrum of transformations, such as cyclization of nitrogen-containing heterocycles in particular pyrroline structures. 3-Pyrrolines are a privileged class of nitrogenous cores, existing as a subunit in many natural products and bioactive molecules. Scaffolds containing 3-pyrroline moieties exhibit various biological activities such as anti-bacterial,[5] antioxidant,[6] anti-inflammatory,[7] anti-tumor,[8] and anti-microbial[9] effects (Fig. 1).

In recent years, a wide range of synthetic approaches have been developed for the synthesis of pyrroline backbones using different catalytic systems.[10,11] *N*-Carbamoyl allenes were used as starting materials and their cyclization was done using silver ions to get 3-pyrrolines.[10a] Tanaka *et al.* reported the cyclization of unactivated allenes with potassium carbonate under reflux conditions to access 3-pyrrolines.[10d] Recently, [3 + 2] annulation of allenoates with azomethine ylides (Scheme 1c) has been reported by Zhou *et al.* as an efficient approach for the synthesis of 3-pyrrolines.[11a]

Due to the importance of allenes in cyclization reactions, designing suitable reactions for the synthesis of functionalized heterocyclic backbones is an interesting subject in organic synthesis. In this regard, using generation of allenes in multicomponent reactions such as the Ugi reaction shows high potential for the synthesis of multifunctional compounds. Also, post-transformation reactions represent the most powerful methodology for the generation of complex molecules.[12] Since the presence of an active functional compound plays an essential role in cyclization reactions, formation of an allene moiety in the structure of the molecule could enhance its activity for the cyclization reaction. Recently as part of our ongoing interest in designing post-transformation reactions,[13] we decided to synthesize a new class of stable allene moiety containing pseudo-peptides through the homologation reaction of terminal

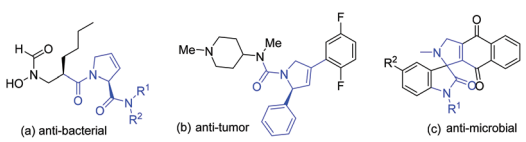

Fig. 1 Examples of bioactive 3-pyrroline structures.

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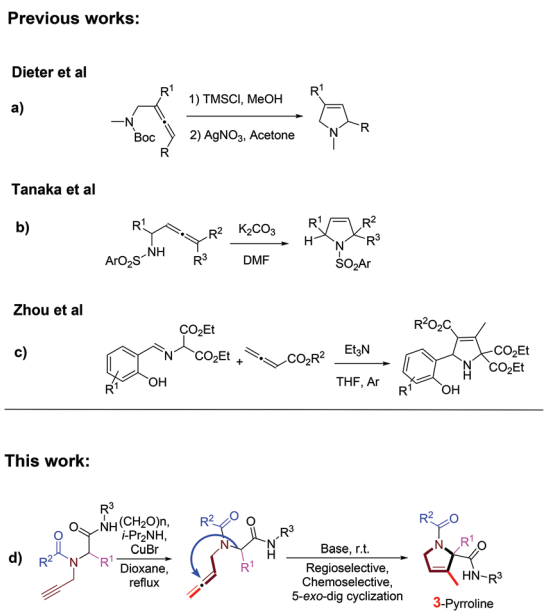
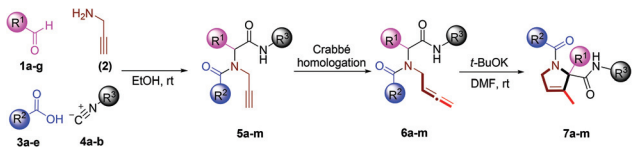
†Dedicated to Prof. Barahman Movassagh on the occasion of his 60th birthday.

‡Electronic supplementary information (ESI) available. CCDC 1904044 and 1904045. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob01963d



Scheme 1 Representative reactions for the synthesis of a 3-pyrroline structure and synthesis of allenic-Ugi products.



Scheme 2 Synthesis of a 3-pyrroline skeleton.

alkynes of Ugi-adducts. This novel class of allenic pseudopeptides are highly stable and desirable and have not been reported so far. Subsequently, the cyclization reaction was employed for the regio- and chemo-selective synthesis of 3-pyrroline skeletons as shown in Scheme 2.

Results and discussion

At the outset of our study, we selected the reaction of benzaldehyde **1a** and propargylamine as a source of terminal alkyne **2**, benzoic acid **3a**, and *t*-butyl isocyanide **4a** in EtOH at room temperature as a model reaction in order to access the Ugi-adduct **5a**. To extend the diversity of the reactions, different carboxylic acids, isocyanides and benzaldehyde derivatives were used. The data are shown in Table 1. In the second step, we envisioned the preparation of an allenic-Ugi product by the homologation reaction, according to previously reported conditions.[14] Reaction conditions were optimized by performing the homologation of terminal alkyne containing pseudopeptides with different secondary amines and paraformaldehyde in the presence of various copper catalysts resulting in the construction of **6a**. As shown in Table 2, the best result for the ATA reaction was obtained by using diisopropylamine in the presence of 60 mol% CuBr at 100 °C in dioxane (Table 2, entry 3). The compound **6a** was separated and its structure was determined by ^{1}H and ^{13}C NMR spectroscopic, HRMS (ESI) and FT-IR analyses.

To further extend the reaction scope, we examined some other aldehydes, carboxylic acids, and isocyanides. The structures of the other allenic-Ugi products are shown in Table 3.

Finally, we tried to explore the optimized reaction conditions for a 5-*exo*-dig intramolecular cyclization reaction of an allenic-Ugi adduct. In this regard, the model reaction was examined with various bases in different solvents and the results are summarized in Table 4. Initially to screen the

Table 1 Substrate scope for the synthesis of compounds **5a–m**

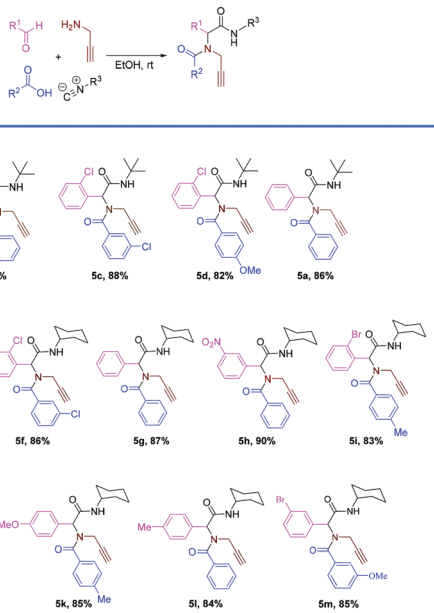
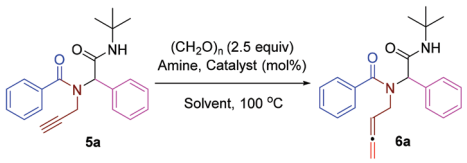


Table 2 Optimization of reaction conditions for the synthesis of **6a**



Entry	Catalyst (mol%)	Solvent	Amine (mmol)	Yield[a,b] (%)
1	CuBr (40)	Dioxane	DIPEA (2.5)	37
2	CuBr (50)	Dioxane	DIPEA (2.5)	61
3	**CuBr (60)**	**Dioxane**	**DIPEA (2.5)**	**84**
4	CuBr (60)	Dioxane	DIPEA (2)	77
5	CuI (60)	Dioxane	DIPEA (2.5)	42
6	CuCl (60)	Dioxane	DIPEA (2.5)	16
7	CuOAc (60)	Dioxane	DIPEA (2.5)	19
8	CuBr (60)	Toluene	DIPEA (2.5)	68
9	CuBr (60)	Dioxane	Pyrrolidine (2.5)	53
10	CuBr (60)	Dioxane	Morpholine (2.5)	24

[a] Isolated yields. [b] Time of reaction was 12 h.

Table 3 Substrate scope for the synthesis of allenic-Ugi products **6a–m**

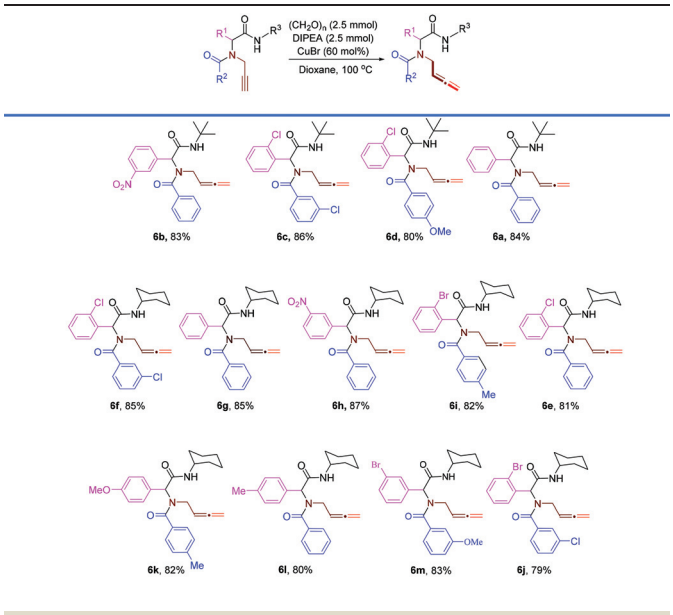
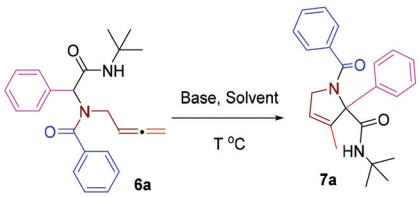


Table 4 Optimized reaction conditions for the synthesis of **7a**

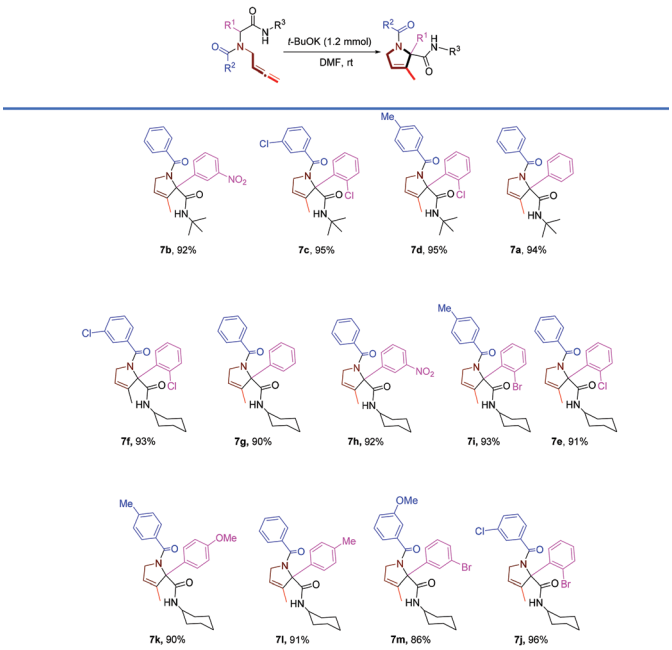


Entry	Base	Solvent	Temp (°C)	Yield[a,b] (%)
1	K_2CO_3	DMF	rt	11
2	Cs_2CO_3	DMF	rt	63
3	***t*-BuOK**	**DMF**	**rt**	**94**
4	*t*-BuOK	DMF	rt	81[c]
5	*t*-BuOK	DMSO	rt	93
6	*t*-BuOK	Toluene	rt	16
7	*t*-BuOK	Dioxane	rt	21
8	*t*-BuOK	MeCN	rt	23
9	*t*-BuOK	DCE	rt	15
10	*t*-BuOK	MeOH	rt	—
11	K_2CO_3	DMF	80	27
12	Cs_2CO_3	DMF	80	88
13	*t*-BuOK	DMF	80	94

[a] Isolated yields. [b] In all cases the amount of the base was 1.2 mmol. [c] Amount of the base was 1 mmol.

effect of the employed base, the reaction was performed by using 1.2 equivalents of K_2CO_3 at room temperature in DMF. However, the isolated yield was very low (Table 2, entry 1). We explored different bases such as K_2CO_3, Cs_2CO_3, and *t*-BuOK. Consequently, the best result was obtained with *t*-BuOK (Table 4, entry 3). Reducing the amount of the base from 1.2 equiv. to 1 equiv. had a negative impact on yields (Table 4, entry 4). For improving the yield of the cyclization reaction, the effects of different solvents were studied

Table 5 Structures of synthesized 3-pyrroline skeletons **7a–m**



(Table 4, entries 5–10). We achieved the best result in DMF (Table 4, entry 3). Although the reaction proceeded well in DMSO, the best solvent was DMF and other solvents gave inferior results. It is noteworthy that raising the reaction temperature to 80 °C did not improve the yield (Table 4, entries 11–13). Based on these results, we defined the reaction of the allenic-Ugi adduct (1 mmol) and *t*-BuOK (1.2 mmol) in DMF (2 mL) at room temperature as the best-optimized reaction conditions.

The scope and generality of the 5-*exo*-dig cyclization reaction were then investigated *via* the optimized reaction conditions, and the results are summarized in Table 5.

The structures of compounds **7a** and **7f** were further confirmed by single-crystal diffraction analysis (Fig. 2).

The experimental results show that intra C-nucleophilic addition to the allene moiety is highly regio- and chemoselective. To explain the selectivity, DFT calculations were carried out at the B3LYP/6-31G(d) level in the gas phase (see computation details). Under the basic reaction conditions, it is possible to form two deprotonated isomers of the allenic-Ugi product (anions A and B) (Fig. 3) in which the relative free energy (G_{rel}) and chemical hardness (η) of anion **B** (G_{rel} = 0.0 kcal mol^{-1}, η = 2.80 eV) are lower than those of anion **A** (G_{rel} = 1.1 kcal mol^{-1}, η = 3.52 eV); thus anion **B** is more reactive than anion **A** and the possibility of formation of anion **B** is higher than that of anion **A**.

Six probable intramolecular attacks and their related transition states (TS) have been considered (Fig. 4). Among all, the addition of a deprotonated chiral center to β carbon (TS2) has the lowest activation energy ($\Delta E^{\ddagger}$) which is 21.0 kcal mol^{-1} and can be performed at the reaction temperature

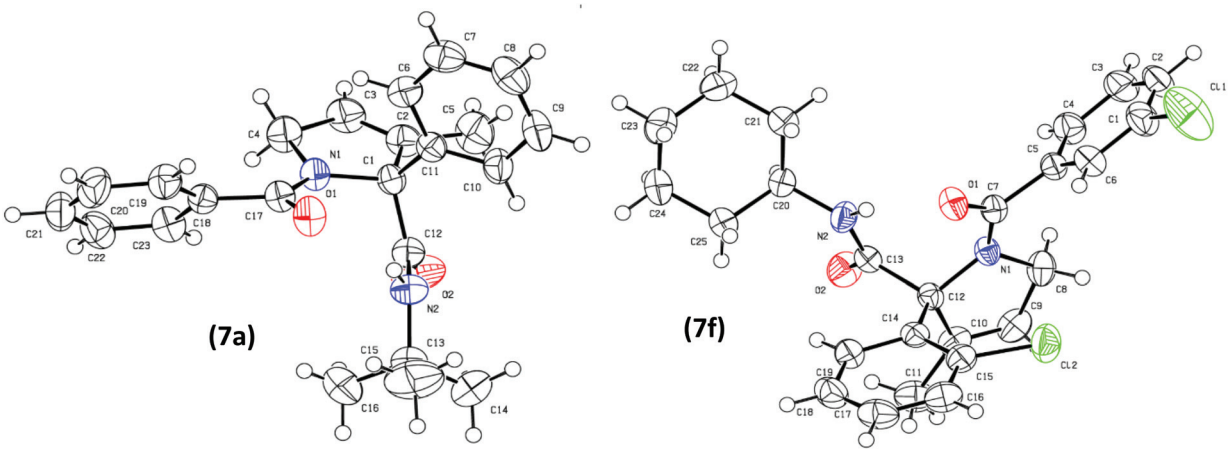


Fig. 2 ORTEP structures of **7a** and **7f**.

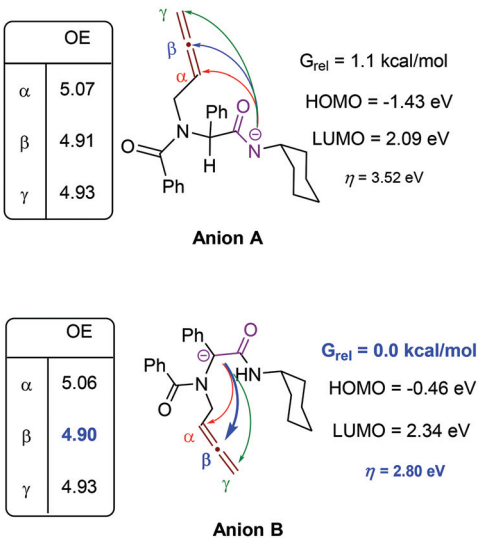


Fig. 3 DFT details for anions A and B (calculated at the PCM (DMF)/B3LYP/6-31G(d) level).

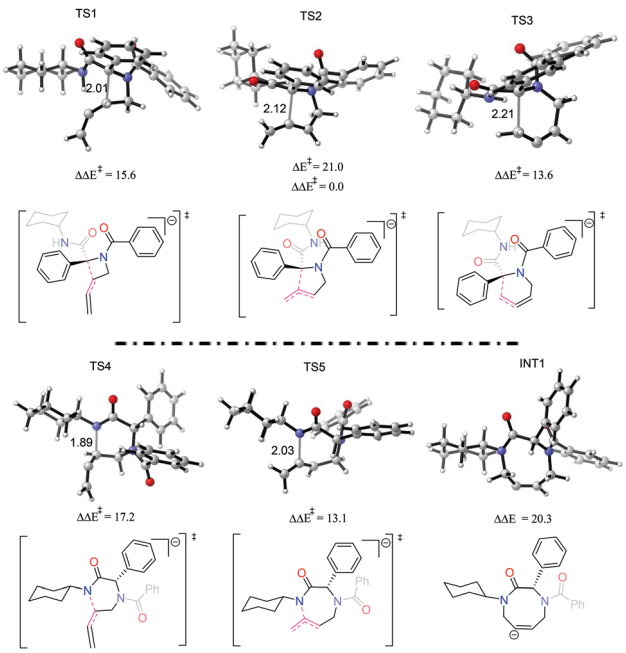
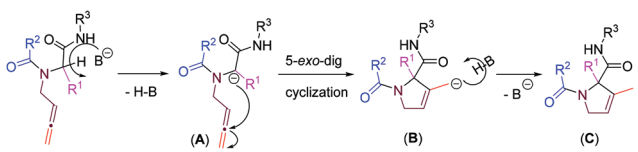


Fig. 4 Relative activation energies, the geometry of transition state structures and the intermediate (Δ*E* is related to the reaction of anion **A** to form INT1, $\Delta E^{\ddagger}$ is the activation energy and $\Delta\Delta E^{\ddagger}$ is the relative activation energy; energies are given in kcal mol^{-1}).

(Fig. 4). The attack of the amide moiety on γ carbon is barrierless (Scheme S1‡); thus, its intermediate (INT1) has been compared with other transition states. The energy of INT1 is higher than that of TS2 (41.4 kcal mol^{-1}); so it can be said that formation of INT1 is impossible under the reaction conditions.

The local Fukui function[15] and LUMO contribution analysis (LUMO-CA)[16] model (Scheme S2, ESI‡) cannot predict the regioselectivity of the reaction, but β carbon has the lowest orbital electronegativity (OE)[17] and the highest Mulliken charge (Fig. 3 and S2, ESI‡). Therefore, it is reasonable that an intra-C-nucleophile attack on β carbon has the lowest barrier energy which leads to the main product.

On the basis of the above observations, a tentative mechanism pathway is drawn in Scheme 3. Under basic reaction conditions, the intermediate **A** is formed, followed by an attack on the central position of the allene in a 5-*exo*-dig fashion to provide the preferentially 5-membered ring products **C** after protonation of **B**.



Scheme 3 A plausible mechanism for formation of 3-pyrroline derivatives.

Conclusion

In conclusion, we have successfully established an efficient and novel route for the regio- and chemo-selective synthesis of 3-pyrroline skeletons through a 5-*exo*-dig intramolecular cyclization reaction of a stable allenic-Ugi intermediate, generated by the ATA reaction from Ugi-adducts. The regio- and chemoselectivities were explained by DFT calculations. This protocol is highly diverse and productive. Further experiments on asymmetric addition reactions are in progress in our lab.

Experimental section

General information

All reagents and solvents were purchased commercially and used as received without further purification. All reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 F254 plates. Column chromatography purification was performed on silica gel (63–200 mesh ASTM). Melting points (mp) were measured *via* an Electrothermal 9100 apparatus and were uncorrected. Fourier transform infrared (FT-IR) spectra were recorded on an AABFT-IR (FTLA 2000) spectrophotometer with KBr disks. NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker 300 MHz, 400 MHz or 600 MHz NMR spectrometer in $CDCl_3$ or DMSO-d_6 at room temperature. The abbreviations of multiplicity for ^{1}H NMR data are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (J) and chemical shifts (δ) were expressed in Hz and ppm, respectively. High-resolution mass spectrometry (ESI-HRMS) measurements were performed using an Agilent Q-TOF LC-MS spectrometer.

General procedure for the synthesis of Ugi-4CR 5a–m

To a solution of aromatic aldehydes **1a–g** (1 mmol) in ethanol (5 ml) was added the propargyl amine **2** (1 mmol, 55 mg), and the mixture was stirred at room temperature for 1 h. Then, carboxylic acids **3a–e** (1 mmol) were added, and stirring was continued for 15 min, followed by the addition of isocyanides **4a** and **4b** (1 mmol). The mixture was stirred for 24 h at room temperature. The progress of the reaction was monitored by TLC (*n*-hexane/EtOAc 3 : 1). The precipitate formed was filtered and dried. In some cases (**5d**, **5g**, **5k**, **5l**, and **5m**), purification was done using preparative TLC (*n*-hexane/EtOAc 4 : 1). Yields (82–90%).

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(prop-2-yn-1-yl)benzamide (5a).**[18] Colorless solid mp. 141–142 °C, yield 86%, R_f = 0.33 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.54 (m, 2H, H–Ar), 7.45–7.42 (m, 4H, H–Ar), 7.40–7.33 (m, 4H, H–Ar), 5.87 (s, 2H, C(sp^3)–H, NH), 4.18 (dd, J = 18.3, 2.3 Hz, 1H, CH_2–N), 4.01 (d, J = 18.3 Hz, 1H, CH_2–N), 2.00 (s, 1H, propargylic H), 1.39 (s, 9H, H-*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.4, 135.4, 134.7, 130.3, 129.8, 128.9, 128.7, 128.5, 127.1, 96.1, 76.7, 71.6, 62.8, 51.9, 28.7; ESI (−) (*m*/*z*): for $C_{22}H_{23}N_2O_2$ $[M - H]^-$ 347.3.

***N*-(2-(*tert*-Butylamino)-1-(3-nitrophenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)benzamide (5b).** Colorless solid mp. 132–133 °C, yield 85%, R_f = 0.37 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (brs, 1H, H–Ar), 8.20 (t, J = 7.4 Hz, 1H, H–Ar), 7.88–7.78 (m, 1H, H–Ar), 7.60 (t, J = 8.0 Hz, 2H, H–Ar), 7.56 (d, J = 8.0 Hz, 1H, H–Ar), 7.47 (t, J = 7.4 Hz, 2H, H–Ar), 7.45 (d, J = 8.0 Hz, 1H, H–Ar), 6.45 (s, 1H, C(sp^3)–H), 5.96 (brs, 1H, –NH), 4.29 (dd, J = 18.4, 2.4 Hz, 1H, –CHN), 4.09 (dd, J = 18.4, 2.4 Hz, 1H, –CHN), 2.09 (s, 1H, propargylic H), 1.39 (s, 9H, H-*t*Bu); 172.5, 167.5, 148.3, 137.1, 135.5, 134.6, 130.8, 129.7, 128.7, 127.1, 124.6, 123.4, 87.6, 79.2, 72.9, 62.2, 52.0, 28.6; ESI (+) (*m*/*z*): for $C_{22}H_{23}N_3NaO_4$ $[M + Na]^+$ 415.3.

***N*-(2-(*tert*-Butylamino)-1-(2-chlorophenyl)-2-oxoethyl)-3-chloro-*N*-(prop-2-yn-1-yl)benzamide (5c).** Colorless solid, mp. 204–205 °C, yield 88%, R_f = 0.33 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of two rotamers (67 : 33)) δ 7.74–7.52 (m, 3H, H–Ar, mixture of two rotamers), 7.46–7.40 (m, 2H, H–Ar, mixture of two rotamers), 7.38–7.31 (m, 3H, H–Ar, mixture of two rotamers), 6.24 (s, 1H, N–H, major rotamer), 5.70 (s, 1H, C(sp^3)–H, mixture of two rotamers), 5.39 (brs, 1H, N–H, minor rotamer), 4.26–4.14 (m, 1H, –CHN, mixture of two rotamers), 4.12–3.85 (m, 1H, –CHN, mixture of two rotamers), 2.04 (s, 1H, propargylic H, minor rotamer), 1.88 (s, 1H, propargylic H, major rotamer), 1.41 (s, 9H, H-*t*Bu, mixture of two rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) (for the major rotamer) δ 170.8, 168.2, 136.9, 134.4, 132.4, 132.3, 130.8, 130.5, 130.0, 129.9, 127.5, 127.3, 126.0, 125.5, 96.1, 79.2, 71.5, 60.4, 52.0, 28.6; ESI (+) (*m*/*z*): for $C_{44}H_{44}{}^{35}Cl_4N_4NaO_4$ $[2M + Na]^+$ 857.3, and; ESI (−) (*m*/*z*): for $C_{22}H_{22}{}^{35}Cl_2N_2O_2$ $[M - H]^-$ 415.2.

***N*-(2-(*tert*-Butylamino)-1-(2-chlorophenyl)-2-oxoethyl)-4-methoxy-*N*-(prop-2-yn-1-yl)benzamide (5d).** Colorless solid, mp. 164–165 °C, yield 82%, R_f = 0.39 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.49 (m, 3H, H–Ar), 7.43–7.37 (m, 1H, H–Ar), 7.35–7.28 (m, 2H, H–Ar), 6.91 (d, J = 8.6 Hz, 2H, H–Ar), 6.10 (brs, 1H, –NH), 5.93 (s, H, C(sp^3)–H), 4.26 (d, J = 18.2 Hz, 1H, –CHN), 4.00 (dd, J = 18.2, 1.9 Hz, 1H, –CHN), 3.82 (s, 3H, O–CH_3), 1.91 (s, 1H, propargylic H), 1.42 (s, 9H, H-*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.6, 161.3, 136.7, 132.9, 130.8, 130.2, 129.8, 129.4, 127.3, 127.2, 113.6, 96.1, 79.5, 71.2, 60.9, 55.3, 52.0, 28.7; ESI (+) (*m*/*z*): for $C_{23}H_{26}{}^{35}ClN_2O_3$ $[M + H]^+$ 413.2, and for $C_{46}H_{50}{}^{35}Cl_2N_4NaO_6$ $[2M + Na]^+$ 847.3.

***N*-(1-(2-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)benzamide (5e).** Colorless solid, mp. 169–170 °C, yield 84%, R_f = 0.39 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of two rotamers (65 : 35)) δ 7.72–7.53 (m, 3H, H–Ar, mixture of two rotamers), 7.47–7.39 (m, 4H, H–Ar, mixture of two rotamers), 7.36–7.29 (m, 2H, H–Ar, mixture of two rotamers), 6.33 (s, 1H, C(sp^3)–H, major rotamer), 6.11 (brs, 1H, C(sp^3)–H, minor rotamer), 5.91 (s, 1H, NH, major rotamer), δ 5.52 (brs, 1H, NH, minor rotamer), 4.25 (dd, J = 18.0, 2.3 Hz, 1H, –CHN, mixture of two rotamers), 3.95 (d, J = 18 Hz, 1H, –CHN, mixture of two rotamers), 3.82–3.90 (m, 1H H–cyclohexyl, mixture of two rotamers), 2.04–1.88 (m, 3H, propargylic H, H–cyclohexyl, mixture of two rotamers), 1.76–1.60 (m, 3H, H–cyclohexyl, mixture of two rotamers), 1.44–1.34 (m,

2H, H–cyclohexyl, mixture of two rotamers), 1.28–1.11 (m, 3H, H–cyclohexyl, mixture of two rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) (for the major rotamer) δ 172.3, 168.1, 135.2, 132.5, 132.4, 131.0, 130.4, 130.3, 129.9, 128.4, 127.2, 127.1, 96.1, 79.3, 71.3, 59.0, 48.8, 33.0, 25.5, 24.9, 24.8; ESI (–) (*m*/*z*): for $C_{24}H_{24}{}^{35}ClN_2O_2$ $[M - H]^-$ 407.2.

3-Chloro-*N*-(1-(2-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)benzamide (5f). Colorless solid, mp. 173–174 °C, yield 86%, R_f = 0.38 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of two rotamers (64 : 36)) δ 7.67–7.47 (m, 3H, H–Ar, mixture of two rotamers), 7.45–7.40 (m, 2H, H–Ar, mixture of two rotamers), 7.37–7.29 (m, 3H, H–Ar, mixture of two rotamers), 6.33 (s, 1H, C(sp^3)–H, major rotamer), 6.02 (brs, 1H, C(sp^3)–H, minor rotamer), 5.91 (s, 1H, NH, major rotamer), 5.49 (brs, 1H, NH, minor rotamer), 4.23 (d, J = 18 Hz, 1H, –CHN, mixture of two rotamers), 3.93–3.84 (m, 2H, –CHN, N–CH–cyclohexyl, mixture of two rotamers), 2.04–1.91 (m, 3H, propargylic H, H–cyclohexyl, mixture of two rotamers), 1.75–1.61 (m, 3H, H–cyclohexyl, mixture of two rotamers), 1.42–1.32 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.25–1.07 (m, 3H, H–cyclohexyl, mixture of two rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) (for the major rotamer) δ 170.8, 167.9, 136.9, 134.4, 133.0, 132.3, 130.9, 130.5, 130.0, 129.8, 127.6, 127.5, 127.3, 125.3, 96.1, 78.8, 71.6, 58.8, 48.8, 32.8, 25.4, 24.8, 24.8; ESI (+) (*m*/*z*): for $C_{24}H_{25}{}^{35}Cl_2N_2O_2$ $[M + H]^+$ 443.2, and for $C_{48}H_{48}{}^{35}Cl_4N_4NaO_4$ $[2M + Na]^+$ 909.4.

***N*-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(prop-2-yn-1-yl)benzamide (5g).** Colorless solid, mp. 138–139 °C, yield 87%, R_f = 0.38 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.57 (m, 2H, H–Ar), 7.48–7.41 (m, 4H, H–Ar), 7.40–7.37 (m, 4H, H–Ar), 6.02 (brs, 2H, C(sp^3)–H, NH), 4.19 (d, J = 18.4 Hz, 1H, CH_2–N), 3.99 (dd, J = 18.3, 2.5 Hz, 1H, CH_2–N), 3.93–3.85 (m, 1H, N–CH–cyclohexyl), 2.04–1.93 (m, 3H, propargylic H, H–cyclohexyl), 1.73–1.60 (m, 3H, H–cyclohexyl), 1.43–1.32 (m, 2H, H–cyclohexyl), 1.22–1.12 (m, 3H, H–cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.1, 135.3, 134.5, 130.4, 129.7, 128.9, 128.7, 128.6, 127.1, 96.1, 79.7, 72.0, 62.5, 48.7, 32.9, 25.5, 24.9, 24.8; ESI (+) (*m*/*z*): for $C_{24}H_{27}N_2O_2$ $[M + H]^+$ 375.3, and for $C_{48}H_{52}N_4NaO_4$ $[2M + Na]^+$ 771.3.

***N*-(2-(Cyclohexylamino)-1-(3-nitrophenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)benzamide (5h).** Colorless white solid, mp. 174–175 °C, yield 90%, R_f = 0.40 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (brs, 1H, H–Ar), 8.21 (d, J = 8.2 Hz, 1H, H–Ar), 7.84 (brs, 1H, H–Ar), 7.62–7.52 (m, 3H, H–Ar), 7.51–7.42 (m, 3H, H–Ar), 6.68 (brs, 1H, C(sp^3)–H), 6.06 (brs, 1H, NH), 4.32 (d, J = 18.4 Hz, 1H, CH_2–N), 4.09 (dd, J = 18.4, 2.3 Hz, 1H, CH_2–N), 3.90–3.82 (m, 1H, N–CH–cyclohexyl), 2.09 (t, J = 2.3 Hz, 1H, propargylic H), 1.97–1.87 (m, 2H, H–cyclohexyl), 1.72–1.58 (m, 3H, H–cyclohexyl), 1.42–1.32 (m, 2H, H–cyclohexyl), 1.22–1.11 (m, 3H, H–cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.3, 148.3, 137.0, 135.4, 134.5, 130.8, 129.7, 128.7, 127.1, 124.5, 123.4, 96.1, 79.1, 72.9, 62.5, 48.8, 32.7, 32.6, 25.4, 24.8, 24.7; ESI (+) (*m*/*z*): for $C_{24}H_{26}N_3O_4$ $[M + H]^+$ 420.3, and for $C_{48}H_{50}N_6NaO_8$ $[2M + Na]^+$ 861.5.

***N*-(1-(2-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzamide (5i).** Colorless solid, mp. 204–205 °C, yield 83%, R_f = 0.36 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.43 (m, 4H, H–Ar), 7.35 (t, J = 7.2 Hz, 1H, H–Ar), 7.27–7.19 (m, 3H, H–Ar), 6.24 (brs, 1H, C(sp^3)–H), 6.01(brs, 1H, NH), 4.26 (dd, J = 18.3, 2.3 Hz, 1H, CH_2–N), 3.93 (dd, J = 18.3, 2.3 Hz, 1H, CH_2–N), 3.88–3.81 (m, 1H, N–CH–cyclohexyl), 2.37 (s, 3H, –CH_3), 2.01–1.90 (m, 3H, propargylic H, H–cyclohexyl), 1.76–1.58 (m, 3H, H–cyclohexyl), 1.41–1.31 (m, 2H, H–cyclohexyl), 1.24–1.11 (m, 3H, H–cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.3, 140.6, 134.3, 133.2, 132.3, 131.2, 130.4, 129.0, 127.8, 127.4, 127.3, 96.1, 79.3, 71.4, 61.5, 48.8, 32.8, 25.5, 24.9, 24.7, 21.5; ESI (+) (*m*/*z*): for $C_{50}H_{54}{}^{79}Br_2N_4NaO_4$ $[2M + Na]^+$ 957.4.

***N*-(1-(2-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-3-chloro-*N*-(prop-2-yn-1-yl)benzamide (5j).** Colorless solid, mp. 188–190 °C, yield 82%, R_f = 0.39 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of two rotamers (77 : 23)) δ 7.70–7.49 (m, 4H, H–Ar, mixture of two rotamers), 7.44–7.42 (m, 1H, H–Ar, mixture of two rotamers), 7.38 (t, J = 7.6 Hz, 1H, H–Ar, mixture of two rotamers), 7.36 (t, J = 7.6 Hz, 1H, H–Ar, mixture of two rotamers), 7.28 (t, J = 7.5 Hz, 1H, H–Ar, mixture of two rotamers), 6.26 (s, 1H, C(sp^3)–H, major rotamer), 6.01 (s, 1H, C(sp^3)–H, minor rotamer), 5.87 (s, 1H, NH, major rotamer), 5.42 (s, 1H, N–H, minor rotamer), 4.24 (d, J = 17.6 Hz, 1H, –CHN, mixture of two rotamers), 3.99–3.82 (m, 2H, –CHN, N–CH–cyclohexyl, mixture of two rotamers), 2.05–1.90 (m, 3H, propargylic H, H–cyclohexyl, mixture of two rotamers), 1.82–1.62 (m, 3H, CH–cyclohexyl, mixture of two rotamers), 1.48–1.32 (m, 2H, CH–cyclohexyl, mixture of two rotamers), 1.27–1.08 (m, 3H, CH–cyclohexyl, mixture of two rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) (for the major rotamer) δ 170.8, 168.0, 136.9, 134.4, 133.9, 133.3, 131.1, 130.6, 130.5, 129.8, 127.9, 127.6, 127.5, 125.4, 78.8, 77.3, 71.7, 61.3, 48.9, 32.8, 25.4, 24.9, 24.8; ESI (–) (*m*/*z*): for $C_{24}H_{23}{}^{79}Br^{35}ClN_2O_2$ $[M - H]^-$ 483.3.

***N*-(2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzamide (5k).** Colorless solid, mp. 132–133 °C, yield 85%, R_f = 0.35 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.29 (m, 4H, H–Ar), 7.20 (d, J = 7.5 Hz, 2H, H–Ar), 6.87 (d, J = 7.9 Hz, 2H, H–Ar), 6.35 (d, J = 7.7 Hz, 1H, N–H), 5.95 (brs, 1H, C(sp^3)–H), 4.18 (d, J = 18.3 Hz, 1H, –CH_2–N), 3.98 (d, J = 18.3 Hz, 1H, –CH_2–N), 3.90–3.81 (m, 1H, N–CH–cyclohexyl), 3.78 (s, 3H, O–CH_3), 2.36 (s, 3H, –CH_3), 2.05 (s, 1H, propargylic H), 1.97–1.87 (m, 2H, CH–cyclohexyl), 1.72–1.54 (m, 3H, CH–cyclohexyl), 1.42–1.27 (m, 2H, CH–cyclohexyl), 1.19–1.04 (m, 3H, CH–cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.7, 159.7, 140.4, 132.5, 131.0, 129.1, 127.1, 126.6, 114.1, 80.0, 77.4, 71.7, 62.3, 55.2, 48.6, 32.7, 25.4, 24.8, 24.7, 21.4; ESI (+) (*m*/*z*): for $C_{26}H_{31}N_2O_3$ $[M + H]^+$ 419.3, and for $C_{52}H_{60}N_4NaO_6$ $[2M + Na]^+$ 859.6.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-*N*-(prop-2-yn-1-yl)benzamide (5l).** Colorless solid, mp. 151–152 °C, yield 84%, R_f = 0.40 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.48 (m, 2H, H–Ar), 7.47–7.29 (m, 3H, H–Ar), 7.22 (d, J = 7.9 Hz, 2H, H–Ar), 7.21–7.10 (m, 2H, H–Ar), 6.13–5.58 (m, 2H, C(sp^3)–H, N–H), 4.17 (d, J = 18.0 Hz, 1H, –CH_2–N), 3.97 (d, J = 18.0 Hz, 1H, –CH_2–N), 3.89–3.81 (m, 1H,

N–CH–cyclohexyl), 2.36 (s, 3H, CH_3), 2.07 (s, 1H, propargylic H), 2.01–1.91 (m, 2H, CH–cyclohexyl), 1.77–1.56 (m, 3H, CH–cyclohexyl), 1.44–1.31 (m, 2H, CH–cyclohexyl), 1.26–1.09 (m, 3H, CH–cyclohexyl); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 168.4, 140.6, 138.6, 135.4, 132.4, 131.5, 130.3, 129.6, 127.0, 96.1, 79.9, 72.0, 61.6, 48.7, 32.9, 25.5, 24.8, 24.7, 21.8, 21.2; ESI (−) (*m*/*z*): for $C_{25}H_{27}N_2O_2$ $[M - H]^-$ 387.1.

***N*-(1-(3-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-3-methoxy-*N*-(prop-2-yn-1-yl)benzamide (5m).** Colorless solid, mp. 153–154 °C, yield 85%, R_f = 0.38 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.48 (m, 1H, H–Ar), 7.49 (d, J = 7.6 Hz, 1H, H–Ar), 7.47–7.36 (m, 1H, H–Ar), 7.33 (t, J = 7.9 Hz, 1H, H–Ar), 7.27–7.22 (m, 1H, H–Ar), 7.21–7.06 (m, 2H, H–Ar), 6.99 (dd, J = 8.3, 1.9 Hz, 1H, H–Ar), 6.28 (brs, 1H, C(sp^3)–H), 5.97 (brs, 1H, N–H), 4.23 (d, J = 18.3 Hz, 1H, –CH_2–N), 4.03 (dd, J = 18.3, 2.1 Hz, –CH_2–N), 3.92–3.83 (m, 1H, N–CH–cyclohexyl), 3.81 (s, 3H, O–CH_3), 2.08 (s, 1H, propargylic H), 1.99–1.87 (m, 2H, CH–cyclohexyl), 1.76–1.55 (m, 3H, CH–cyclohexyl), 1.41–1.30 (m, 2H, CH–cyclohexyl), 1.21–1.04 (m, 3H, CH–cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 167.7, 159.5, 136.9, 136.1, 132.8, 131.8, 130.3, 129.8, 128.1, 122.7, 119.2, 116.8, 112.1, 96.1, 79.6, 72.3, 61.6, 55.4, 48.7, 32.8, 25.4, 24.8, 24.7; ESI (−) (*m*/*z*): for $C_{25}H_{26}{}^{79}BrN_2O_3$ $[M - H]^-$ 481.2.

General procedure for the synthesis of allenic-Ugi products (6a–m) through sequential Ugi-4CR/ATA reactions

To a stirred solution of propargylamine as a primary amine (1 mmol) in EtOH (2 mL) was added an aldehyde (1 mmol) and the resulting solution was stirred at ambient temperature for 20 min. A carboxylic acid was added to the reaction mixture and stirring was continued for 5 min. Afterwards, an isocyanide (1 mmol) was added and the mixture was stirred at room temperature for 24 h. The reaction progress was monitored by TLC. After consumption of all the starting materials, the solvent was removed on a rotary evaporator. Thereafter, dry dioxane (2 mL), paraformaldehyde (2.5 mmol), CuBr (60 mol%), and diisopropyl amine (2.5 mmol) were added to the desired Ugi-4CR product. The resulting mixture was stirred under an Ar atmosphere for 12 h at 100 °C. After completion of the reaction (based on TLC), the resulting mixture was cooled to room temperature, was diluted with ether (5 mL) and water (5 mL) and then the aqueous layer was extracted with ether (3 × 5 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography (*n*-hexane/EtOAc 3 : 1) to afford the allenic-Ugi product. Yields (82–87%).

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(*tert*-butylamino)-2-oxo-1-phenylethyl)benzamide (6a).** Colorless solid, mp. 130–133 °C, yield 84%, R_f = 0.31 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52–7.49 (m, 3H, H–Ar), 7.43–7.35 (m, 7H, H–Ar), 5.91 (brs, 1H, C(sp^3)–H), 4.73 (brs, 1H, allenic H), 4.52 (brs, 2H, allenic H), 4.02–3.94 (m, 2H, –CH_2–N), 1.40 (s, 9H, H-*t*Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 172.9, 168.8 136.2, 135.2, 129.8, 129.5, 128.8, 128.6, 128.4, 126.9, 87.9, 76.5, 63.1, 51.8, 47.3, 28.6; IR (KBr): ν_{max} = 1959 (C═C═C), 1670 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{27}N_2O_2$ $[M + H]^+$ 363.2091, found 363.2099.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(*tert*-butylamino)-1-(3-nitrophenyl)-2-oxoethyl)benzamide (6b).** Pale yellow, mp. 138–139 °C, yield 83%, R_f = 0.32 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (brs, 1H, H–Ar), 8.19 (dd, J = 8.2, 2.1 Hz, 1H, H–Ar), 7.84–7.81 (m, 1H, H–Ar), 7.57 (t, J = 7.9 Hz, 1H, H–Ar), 7.49 (d, J = 7.3 Hz, 2H, H–Ar), 7.47–7.40 (m, 3H, H–Ar), 6.62 (brs, 1H, NH), 5.88 (brs, 1H, C(sp^3)–H), 4.90 (brs, 1H, allenic H), 4.68–4.60 (m, 2H, allenic H), 4.00–4.08 (m, 2H, –CH_2–N), 1.39 (s, 9H, H-*t*Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.7, 173.2, 167.8, 148.3, 137.7, 135.5, 135.1, 130.3, 129.6, 128.6, 126.8, 124.1, 123.2, 87.6, 77.5, 62.9, 51.9, 47.6, 28.6; IR (KBr): ν_{max} = 1957 (C═C═C), 1651 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{26}N_3O_4$ $[M + H]^+$ 408.1945, found 408.1954.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(*tert*-butylamino)-1-(2-chlorophenyl)-2-oxoethyl)-3-chlorobenzamide (6c).** Colorless solid, mp. 146–148 °C, yield 86%, R_f = 0.30 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of two rotamers (66 : 34)) δ 7.69 (brs, 1H, H–Ar, mixture of two rotamers), 7.49 (s, 1H, H–Ar, mixture of two rotamers), 7.42–7.34 (m, 6H, H–Ar, mixture of two rotamers), 6.15 (brs, 1H, C(sp^3)–H, major rotamer), 5.72 (brs, 1H, NH, major rotamer), 5.37–5.34 (m, 2H, C(sp^3)–H, NH, minor rotamer), 5.13 (brs, 1H, allenic H, minor rotamer), 4.69 (brs, 1H, allenic H, major rotamer), 4.53–4.45 (m, 2H, – allenic H, major rotamer), 4.33 (m, 2H, allenic H, minor rotamer), 3.95–3.86 (m, 2H, –CH_2–N, mixture of two rotamers), 1.42 (s, 9H, H-*t*Bu, mixture of two rotamers); ^{13}C NMR (75 MHz, DMSO-d_6) (for the major rotamer) δ 207.3, 169.7, 168.4, 138.4, 135.4, 134.0, 132.9, 130.9, 130.3, 130.2, 129.7, 127.6, 126.2, 125.7, 125.5, 86.3, 75.6, 62.8, 50.6, 44.1, 28.1; IR (KBr): ν_{max} = 1956 (C═C═C), 1685 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{25}{}^{35}Cl_2N_2O_2$ $[M + H]^+$ 431.1491, found 431.1500.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(*tert*-butylamino)-1-(2-chlorophenyl)-2-oxoethyl)-4-methoxybenzamide (6d).** Colorless solid, mp. 151–154 °C, yield 80%, R_f = 0.34 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (brs, 1H, H–Ar), 7.47 (d, J = 9.0 Hz, 2H, H–Ar), 7.44–7.38 (m, 1H, H–Ar), 7.33–7.28 (m, 2H, H–Ar), 6.87 (d, J = 9.0 Hz, 2H, H–Ar), 5.84 (brs, 2H, C(sp^3)–H, NH), 4.95 (brs, 1H, allenic H), 4.55–4.39 (m, 2H, allenic H), 4.15–3.95 (m, 2H, –CH_2–N), 3.82 (s, 3H, O–CH_3), 1.41 (s, 9H, H-*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 172.7, 168.5, 160.8, 135.8, 133.2, 130.9, 129.9, 129.9, 128.9, 128.4, 127.2, 113.6, 87.5, 76.0, 55.7, 55.3, 54.9, 51.8, 28.6; IR (KBr): ν_{max} = 1958 (C═C═C), 1683 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{28}{}^{35}ClN_2O_3$ $[M + H]^+$ 427.1997, found 427.2007.

***N*-(Buta-2,3-dien-1-yl)-*N*-(1-(2-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)benzamide (6e).** Colorless solid, mp. 165–164 °C, yield 81%, R_f = 0.36 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of two rotamers (63 : 37)) δ 7.72 (brs, 1H, H–Ar, mixture of two rotamers), 7.49 (d, J = 7.1 Hz, 2H, H–Ar, mixture of two rotamers), 7.45–7.37 (m, 4H, H–Ar, mixture of two rotamers), 7.32–7.31 (m, 2H, H–Ar, mixture of two rotamers), 6.19 (s, 1H, C(sp^3)–H, major rotamer), 5.98 (brs, 1H, NH, major rotamer), δ 5.84 (brs, 1H,

C(sp^3)–H, minor rotamer), 5.50 (brs, 1H, NH, minor rotamer), 5.22 (brs, 1H, allenic H, minor rotamer), 4.80 (brs, 1H, allenic H, major rotamer), 4.49–4.40 (m, 2H, allenic H, mixture of two rotamers), 4.14–3.90 (m, 3H, –CH_2–N, CH–cyclohexyl, mixture of two rotamers), 2.01–1.94 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.75–1.69 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.64–1.61 (m, 1H, H–cyclohexyl, mixture of two rotamers), 1.44–1.36 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.22–1.10 (m, 3H, H–cyclohexyl, mixture of two rotamers); ^{13}C NMR (151 MHz, $CDCl_3$) (for the major rotamer) δ 208.3, 172.8, 168.2, 136.2, 135.8, 132.9, 131.1, 130.1, 129.9, 129.8, 128.4, 127.2, 126.9, 87.4, 76.1, 60.1, 48.7, 32.8, 25.5, 24.8, 24.8; IR (KBr): ν_{max} = 1960 (C═C═C), 1650 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{28}{}^{35}ClN_2O_2$ $[M + H]^+$ 423.1995, found 423.2005.

***N*-(Buta-2,3-dien-1-yl)-*N*-(1-(2-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-3-methylbenzamide (6f).** Colorless solid, mp. 152–154 °C, yield 85%, R_f = 0.34 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of two rotamers (69 : 31)) δ 7.69 (brs, 1H, H–Ar, mixture of two rotamers), 7.48 (m, 2H, H–Ar, mixture of two rotamers), 7.40 (t, *J* = 7.2 Hz, 1H, H–Ar, mixture of two rotamers), 7.37 (s, 1H, H–Ar, mixture of two rotamers), 7.36–7.33 (m, 3H, H–Ar, mixture of two rotamers), 6.22 (brs, 1H, C(sp^3)–H, major rotamer), 5.86 (brs, 1H, NH, major rotamer), 5.68 (s, 1H, C(sp^3)–H, minor rotamer), 5.43 (brs, 1H, NH, minor rotamer), 5.16 (brs, 1H, allenic H, minor rotamer), 4.71 (brs, 1H, allenic H, major rotamer), 4.55–4.37 (m, 2H, allenic H, mixture of two rotamers), 4.20–3.81 (m, 3H, –CH_2–N, CH–cyclohexyl, mixture of two rotamers), 2.00–1.94 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.75–1.69 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.63 (d, *J* = 12.8 Hz, 1H, H–cyclohexyl, mixture of two rotamers), 1.42–1.35 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.22–1.09 (m, 3H, H–cyclohexyl, mixture of two rotamers); 1H NMR (300 MHz, chloroform-d at 55 °C) δ 7.61 (brs, 1H, H–Ar), 7.45–7.24 (m, 7H, H–Ar), 5.96 (brs, 1H, C(sp^3)–H), 5.67 (brs, 1H, NH), 4.85 (brs, 1H, allenic H), 4.55–4.38 (m, 2H, allenic H), 3.97–3.80 (m, 3H, –CH_2–N, CH–cyclohexyl), 1.99–1.87 (m, 2H, H–cyclohexyl), 1.71–1.57 (m, 3H, H–cyclohexyl), 1.43–1.32 (m, 2H, H–cyclohexyl), 1.23–1.09 (m, 3H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) (for the major rotamer) δ 208.4, 171.3, 167.9, 137.9, 135.8, 134.3, 132.7, 131.1, 130.3, 130.1, 130.9, 129.8, 127.3, 127.1, 125.1, 87.3, 76.2, 59.8, 48.8, 47.3, 32.8, 25.4, 24.8, 24.7; IR (KBr): ν_{max} = 1957 (C═C═C), 1684 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{27}{}^{35}Cl_2N_2O_2$ $[M + H]^+$ 457.1651, found 457.1662.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)benzamide (6g).** Colorless solid, mp. 140–142 °C, yield 85%, R_f = 0.38 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of two rotamers (80 : 20)) δ 7.51–7.43 (m, 4H, H–Ar, mixture of two rotamers), 7.38–7.30 (m, 6H, H–Ar, mixture of two rotamers), 6.09–5.76 (m, 2H, C(sp^3)–H, NH, major rotamer), 5.44 (brs, 1H, C(sp^3)–H, minor rotamer), 5.13 (s, 1H, NH, minor rotamer), 4.70 (brs, 1H, allenic H, mixture of two rotamers), 4.47 (brs, 2H, allenic H, mixture of two rotamers), 3.98–3.90 (m, 2H, –CH_2–N, mixture of two rotamers), 3.84–3.81 (m, 1H, H–cyclohexyl, mixture of two rotamers), 1.90 (dd, *J* = 12.6, 4.5 Hz, 2H, H–cyclohexyl, mixture of two rotamers), 1.67–1.63 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.56 (d, *J* = 13.4 Hz, 1H, H–cyclohexyl, mixture of two rotamers), 1.36–1.30 (m, 2H, H–cyclohexyl, mixture of two rotamers), 1.14–1.04 (m, 3H, H–cyclohexyl, mixture of two rotamers); ^{13}C NMR (151 MHz, $CDCl_3$) (for the major rotamer) δ 208.5, 172.9, 168.5, 136.2, 135.1, 129.8, 129.4, 128.8, 128.5, 128.4, 126.8, 87.8, 76.5, 62.7, 48.6, 47.4, 32.8, 25.5, 24.8, 24.7; IR (KBr): ν_{max} = 1956 (C═C═C), 1681 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{29}N_2O_2$ $[M + H]^+$ 389.2252, found 389.2261.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(cyclohexylamino)-1-(3-nitrophenyl)-2-oxoethyl)benzamide (6h).** Pale yellow solid, mp. 148–149 °C, yield 87%, R_f = 0.37 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (brs, 1H, H–Ar), 8.21 (d, *J* = 8.2 Hz, 1H, H–Ar), 7.90–7.80 (m, 1H, H–Ar), 7.58 (t, *J* = 8.0 Hz, 1H, H–Ar), 7.51–7.44 (m, 5H, H–Ar), 6.68 (brs, 1H, C(sp^3)–H), 5.90 (brs, 1H, NH), 4.93 (brs, 1H, allenic H), 4.71–4.62 (m, 2H, allenic H), 4.05 (brs, 2H, –CH_2–N), 3.92–3.86 (m, 1H, H–cyclohexyl), 1.99–1.93 (m, 2H, H–cyclohexyl), 1.74–1.69 (m, 2H, H–cyclohexyl), 1.64–1.61 (m, 1H, H–cyclohexyl), 1.44–1.36 (m, 2H, H–cyclohexyl), 1.24–1.15 (m, 3H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.7, 173.2, 167.5, 148.4, 137.5, 135.4, 134.9, 130.4, 129.6, 128.7, 126.8, 124.0, 123.2, 87.4, 77.4, 62.8, 48.7, 47.0, 32.8, 32.7, 25.5, 24.7. IR (KBr): ν_{max} = 1965 (C═C═C), 1666 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{28}N_3O_4$ $[M + H]^+$ 434.2100, found 434.2110.

***N*-(1-(2-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(buta-2,3-dien-1-yl)-4-methylbenzamide (6i).** Colorless solid, mp. 143–145 °C, yield 82%, R_f = 0.34 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71–7.63 (m, 2H, H–Ar), 7.41 (d, *J* = 7.9 Hz, 2H, H–Ar), 7.36 (t, *J* = 7.5 Hz, 1H, H–Ar), 7.24 (t, *J* = 7.8 Hz, 1H, H–Ar), 7.20 (d, *J* = 7.9 Hz, 2H, H–Ar), 6.07–5.92 (m, 2H, C(sp^3)–H, NH), 4.84 (brs, 1H, allenic H), 4.53–4.4 (m, 2H, allenic H), 3.97–3.89 (m, 3H, –CH_2–N, H–cyclohexyl), 2.38 (s, 3H, –CH_3), 2.01–1.95 (m, 2H, H–cyclohexyl), 1.72–1.61 (m, 3H, H–cyclohexyl), 1.43–1.36 (m, 2H, H–cyclohexyl), 1.23–1.12 (m, 3H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.3, 172.9, 168.3, 139.9, 134.6, 133.4, 133.2, 131.4, 130.2, 128.9, 127.8, 127.1, 126.4, 87.5, 76.1, 62.7, 48.7, 32.8, 25.5, 24.8, 24.8, 21.4; IR (KBr): ν_{max} = 1957 (C═C═C), 1672 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{30}{}^{79}BrN_2O_2$ $[M + H]^+$ 481.1321, found 481.1309.

***N*-(1-(2-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(buta-2,3-dien-1-yl)-3-chlorobenzamide (6j).** Colorless solid, mp. 158–160 °C, yield 79%, R_f = 0.38 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of two rotamers (70 : 30)) δ 7.66 (brs, 2H, H–Ar, mixture of two rotamers), 7.49 (s, 1H, H–Ar, mixture of two rotamers), 7.42–7.32 (m, 5H, H–Ar, mixture of two rotamers), 6.16 (brs, 1H, C(sp^3)–H, major rotamer), 5.85 (brs, 1H, NH, major rotamer), 5.66 (s, 1H, C(sp^3)–H, minor rotamer), 5.35 (brs, 1H, N–H, minor rotamer), 5.16 (brs, 1H, allenic H, minor rotamer), 4.71 (brs, 1H, allenic H, major rotamer), 4.53–4.42 (m, 2H, allenic H, mixture of two rotamers), 3.95–3.79 (m, 3H, –CH_2–N, N–CH–cyclohexyl,

mixture of two rotamers), 1.99–1.93 (m, 2H, CH–cyclohexyl, mixture of two rotamers), 1.74–1.60 (m, 3H, CH–cyclohexyl, mixture of two rotamers), 1.43–1.34 (m, 2H, CH–cyclohexyl, mixture of two rotamers), 1.20–1.07 (m, 3H, CH–cyclohexyl, mixture of two rotamers); 1H NMR (300 MHz, chloroform-*d* at 55 °C) δ 7.72–7.58 (m, 2H, H–Ar), 7.51–7.44 (m, 1H, H–Ar), 7.39–7.18 (m, 5H, H–Ar), 5.92 (brs, 1H, C(sp^3)–H), 5.65 (brs, 1H, NH), 4.85 (brs, 1H, allenic H), 4.61–4.36 (m, 2H, allenic H), 3.98–3.79 (m, 3H, $-CH_2-$N, N–CH–cyclohexyl), 2.05–1.90 (m, 2H, CH–cyclohexyl), 1.73–1.56 (m, 3H, CH–cyclohexyl), 1.44–1.30 (m, 2H, CH–cyclohexyl), 1.26–1.10 (m, 3H, CH–cyclohexyl), ^{13}C NMR (151 MHz, $CDCl_3$) (for the major rotamer) δ 208.3, 171.2, 167.9, 137.8, 134.3, 133.4, 131.3, 130.5, 129.8, 129.7, 127.9, 127.2, 126.5, 125.2, 125.1, 87.3, 76.2, 62.2, 48.8, 47.3, 32.8, 25.4, 24.8, 24.8; IR (KBr): ν_{max} = 1954 (C═C═C), 1688 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{27}{}^{79}Br^{35}ClN_2O_2$ $[M + H]^+$ 501.0857, found 501.0844.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-4-methylbenzamide (6k).** Colorless solid, mp. 149–150 °C, yield 82%, R_f = 0.32 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.8 Hz, 4H, H–Ar), 7.17 (d, J = 7.8 Hz, 2H, H–Ar), 6.86 (d, J = 8.2 Hz, 2H, H–Ar), 5.95–5.67 (m, 2H, C(sp^3)–H, N–H), 4.72 (brs, 1H, allenic H), 4.59–4.44 (m, 2H, allenic H), 3.97–3.87 (m, 2H, $-CH_2-$N), 3.82–3.80 (m, 1H, N–CH–cyclohexyl), 3.78, (s, 3H, O–CH_3), 2.34 (s, 3H, CH_3), 1.92–1.89 (m, 2H, CH–cyclohexyl), 1.66–1.64 (m, 2H, CH–cyclohexyl), 1.58–1.55 (m, 1H, CH–cyclohexyl), 1.37–1.30 (m, 2H, CH–cyclohexyl), 1.16–1.05 (m, 3H, CH–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 173.0, 168.8, 159.6, 139.8, 133.4, 130.9, 129.0, 127.1, 126.9, 114.1, 88.1, 76.5, 62.2, 55.3, 48.5, 47.2, 32.9, 25.5, 24.8, 24.8, 21.4; IR (KBr): ν_{max} = 1955 (C═C═C), 1643 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{27}H_{33}N_2O_3$ $[M + H]^+$ 433.2219, found 433.2207.

***N*-(Buta-2,3-dien-1-yl)-*N*-(2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)benzamide (6l).** Colorless solid, mp. 145–147 °C, yield 80%, R_f = 0.36 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49–3.24157.44 (m, 2H, H–Ar), 7.44–7.35 (m, 5H, H–Ar), 7.20–7.19 (m, 2H, H–Ar), 5.91 (brs, 2H, C(sp^3)–H, N–H), 4.74 (brs, 1H, allenic H), 4.51 (brs, 2H, allenic H), 3.97–3.87 (m, 3H, $-CH_2-$N, CH–cyclohexyl), 2.37 (s, 3H, CH_3), 1.98–1.94 (m, 2H, CH–cyclohexyl), 1.72–1.68 (m, 3H, CH–cyclohexyl), 1.42–1.35 (m, 2H, CH–cyclohexyl), 1.22–1.09 (m, 3H, CH–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 172.3, 168.7, 138.4, 136.3, 132.0, 130.2, 129.7, 129.5, 128.4, 126.8, 87.9, 76.4, 62.5, 48.6, 47.3, 32.9, 25.5, 24.8, 24.8, 21.2; IR (KBr): ν_{max} = 1961 (C═C═C), 1683 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{31}N_2O_2$ $[M + H]^+$ 403.2406, found 403.2415.

***N*-(1-(3-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(buta-2,3-dien-1-yl)-3-methoxybenzamide (6m).** Colorless solid, mp. 154–155 °C, yield 83%, R_f = 0.39 (*n*-hexane/EtOAc 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2H, H–Ar), 7.37–7.28 (m, 3H, H–Ar), 7.01 (dt, J = 7.5, 1.2 Hz, 1H, H–Ar), 6.98–6.94 (m, 2H, H–Ar), 6.20 (s, 1H, C(sp^3)–H), 5.83 (s, 1H, N–H), 4.78 (brs, 1H, allenic H), 4.57–4.55 (m 2H, allenic H), 3.98–3.97 (m, 2H, $-CH_2-$N), 3.85–3.82 (m, N–CH–cyclohexyl), 3.81 (s, 3H, O–CH_3), 1.93–1.88 (m, 2H, CH–cyclohexyl), 1.67–1.58 (m, 2H, CH–cyclohexyl), 1.40–1.31 (m, 2H, CH–cyclohexyl), 1.26 (t, J = 6.6 Hz, 1H, CH–cyclohexyl), 1.16–1.07 (m, 3H, CH–cyclohexyl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 172.7, 168.0, 159.5, 137.1, 134.3, 131.9, 131.1, 129.7, 128.8, 122.7, 119.0, 118.9, 115.9, 112.1, 87.9, 76.8, 62.2, 55.4, 48.6, 47.4, 32.8, 25.4, 24.8, 24.7; IR (KBr): ν_{max} = 1956 (C═C═C), 1683 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{30}{}^{79}BrN_2O_3$ $[M + H]^+$ 497.1471, found 497.1482.

General procedure for the synthesis of 3-pyrroline (7a–m) through 5-*exo*-dig cyclization

In a round-bottom flask, to a solution of the allenic-Ugi adduct (1.0 mmol) in DMF (2.0 mL) was added *t*-BuOK (1.2 mmol) and stirred for 6 h at room temperature. The progress of the reaction was monitored using TLC. After completion of the reaction, the reaction mixture was washed with water and extracted with EtOAc (3 × 5 mL). The organic phase was washed with saturated brine and dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Purification of the residue was accomplished by column chromatography (*n*-hexane/OAcEt 4 : 1) to afford the 3-pyrroline. Yields (86–96%).

1-Benzoyl-*N*-(*tert*-butyl)-3-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7a). Colorless solid, mp. 141–142 °C, yield 94%, R_f = 0.32 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H, NH), 7.44–7.27 (m, 10H, H–Ar), 5.49 (q, J = 1.9 Hz, 1H, ═CH), 4.49 (dt, J = 14.4, 2.1 Hz, 1H, CH_2-N), 4.20 (dt, J = 14.5, 2.1 Hz, 1H, CH_2-N), 1.63 (d, J = 1.9 Hz, 3H, CH_3), 1.42 (s, 9H, H-*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 169.6, 142.2, 138.5, 137.3, 129.7, 128.6, 128.2, 127.5, 126.2, 125.8, 118.4, 82.6, 57.0, 51.2, 28.7, 14.3.; IR (KBr): ν_{max} = 1694 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{27}N_2O_2$ $[M + H]^+$ 363.2152, found 363.2160.

1-Benzoyl-*N*-(*tert*-butyl)-3-methyl-2-(3-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7b). Pale yellow solid, mp. 125–126 °C, yield 92%, R_f = 0.32 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H, NH), 8.19 (d, J = 2.5 Hz, 1H, H–Ar), 7.77 (d, J = 7.9 Hz, 1H, H–Ar), 7.70 (s, 1H, H–Ar), 7.59 (t, J = 7.9 Hz, 1H, H–Ar), 7.48–7.45 (m, 3H, H–Ar), 7.42–7.41 (m, 2H, H–Ar), 5.63 (s, 1H, ═CH), 4.42 (d, J = 14.2 Hz, 1H, CH_2-N), 4.31 (d, J = 14.2 Hz, 1H, CH_2-N), 1.66 (s, 3H, CH_3), 1.43 (s, 9H, H-*t*Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 168.4, 148.3, 141.1, 140.7, 136.4, 133.0, 130.2, 129.1, 128.8, 125.8, 122.6, 121.6, 120.1, 81.6, 56.8, 51.6, 28.6, 14.1; IR (KBr): ν_{max} = 1682 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{26}N_3O_4$ $[M + H]^+$ 408.2008, found 408.2017.

***N*-(*tert*-Butyl)-1-(3-chlorobenzoyl)-2-(2-chlorophenyl)-3-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7c).** Colorless solid, mp. 127–128 °C, yield 95%, R_f = 0.35 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H, NH), 7.48 (d, J = 7.8 Hz, 1H, H–Ar), 7.44–7.42 (m, 2H, H–Ar), 7.41–7.40 (m, 1H, H–Ar), 7.38–7.37 (m, 1H, H–Ar), 7.36–7.33 (m, 2H, H–Ar), 7.32–7.30 (m, 1H, H–Ar), 5.59 (d, J = 2.1, 1H, ═CH), 4.39 (dt, J = 14.3, 2.3 Hz, 1H, CH_2-N), 4.10 (dt, J = 14.2, 2.3 Hz, 1H, CH_2-N), 1.60 (d, J = 2.1, 3H, CH_3), 1.43 (s, 9H, H-*t*Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 169.3, 145.5, 138.4, 134.6, 133.6, 131.8, 131.7,

130.0, 129.9, 129.0, 126.8, 126.4, 124.4, 124.3, 120.3, 82.3, 56.7, 51.3, 29.7, 28.7; IR (KBr): ν_{max} = 1687 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{25}{}^{35}Cl_2N_2O_2$ $[M + H]^+$ 431.1329, found 431.1339.

***N*-(*tert*-Butyl)-2-(2-chlorophenyl)-1-(4-methoxybenzoyl)-3-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7d).** Colorless solid, mp. 135–137 °C, yield 95%, R_f = 0.37 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H, NH), 7.47 (dd, *J* = 7.9, 1.5 Hz, 1H, H–Ar), 7.44 (d, *J* = 8.4 Hz, 2H, H–Ar), 7.37 (dd, *J* = 7.8, 1.3 Hz, 1H, H–Ar), 7.33 (t, *J* = 7.5 Hz, 1H, H–Ar), 7.28–7.25 (m, 1H, H–Ar), 6.93 (d, *J* = 8.4 Hz, 2H, H–Ar), 5.58 (brs, 1H, ═CH), 4.44 (d, *J* = 14.5 Hz, 1H, CH_2–N), 4.14 (d, *J* = 14.4 Hz, 1H, CH_2–N), 3.85 (s, 3H, O–CH_3), 1.59 (brs, 3H, CH_3), 1.41 (s, 9H, H-*t*Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 170.6, 160.7, 137.2, 134.1, 131.8, 131.6, 129.8, 129.1, 128.8, 128.2, 126.7, 120.6, 113.7, 82.3, 56.8, 55.4, 51.2, 28.7 (*t*-Bu and CH_3 overlapped); IR (KBr): ν_{max} = 1678 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{28}{}^{35}ClN_2O_3$ $[M + H]^+$ 427.2013, found 427.2023.

1-Benzoyl-2-(2-chlorophenyl)-*N*-cyclohexyl-3-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7e). Colorless solid, mp. 137–140 °C, yield 91%, R_f = 0.37 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H, NH), 7.46–7.45 (m, 2H, H–Ar), 7.44–7.42 (m, 3H, H–Ar), 7.39 (d, *J* = 7.8 Hz, 1H, H–Ar), 7.32 (t, *J* = 7.5 Hz, 1H, H–Ar), 7.28 (d, *J* = 7.6 Hz, 1H, H–Ar), 5.58 (brs, 1H, ═CH), 4.37 (d, *J* = 14.4 Hz, 1H, CH_2–N), 4.10 (d, *J* = 14.4 Hz, 1H, CH_2–N), 3.95–3.89 (m, 1H, H–cyclohexyl), 2.03–1.97 (m, 1H, H–cyclohexyl), 1.92–1.87 (m, 1H, H–cyclohexyl), 1.72–1.64 (m, 2H, H–cyclohexyl), 1.61 (brs, 3H, CH_3), 1.57–1.54 (m, 1H, H–cyclohexyl), 1.45–1.35 (m, 3H, H–cyclohexyl), 1.31–1.18 (m, 2H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.7, 137.3, 136.9, 133.8, 131.8, 131.6, 129.9, 129.7, 128.9, 128.5, 126.7, 126.2, 120.4, 81.6, 56.8, 48.2, 32.6, 32.2, 25.6, 24.4, 14.5; IR (KBr): ν_{max} = 1668 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{28}{}^{35}ClN_2O_2$ $[M + H]^+$ 423.2067, found 423.2077.

1-(3-Chlorobenzoyl)-2-(2-chlorophenyl)-*N*-cyclohexyl-3-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7f). Colorless solid, mp. 145–147 °C, yield 93%, R_f = 0.36 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.0 Hz, 1H, NH), 7.44 (s, 1H, H–Ar), 7.42 (d, *J* = 8.8 Hz, 2H, H–Ar), 7.41–7.38 (m, 1H, H–Ar), 7.36–7.32 (m, 3H, H–Ar), 7.31.7.21 (m, 1H, H–Ar), 5.58 (brs, 1H, ═CH), 4.37 (d, *J* = 14.3, 1H, CH_2–N), 4.11 (d, *J* = 14.3, 1H, CH_2–N), 3.94–3.88 (m, 1H, H–cyclohexyl), 2.02–1.99 (m, 1H, H–cyclohexyl), 1.90–1.86 (m, 1H, H–cyclohexyl), 1.72–1.64 (m, 2H, H–cyclohexyl), 1.61 (brs, 3H, CH_3), 1.58–1.54 (m, 1H, H–cyclohexyl), 1.45–1.38 (m, 2H, H–cyclohexyl), 1.37–1.31 (m, 1H, H–cyclohexyl), 1.27–1.20 (m, 2H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 169.4, 138.3, 137.3, 134.6, 133.4, 131.7, 131.7, 130.1, 130.0, 129.9, 129.1, 126.8, 126.4, 124.3, 120.3, 81.7, 56.8, 48.2, 32.6, 32.2, 25.5, 24.4, 14.5; IR (KBr): ν_{max} = 1669 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{27}{}^{35}Cl_2N_2O_2$ $[M + H]^+$ 457.1481, found 457.1492.

1-Benzoyl-*N*-cyclohexyl-3-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7g). Colorless solid, mp. 140–141 °C, yield 90%, R_f = 0.34 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.1 Hz, 1H, NH), 7.45–7.43 (m, 3H, H–Ar), 7.43–7.41 (m, 2H, H–Ar), 7.40–7.38 (m, 2H, H–Ar), 7.34–7.32 (m, 3H, H–Ar), 5.51 (brs, 1H, ═CH), 4.38 (d, *J* = 14.6, 1H, CH_2–N), 4.23 (d, *J* = 14.7, 1H, CH_2–N), 3.96–3.88 (m, 1H, H–cyclohexyl), 2.03–2.00 (m, 1H, H–cyclohexyl), 1.92–1.8 (m, 1H, H–cyclohexyl), 1.72–1.67 (m, 1H, H–cyclohexyl), 1.65 (brs, 3H, CH_3), 1.59–155 (m, 1H, H–cyclohexyl), 1.43–1.37 (m, 2H, H–cyclohexyl), 1.34–1.30 (m, 1H, H–cyclohexyl), 1.27–1.17 (m, 3H, H–cyclohexyl); ^{13}C NMR (75 MHz, CDCl3) δ 170.2, 169.6, 142.1, 138.4, 137.3, 129.7, 128.6, 128.2, 127.5, 126.2, 125.8, 118.4, 82.1, 56.9, 48.3, 32.6, 32.5, 29.7, 25.6, 24.5; IR (KBr): ν_{max} = 1691 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{29}N_2O_2$ $[M + H]^+$ 389.2288, found 389.2297.

1-Benzoyl-*N*-cyclohexyl-3-methyl-2-(3-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7h). Pale yellow solid, mp. 132–135 °C, yield 92%, R_f = 0.38 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H, H–Ar), 8.18 (d, *J* = 6.1 Hz, 1H, NH), 7.74 (d, *J* = 7.6 Hz, 2H, H–Ar), 7.57 (t, *J* = 7.6 Hz, 1H, H–Ar), 7.47–7.45 (m, 3H, H–Ar), 7.41–7.39 (m, 2H, H–Ar), 5.62 (q, *J* = 2.2 Hz, 1H, ═CH), 4.41 (dt, *J* = 14.7, 2.2 Hz, 1H), 4.31 (dt, *J* = 14.7, 2.2 Hz, 1H), 3.96–3.87 (m, 1H, H–cyclohexyl), 2.04–1.99 (m, 1H, H–cyclohexyl), 1.91–1.85 (m, 1H, H–cyclohexyl), 1.72–1.69 (m, 1H, H–cyclohexyl), 1.65 (d, *j* = 2.2 Hz, 3H, CH_3), 1.59–1.54 (m, 1H, H–cyclohexyl), 1.47–1.37 (m, 2H, H–cyclohexyl), 1.35–1.27 (m, 2H, H–cyclohexyl), 1.26–1.15 (m, 2H, H–cyclohexyl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 168.4, 148.3, 140.9, 140.6, 136.3, 132.9, 130.2, 129.1, 128.8, 125.8, 122.6, 121.5, 120.1, 81.1, 56.8, 48.4, 32.5, 30.1, 25.5, 24.5, 14.1; IR (KBr): ν_{max} = 1683 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{28}N_3O_4$ $[M + H]^+$ 434.2080, found 434.2085.

2-(2-Bromophenyl)-*N*-cyclohexyl-3-methyl-1-(4-methylbenzoyl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7i). Colorless solid, mp. 142–144 °C, yield 93%, R_f = 0.37 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 1H, NH), 7.62 (d, *J* = 7.9 Hz, 1H, H–Ar), 7.45 (d, *J* = 7.8 Hz, 1H, H–Ar), 7.40 (d, *J* = 7.8 Hz, 2H, H–Ar), 7.36 (t, *J* = 7.6 Hz, 1H, H–Ar), 7.23 (d, *J* = 7.8 Hz, 2H, H–Ar), 7.19 (t, *J* = 7.6 Hz, 1H, H–Ar), 5.59 (brs, 1H, ═CH), 4.44 (d, *J* = 14.4 Hz, 1H, CH_2–N), 4.16 (d, *J* = 14.4 Hz, 1H, CH_2–N), 3.94–3.88 (m, 1H, H–cyclohexyl), 2.40 (s, 3H, –CH_3), 2.01–1.98 (m, 1H, H–cyclohexyl), 1.88–1.85 (m, 1H, H–cyclohexyl), 1.70–1.63 (m, 3H, H–cyclohexyl), 1.58 (brs, 3H, CH_3–vinyl), 1.43–1.32 (m, 3H, H–cyclohexyl), 1.26–1.18 (m, 2H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0 (two carbonyl peaks), 139.9, 135.3, 134.9, 134.8, 133.8, 130.2, 129.1, 129.0, 127.3, 126.5, 126.4, 120.9, 82.4, 56.9, 48.2, 32.6, 32.2, 25.6, 24.5, 24.4, 21.4; IR (KBr): ν_{max} = 1673 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{30}{}^{79}BrN_2O_2$ $[M + H]^+$ 481.1203 found 481.1194.

2-(2-Bromophenyl)-1-(3-chlorobenzoyl)-*N*-cyclohexyl-3-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7j). Colorless solid, mp. 130–132 °C, yield 96%, R_f = 0.39 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H, NH), 7.63 (d, *J* = 7.9 Hz, 1H, H–Ar), 7.48–7.47 (m, 1H, H–Ar), 7.45 (d, *J* = 8.0 Hz, 1H, H–Ar), 7.44–7.42 (m, 1H, H–Ar), 7.39–7.36 (m, 3H, H–Ar), 7.21 (t, *J* = 7.6 Hz, 1H, H–Ar), 5.60 (brs, 1H, ═CH), 4.40 (d, *J* = 14.3 Hz, 1H, CH_2–N), 4.15 (d, *J* = 14.2 Hz, 1H, CH_2–N), 3.94–3.89 (m, 1H, H–cyclohexyl), 2.03–1.99 (m, 1H, H–cyclo-

hexyl), 1.90–1.86 (m, 1H, H–cyclohexyl), 1.72–1.65 (m, 3H, H–cyclohexyl), 1.59 (brs, 3H, CH_3), 1.45–1.29 (m, 3H, H–cyclohexyl), 1.27–1.18 (m, 2H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 169.3, 138.3, 137.2, 135.4, 134.5, 134.4, 130.3, 130.0, 129.9, 129.3, 127.4, 126.6, 124.4, 120.7, 120.4, 82.5, 56.9, 48.2, 32.7, 32.2, 25.5, 24.5, 14.5; IR (KBr): ν_{max} = 1670 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{27}{}^{79}Br^{35}ClN_2O_2$ $[M + H]^+$ 501.0689, found 501.0677.

***N*-Cyclohexyl-2-(4-methoxyphenyl)-3-methyl-1-(4-methylbenzoyl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7k).** Colorless solid, mp. 142–144 °C, yield 90%, R_f = 0.34 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 1H, NH), 7.31 (d, J = 7.8 Hz, 2H, H–Ar), 7.26 (d, J = 8.6 Hz, 2H, H–Ar), 7.22 (d, J = 7.9 Hz, 2H, H–Ar), 6.91 (d, J = 8.6 Hz, 2H, H–Ar), 5.50 (brs, 1H, ═CH), 4.35 (d, J = 14.5 Hz, 1H, CH_2–N), 4.23 (d, J = 14.4 Hz, 1H, CH_2–N), 3.93–3.90 (m, 1H, H–cyclohexyl), 3.83 (s, 3H, O–CH_3), 2.39 (s, 3H, CH_3), 2.01–1.98 (m, 1H, H–cyclohexyl), 1.91–1.88 (m, 1H, H–cyclohexyl), 1.72–1.68 (m, 2H, H–cyclohexyl), 1.65 (brs, 3H, CH_3), 1.58–1.55 (m, 1H, H–cyclohexyl), 1.42–1.35 (m, 2H, H–cyclohexyl), 1.29–1.17 (m, 3H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 169.8, 158.8, 142.0, 139.8, 134.5, 130.5, 129.1, 127.7, 126.0, 118.5, 113.6, 81.6, 56.8, 55.2, 48.3, 32.6, 29.7, 25.6, 24.6, 21.4, 14.3; IR (KBr): ν_{max} = 1673 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{27}H_{33}N_2O_3$ $[M + H]^+$ 433.2235, found 433.2223.

1-Benzoyl-*N*-cyclohexyl-3-methyl-2-(p-tolyl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide (7l). Colorless solid, mp. 141–142 °C, yield 91%, R_f = 0.34 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1 Hz, 1H, NH), 7.44–7.40 (m, 5H, H–Ar), 7.20 (d, J = 8.3 Hz, 2H, H–Ar), 7.22 (d, J = 8.3 Hz, 2H, H–Ar), 5.49 (brs, 1H, ═CH), 4.36 (d, J = 14.6 Hz, 1H, CH_2–N), 4.21 (d, J = 14.5 Hz, 1H, CH_2–N), 3.95–3.89 (m, 1H, H–cyclohexyl), 2.37 (s, 3H, CH_3), 2.03–1.98 (m, 1H, H–cyclohexyl), 1.94–1.88 (m, 1H, H–cyclohexyl), 1.75–1.67 (m, 2H, H–cyclohexyl), 1.65 (brs, 3H, CH_3), 1.60–1.54 (m, 1H, H–cyclohexyl), 1.45–1.35 (m, 2H, H–cyclohexyl), 1.33–1.17 (m, 3H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 169.8, 142.1, 137.3, 137.2, 135.4, 129.7, 129.0, 128.6, 126.2, 125.9, 118.4, 81.9, 57.0, 48.3, 32.6, 32.5, 25.6, 24.6, 21.1, 14.4; IR (KBr): ν_{max} = 1672 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{31}N_2O_2$ $[M + H]^+$ 403.2174, found 403.2165.

2-(3-Bromophenyl)-*N*-cyclohexyl-1-(3-methoxybenzoyl)-3-methyl-2,5-dihydro-1*H*-pyrrole-2-carboxamide (3m). Colorless solid, mp. 139–141 °C, yield 86%, R_f = 0.37 (*n*-hexane/EtOAc 4 : 1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H, NH), 7.45 (d, J = 8.5 Hz, 1H, H–Ar), 7.44 (s, 1H, H–Ar), 7.36 (t, J = 7.9 Hz, 1H, H–Ar), 7.30–7.25 (m, 2H, H–Ar), 6.99 (t, J = 7.5 Hz, 2H, H–Ar), 6.91 (brs, 1H, H–Ar), 5.54 (brs, 1H, ═CH), 4.38 (d, J = 14.7 Hz, 1H, CH_2–N), 4.24 (d, J = 14.7 Hz, 1H, CH_2–N), 3.94–3.90 (m, 1H, H–cyclohexyl), 3.84 (s, 3H, O–CH_3), 2.01–1.98 (m, 1H, H–cyclohexyl), 1.90–1.86 (m, 1H, H–cyclohexyl), 1.73–1.68 (m, 1H, H–cyclohexyl), 1.65 (brs, 3H, CH_3), 1.58–1.55 (m, 1H, H–cyclohexyl), 1.45–1.33 (m, 3H, H–cyclohexyl), 1.31–1.21 (m, 3H, H–cyclohexyl); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.0, 168.9, 159.7, 141.5, 140.8, 138.0, 130.7, 129.9, 129.8, 129.4, 125.1, 122.5, 119.2, 117.9, 115.6, 111.5, 81.4, 56.9, 55.4, 48.3, 32.5, 32.5, 25.6, 2.5, 14.3; IR (KBr): ν_{max} = 1682 (C═O) cm^{-1}; HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{30}{}^{59}BrN_2O_3$ $[M + H]^+$ 497.1022, found 497.1014.

Computational details

The structures of transition states have been fully optimized at the B3LYP/6-31G(d)[19] level in the gas phase (at 298.15 K). For accurate comparison of anion (A and B) stability, optimized anion structures were calculated at the PCM (DMF)/B3LYP/6-31G(d) level. The compound **6g** was selected as a model to investigate the mechanism. Transition states (TS) were verified with an intrinsic reaction coordinate (IRC) and single imaginary frequency. The LUMO-CA was done through the Hirshfeld method with Multiwfn[20] (version 3.3.8). The other calculations were performed *via* the Gaussian 09 program.[21] The optimized structures were outlined with the CYLView software.[22] The orbital electronegativity was calculated based on related references using MarvinSketch 17.12.[23] Chemical hardness η and Local Fukui functions (electrophilicity index)[15c,24] were calculated based on the subsequent formulas:

$$\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO} \quad (1)$$

$$f_k{}^+ = q_K^N - q_K^{N+1} \quad (2)$$

Conflicts of interest

There are no conflicts to declare.

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