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ORIGINAL ARTICLE

Isocyanide-based consecutive Bargellini/Ugi reactions: an efficient method for the synthesis of pseudo-peptides containing three amide bonds

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Abstract

Isocyanide-based consecutive Bargellini/Ugi multicomponent reactions as a combinatorial strategy have been developed for the synthesis of new class of pseudo-peptides. Via Bargellini reaction 3-carboxamido-isobutyric acids are prepared using acetone, chloroform, sodium hydroxide, and isocyanides. Then, using Ugi multicomponent reaction strategy, pseudo-peptides containing three amide bonds are synthesized using the Bargellini reaction product, aldehydes, amines, and isocyanides. This is an efficient and eco-friendly approach for easy access to wide variety of structurally diverse, drug-like pseudo-peptides from cheap and readily available precursors in high yields.

Keywords Consecutive multicomponent reaction · Pseudo-peptide · Bargellini reaction · Ugi reaction · Isocyanide

Introduction

Peptides and proteins perform essential task in both unicellular and multicellular organisms and living without them would be impossible (Avan et al. 2014). Among them, short peptides are sorely significant bioactive compounds and exhibiting an extensive variety of biological activities. For example, glutathione operates as an antioxidant, detoxificant, and anti-aging agent. Other examples of short peptides are endomorphin-2 and tetrapeptide GE81112A, which act as natural inhibitor of stress and antibiotic, respectively (Fig. 1) (Jürjens et al. 2018; Vorobyeva et al. 2012).

Accordingly, drug discovery based on peptides is an extensively investigated area in biomedical research and peptides synthesis has been very much considered in organic chemistry (Comegna et al. 2015). The therapeutic utilization of peptides and proteins is limited by their short-time life, nonselective receptor binding and low absorption (Rabong et al. 2010). Amide bonds are typically provided from the reaction between carboxylic acids and amines; however, these reactions do not proceed spontaneously at ambient temperature because of formation the stable salts. The direct condensation of the salt can occur at high temperature (160–180 °C). For this reason, it is usually necessary to activate the carboxylic acid via a coupling reagent prior to treatment with the amine (Montalbetti and Falque 2005; Valeur and Bradley 2009). Therefore, the synthesis of peptides composes of difficult sequences, with a numerous residues, such as active pharmaceutical ingredients (Carbajo et al. 2019). To overcome the disadvantages mentioned, chemists explored efficient methods to design pseudo-peptides (peptidomimetics), which have better pharmacological properties and maintain the activities of original peptide (Khalesi et al. 2019; Nielsen 2004).

Isocyanide-based multicomponent reactions (I-MCRs) have already been proven as an extremely efficient strategy for the synthesis of pseudo-peptides. This highly convergent approach supplies conspicuous diversity and complexity (Chandgude and Dömling 2016). Therefore, invention of

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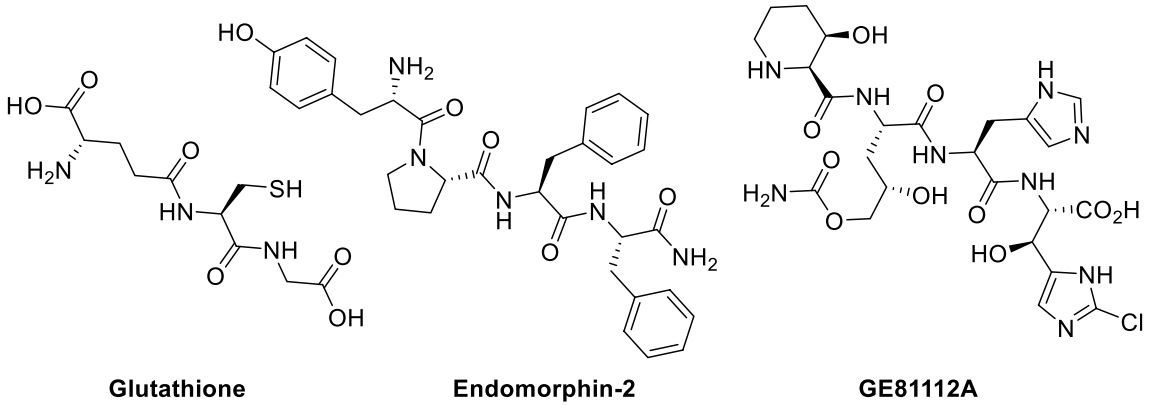


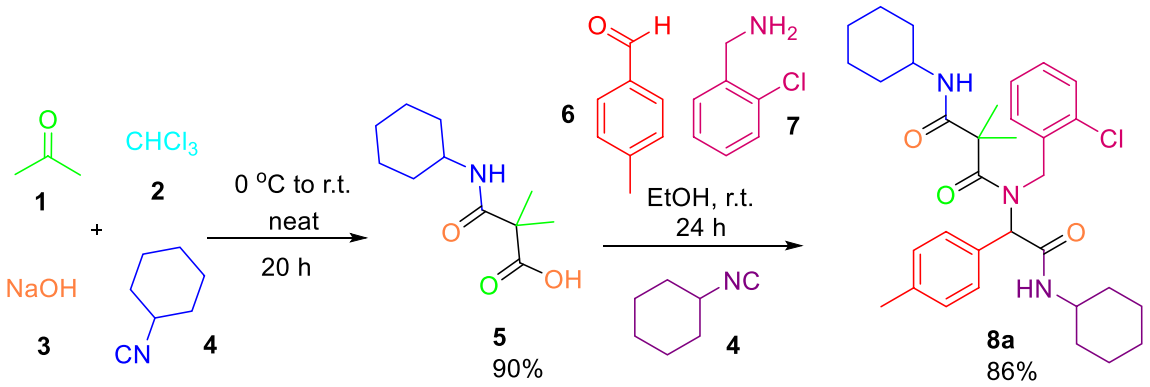
Fig. 1 Examples of some biologically active of short peptides

novel approach based on I-MCRs for the synthesis of peptidomimetics has been very much attended (Chandgude and Dömling 2017; Zakharova et al. 2019). The Ugi reaction is known as a potent method for the synthesis of the tripeptide scaffold and has found widespread applications in combinatorial synthesis (Mroczkiewicz and Ostaszewski 2009; Toure and Hall 2009). The Bargellini reaction is an efficient classic MCR in which phenol is reacted with acetone and chloroform in the presence of a strong base to produce α-phenoxyisobutyric acid (Butcher and Hurst 2009). Since the initial report, variants of nucleophiles have been investigated to increase complexity, functionality and diversity (Alanine et al. 2016; Mahdavi et al. 2012). Recently, Giustiniano et al. reported a successful replacement of phenols with isocyanides in the Bargellini reaction that afford 3-carboxamidoisobutyric acid (Giustiniano et al. 2016). In view of our interests in design of combinatorial I-MCRs, (Shaabani and Hooshmand 2018; Shaabani et al. 2014) herein, we report a novel method for the synthesis of new pseudo-peptides via isocyanide-based consecutive Bargellini/Ugi reactions.

Results and discussion

New pseudo-peptides containing three amide bonds as structurally interesting compounds were simply obtained in two steps. In the first step, isocyanide-based Bargellini reaction was used for the synthesis of 3-carboxamido-isobutyric acids. In the second step, the prepared acids were applied in Ugi reaction. In a pilot experiment, acetone (**1**), chloroform (**2**), sodium hydroxide (**3**) and cyclohexyl isocyanide (**4**) were mixed and stirred at 0 °C for 30 min and then at room temperature for 20 h to afford 3-(cyclohexylamino)-2,2-dimethyl-3-oxopropanoic acid (**5**). Then, the prepared acid (**5**), 4-methylbenzaldehyde (**6**), (2-chlorophenyl)methanamine (**7**), and cyclohexyl isocyanide (**4**) were mixed in EtOH and stirred at room temperature. After completion of the reaction (24 h), the desired product (**8a**) was isolated in 86% yield (Scheme 1).

The reactions did not need any optimization. To investigate the scope and limitations of this protocol, various primary amines, isocyanides, aliphatic and aromatic aldehydes containing electron-donating as well as electron-withdrawing



Scheme 1 Consecutive Bargellini/Ugi reactions for the synthesis of pseudo-peptide **8a**

groups were used (Scheme 2). As shown in Fig. 2, the reactions proceeded very efficiently at room temperature and led to formation of new class of the pseudo-peptides in high yields without using column chromatography. In this process, eight new bonds are formed, such as carbon–carbon, carbon–nitrogen, and carbon–oxygen in two steps, which is significant privilege of this synthetic protocol. It is noteworthy that all prepared compounds are racemates.

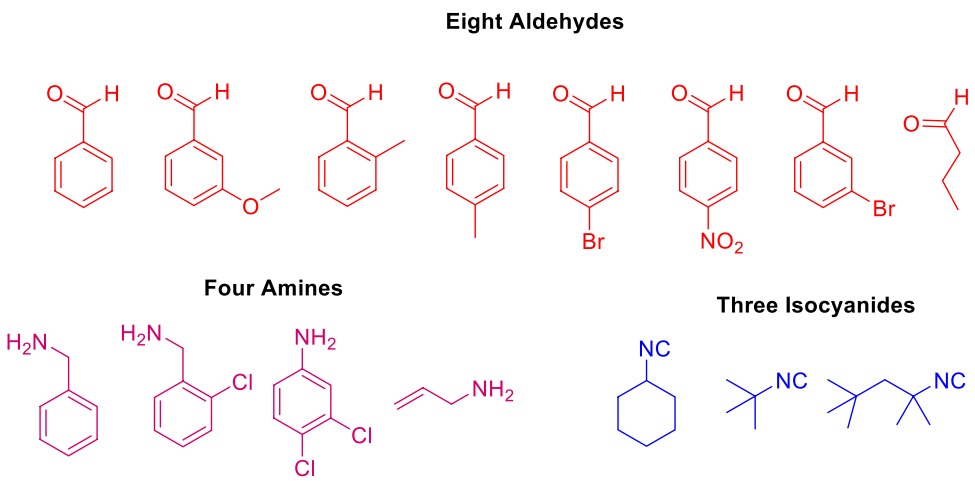
The structures of all products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and CHN analysis data. For example, compound **8b** is observed as a mixture of rotamers in its ^{1}H NMR spectrum due to amide rotation. This spectrum consisted of a multiple for N*H* groups ($\delta = 7.78$–7.60 ppm, 2H), a multiple for aromatic protons ($\delta = 7.26$–6.82 ppm, 10H), two singlets for two benzylic C*H* groups ($\delta = 5.51$ ppm, 0.4H and $\delta = 5.35$ ppm, 0.6H), a multiple for CH_2 of benzyl amine ($\delta = 4.55$–4.46 ppm, 1.4H), a doublet for CH_2 of benzyl amine ($\delta = 4.16$ ppm, $J = 17.3$ Hz, 0.6H), a multiple for the NH–C*H* of cyclohexyl rings ($\delta = 3.71$–3.41 ppm, 2H), and a multiple for the methylene protons of the cyclohexyl rings and methyl groups ($\delta = 1.85$–0.97 ppm, 26H). In addition, the ^{1}H decoupled ^{13}C NMR spectrum of compound **8b** indicated the presence of six amide carbonyls, which confirmed the existence of mixture of rotamers. The mass spectra of these compounds demonstrated molecular ion peaks at the appropriate *m*/*z* values. Finally, the structure of compound **8b** was verified unambiguously by single-crystal X-ray analysis (Fig. 3).

^{1}H NMR spectrum of some derivatives was indicated products as a mixture of rotamers. We decided to investigate the influence of temperature on compound **8a** using variable temperature ^{1}H NMR spectroscopy. The spectrum at 25 °C (Fig. 4, spectrum 1) shows two singlets for the benzylic C*H* group ($\delta = 5.57$ ppm and $\delta = 5.50$ ppm) and one doublet ($\delta = 4.64$ ppm, $J = 16.8$ Hz) and one multiple for CH_2 of benzyl ($\delta = 4.45$–4.34 ppm). Increasing the temperature causes broaden and coalescence of the C*H* and CH_2 resonances (Fig. 4, spectrums 2–7), and they appear as a singlet (C*H* group) and an AB quartet system (CH_2 group) at 80 °C (Fig. 4, spectrum 8). For more simplification, ^{1}H NMR spectrum of **8a** was provided in the presence of D_2O, due to assign the exchangeable N*H* groups (Fig. 4, spectrum 9).

A proposed mechanism for the formation of products is demonstrated in Scheme 3. In the Bargellini four-component reaction, sodium hydroxide abstracts a proton from chloroform (**2**) and generates a carbanion (**9**). The carbanion (**9**) attacks acetone (**1**) to form the unstable carbinol (**10**), which cyclizes to produce the 2,2-dichloro-3,3-dimethyloxirane intermediate (**11**). Then, an isocyanide (**12**) attacks the intermediate (**11**) to form nitrilium ion (**13**), which is intercepted by the hydroxide ion to generate the iminol (**14**) that tautomerizes to the more stable amide (**15**). Concomitantly, the acyl chloride (**15**) is transformed to the product (**16**) (Giustiniano et al. 2016). When the prepared acid is applied in Ugi four-component reaction, according to the commonly accepted Ugi mechanism, (Okandeji et al. 2008) the acid, amine and aldehyde participate in equilibrium with iminium carboxylates (**21**). The addition of the terminal C atom of the isocyanides (**21**) onto the iminium group followed by the addition of the carboxylate ion onto the C atom of the nitrillium ion leads to the formation of the adduct (**22**), which rearranges by Mumm rearrangement to afford the desired product (**8**) (Scheme 3).

Conclusion

In summary, we have introduced an efficient method for the synthesis of novel pseudo-peptides containing three amide bonds by combination of two isocyanide-based Bargellini and Ugi reactions. This approach is catalyst- and additive-free and has expeditious procedure and easy workup without using column chromatography, which



Scheme 2 Diversity of substrates for the synthesis of pseudo-peptides

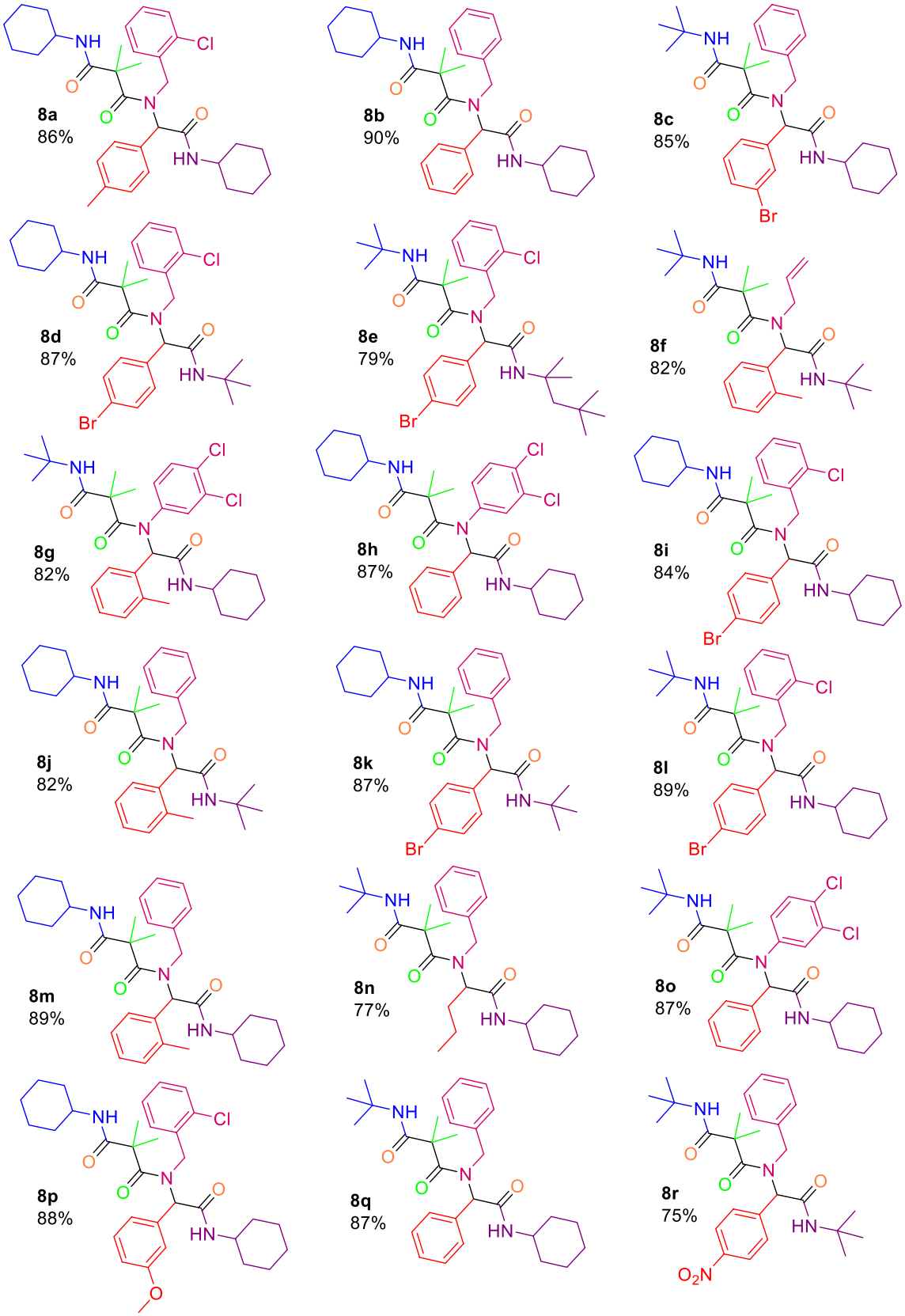
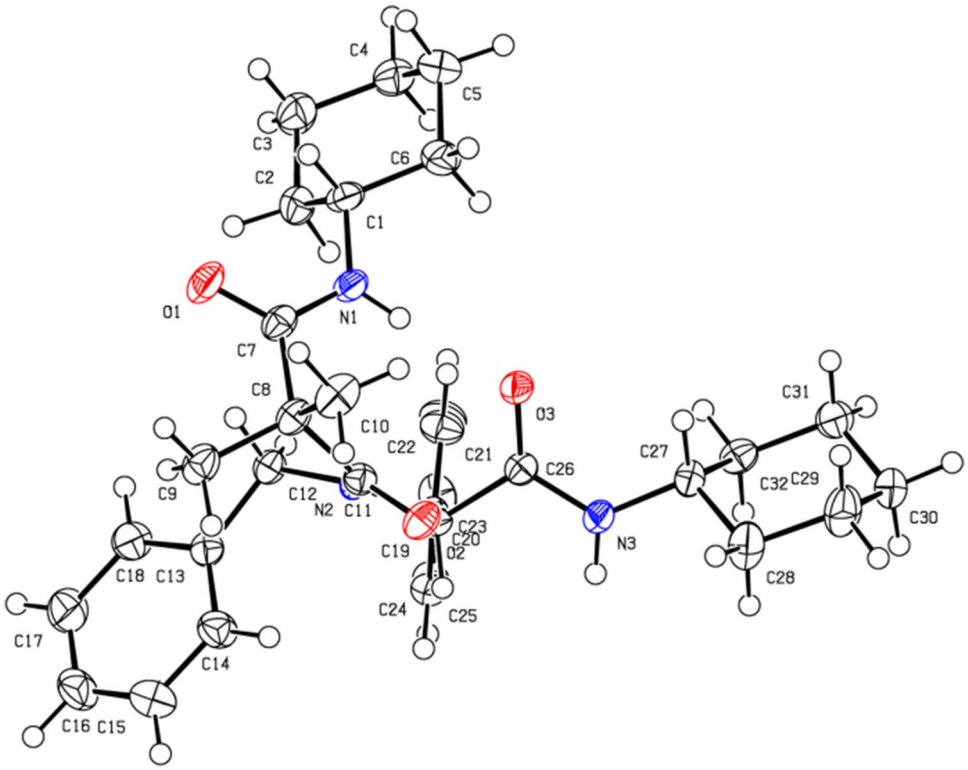


Fig. 2 Structure and isolated yields of the products **8**

Fig. 3 ORTEP diagram for **8b**



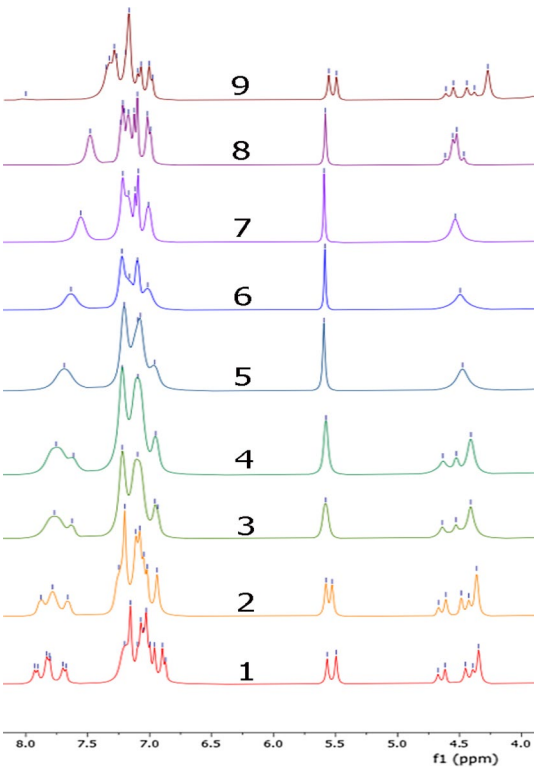


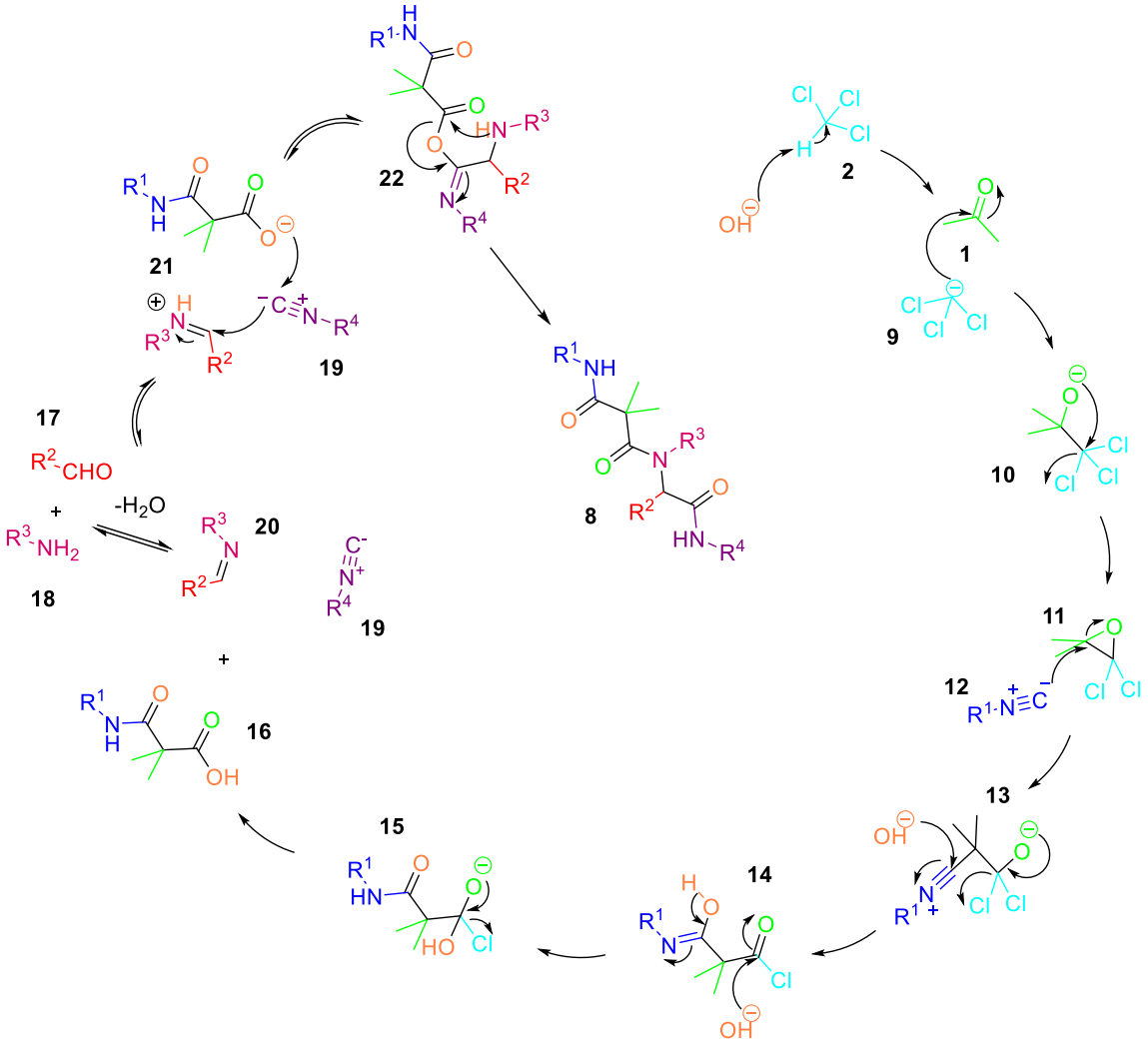
Fig. 4 Partial of DNMR spectra (25 °C-80 °C) of compound **8a** (DMSO-d_6, 300 MHz); spectrum 1: 25 °C, spectrum 2: 35 °C, spectrum 3: 40 °C, spectrum 4: 45 °C, spectrum 5: 50 °C, spectrum 6: 60 °C, spectrum 7: 70 °C, spectrum 8: 80 °C, spectrum 9: 25 °C and in the presence of D_2O

meets many green chemistry criteria. In this process, eight new bonds are formed in two steps, which is remarkable from synthetic point of view. The potential utilization of this method in synthetic and medicinal chemistry may be considerable.

Experimental section

General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were measured with an Electrothermal 9200 apparatus. IR spectra were recorded on a Thermo Nicolet NEXUS 470 FT-IR spectrometer in cm^{-1}. ^1H NMR spectra were recorded on a BRUKER AVANCE DRX-500 and DRX-300 spectrometer at 500 and 300 MHz. ^{13}C NMR spectra were recorded on BRUKER AVANCE DRX-500 and DRX-300 spectrometers at 125 and 75 MHz. NMR spectra were obtained in $CDCl_3$ and DMSO-d_6. Mass spectra of the products were obtained with an HP (Agilent technologies) 5973 Mass Selective Detector. Elemental analyses were performed on an elementar analysensysteme GmbH VarioEL CHNS mode.



Scheme 3 Possible mechanism for isocyanide-based consecutive Bargellini/Ugi reactions

General procedure for the synthesis of acid derivatives 5

In a round-bottom flask, acetone (5 mmol), chloroform (7.5 mmol), sodium hydroxide (7.5 mmol), and an isocyanide (1 mmol) were mixed and stirred at 0 °C for 30 min and then at ambient temperature overnight. The reaction mixture was diluted with water, which was acidified to pH 2 with 2 M HCl and extracted with EtOAc (three times). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the pure product (Giustiniano et al. 2016).

General procedure for the synthesis of pseudo-peptide derivatives 8

A solution of an acid derivative (1 mmol), an amine (1 mmol), an aldehyde (1 mmol) and an isocyanide (1 mmol) in EtOH (5 mL) was stirred at room temperature. The reaction progress was monitored by TLC. After 24 h, the solvent was evaporated and the residue was recrystallized in EtOAc to afford the pure product.

Characterization data of 8a–8r

***N*^{1}-(2-Chlorobenzyl)-*N*^{3}-cyclohexyl-*N*^{1}-(2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-2,2-dimethylmalonamide (8a)** White powders: 487 mg, 86% yield; mp 215–216 °C. IR (ATR) cm^{-1}: 3236, 3064, 2932, 2855, 1659, 1631, 1552. ^{1}H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 7.94–7.68 (m, 2H, NH), 7.21–6.96 (m, 7H, H_{Ar}), 6.89–6.87 (m, 1H, H_{Ar}), 5.57 (s, 0.6H, CH–N), 5.50 (s, 0.4H, CH–N), 4.64 (d, J = 16.8 Hz, 0.5H, CH_2–N), 4.45–4.34 (m, 1.5H, CH_2–N), 3.74–3.51 (m, 2H, HCN of cyclohexyl), 2.15 (s, 3H, H_{Me-Ar}) 1.82–1.54 (m, 10H, $H_{Aliphatic}$), 1.37–0.93 (m, 16H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of

rotamers) δ 175.13, 173.91, 173.25, 172.91, 169.94, 168.31, 137.79, 137.32, 135.78, 135.58, 133.53, 131.15, 130.93, 130.83, 130.56, 129.15, 128.98, 128.68, 128.43, 127.53, 126.98, 126.42, 64.43, 63.26, 50.22, 49.10, 48.80, 48.31, 47.77, 32.47, 27.47, 26.06, 25.67, 25.53, 25.26, 24.89, 23.99, 23.51, 20.99. MS *m/z*: 567 ($M^+ + 2$, 0.63), 565 (M^+, 1.55), 439 (12.89), 369 (13.71), 335 (38.05), 315 (34.45), 244 (100), 196 (32.03), 125 (41.59), 83 (59.43), 55 (44.73). Anal. Calcd for $C_{33}H_{44}ClN_3O_3$: C, 70.01; H, 7.83; N, 7.42; found C, 69.91; H, 7.99; N, 7.49.

N^1-Benzyl-N^3-cyclohexyl-N^1-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-2,2-dimethylmalonamide (**8b**) White powders: 466 mg, 90% yield; mp 210–212 °C. IR (ATR) cm^{-1}: 3282, 3062, 2926, 2850, 1659, 1626, 1557. ^1H NMR (500 MHz, DMSO-d_6): (mixture of rotamers) δ 7.78–7.60 (m, 2H, NH), 7.26–6.98 (m, 9H, H_{Ar}), 6.84–6.82 (m, 1H, H_{Ar}), 5.51 (s, 0.4H, CH–N), 5.35 (s, 0.6H, CH–N), 4.55–4.46 (5, 1.4H, CH_2–N), 4.16 (d, $J = 17.3$ Hz, 0.6H, CH_2–N), 3.41–3.71 (m, 2H, HCN of cyclohexyl), 1.85–1.74 (m, 6H, $H_{Aliphatic}$), 1.65–1.50 (m, 6H, $H_{Aliphatic}$), 1.38–0.97 (m, 14H, $H_{Aliphatic}$). ^{13}C NMR (125 MHz, DMSO-d_6): (mixture of rotamers) δ 173.92, 173.02, 172.08, 168.69, 167.04, 138.13, 137.14, 135.93, 133.83, 129.59, 128.08, 127.44, 127.33, 127.18, 126.95, 126.63, 126.07, 125.92, 125.66, 124.91, 64.08, 62.54, 49.48, 49.24, 48.52, 48.04, 47.73, 47.22, 31.52, 31.42, 31.22, 30.92, 26.17, 24.65, 24.48, 24.26, 23.87, 23.74, 23.03. MS *m/z*: 517 (M^+, 1.91), 391 (17.77), 321 (32.78), 301 (90.06), 196 (100), 91 (45.34), 55 (15.84). Anal. Calcd for $C_{32}H_{43}N_3O_3$: C, 74.24; H, 8.37; N, 8.12; found C, 74.16; H, 8.44; N, 8.19.

N^1-Benzyl-N^1-(1-(3-bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-N^3-(*tert*-butyl)-2,2-dimethylmalonamide (**8c**) White powders: 484 mg, 85% yield; mp 188–190 °C. IR (ATR) cm^{-1}: 3305, 3067, 2929, 2845, 1657, 1628, 1552. ^1H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 8.01–7.88 (m, 2H, NH), 7.31–7.22 (m, 1H, H_{Ar}), 7.21–7.03 (m, 7H, H_{Ar}), 6.87–6.84 (m, 2H, H_{Ar}), 5.42 (s, 0.2H, CH–N), 5.28 (s, 0.8H, CH–N), 4.76 (d, $J = 15.0$ Hz, 0.2H, CH_2–N), 4.50 (d, $J = 15.0$ Hz, 0.8H, CH_2–N), 4.27 (d, $J = 15.0$ Hz, 0.2H, CH_2–N), 4.18 (d, $J = 15.0$ Hz, 0.8H, CH_2–N), 3.53–3.47 (m, 1H, HCN of cyclohexyl), 1.74–1.49 (m, 5H, $H_{Aliphatic}$), 1.39–0.97 (m, 20H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (major of rotamers) δ 175.02, 173.48, 168.87, 137.70, 137.62, 133.89, 130.96, 130.02, 129.22, 128.42, 127.38, 126.93, 121.13, 64.27, 51.29, 50.88, 48.32, 32.41, 28.88, 28.67, 26.92, 25.66, 24.88, 24.77, 24.20. MS *m/z*: 572 ($M^+ + 2$, 3.10), 570 (M^+, 3.40), 497 (6.63), 471 (9.71), 379 (29.72), 301 (68.77), 274 (52.84), 196 (100), 91 (85.45), 57 (65.47). Anal. Calcd for $C_{30}H_{40}BrN_3O_3$: C, 63.15; H, 7.07; N, 7.36; found C, 63.03; H, 7.01; N, 7.44.

N^1-(1-(4-Bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-N^1-(2-chlorobenzyl)-N^3-cyclohexyl-2,2-dimethylmalonamide (**8d**) White powders: 525 mg, 87% yield; mp 198–199 °C. IR (ATR) cm^{-1}: 3335, 3241, 2929, 2847, 1669, 1628, 1549. ^1H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 7.83–7.62 (m, 2H, NH), 7.48–7.39 (m, 2H, H_{Ar}), 7.28–7.05 (m, 6H, H_{Ar}), 5.65 (s, 0.5H, CH–N), 5.41 (s, 0.5H, CH–N), 4.62–4.43 (m, 2H, CH_2–N), 3.75 (bs, 0.5H, HCN of cyclohexyl), 3.60–3.56 (m, 0.5H, HCN of cyclohexyl), 1.85–1.57 (m, 5H, $H_{Aliphatic}$), 1.40–1.12 (m, 20H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers) δ 175.06, 174.48, 173.57, 172.67, 169.84, 167.56, 136.26, 135.36, 135.20, 134.37, 132.57, 131.42, 131.12, 130.95, 129.32, 129.21, 129.06, 128.66, 127.88, 126.95, 126.62, 121.75, 121.32, 63.94, 63.55, 51.11, 50.41, 50.33, 49.14, 48.74, 48.09, 47.65, 32.64, 32.43, 32.34, 32.21, 28.60, 28.30, 27.26, 25.78, 25.53, 25.22, 24.73, 23.76. MS *m/z*: 607 ($M^+ + 4$, 0.34), 605 ($M^+ + 2$, 1.04), 603 (M^+, 0.80), 505 (6.97), 409 (10.12), 379 (28.74), 335 (51.47), 310 (63.44), 196 (100), 125 (66.17), 83 (62.33), 57 (81.90). Anal. Calcd for $C_{30}H_{39}BrClN_3O_3$: C, 59.56; H, 6.50; N, 6.95; found C, 59.70; H, 6.59; N, 6.82.

N^1-(1-(4-Bromophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)-N^3-(*tert*-butyl)-N^1-(2-chlorobenzyl)-2,2-dimethylmalonamide (**8e**) White powders: 501 mg, 79% yield; mp 78–81 oC. IR (ATR) cm^{-1}: 3299, 2965, 2863, 1664, 1636, 1534. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (bs, 1H, NH), 7.29–7.24 (m, 1H, H_{Ar}), 7.16 (d, $J = 7.8$ Hz, 1H), 7.10–7.04 (m, 3H, H_{Ar}), 6.99–6.98 (m, 3H, H_{Ar}), 5.33 (s, 1H, CH–N), 4.85 (bs, 1H, NH), 4.69–4.63 (m, 2H, CH_2–N), 1.73–1.26 (m, 23H, $H_{Aliphatic}$), 0.86 (s, 9H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.99, 172.87, 167.95, 133.79, 132.50, 132.09, 131.54, 129.29, 128.98, 128.42, 126.32, 122.78, 55.98, 52.69, 51.77, 50.85, 31.45, 31.35, 28.58, 28.53, 28.17, 25.48, 24.96. MS *m/z*: 637 ($M^+ + 4$, 0.53), 635 ($M^+ + 2$, 0.87), 633 (M^+, 0.44), 507 (5.86), 353 (22.85), 309 (43.99), 170 (48.42), 125 (31.33), 57 (100). Anal. Calcd for $C_{32}H_{45}BrClN_3O_3$: C, 60.52; H, 7.14; N, 6.62; found C, 60.72; H, 7.23; N, 6.50.

N^1-Allyl-N^3-(*tert*-butyl)-N^1-(2-(*tert*-butylamino)-2-oxo-1-(*o*-tolyl)ethyl)-2,2-dimethylmalonamide (**8f**) White powders: 352 mg, 82% yield; mp 200–202 °C. IR (ATR) cm^{-1}: 3312, 3271, 2972, 2934, 1669, 1628, 1549. ^1H NMR (300 MHz, DMSO-d_6): δ 7.66 (s, 1H, NH), 7.25–7.11 (m, 4H, H_{Ar}), 6.68 (s, 1H, NH), 5.90 (s, 1H, CH–N), 5.22–5.07 (m, 1H, H_{Alkene}), 4.46–4.33 (m, 2H, H_{Alkene}), 3.79–3.63 (m, 2H, CH_2–N), 2.23 (s, 3H, $H_{Me–Ar}$), 1.36–1.27 (m, 24H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.41, 173.23, 170.49, 139.35, 135.23, 134.95, 130.20, 130.00, 128.56, 126.13, 115.04, 60.32, 51.27, 51.21, 50.97, 50.81, 49.30, 28.95, 28.83, 28.54, 27.54, 23.54, 19.37. MS *m/z*: 429 (M^+, 2.46), 357 (7.40), 329 (13.25), 289 (19.62), 259 (22.03), 160 (100), 57 (75.61). Anal. Calcd for $C_{25}H_{39}N_3O_3$: C, 69.90; H, 9.15; N, 9.78; found C, 69.75; H, 9.25; N, 9.62.

***N*^{1}-(*tert*-Butyl)-*N*^{3}-(2-(cyclohexylamino)-2-oxo-1-(*o*-tolyl)ethyl)-*N*^{3}-(3,4-dichlorophenyl)-2,2-dimethylmalonamide** (**8g**) White powders: 459 mg, 82% yield; mp 155–157 °C. IR (ATR) cm^{-1}: 3338, 3092, 3934, 2850, 1634, 1526. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17–7.93 (m, 2H, NH), 7.48–6.99 (m, 3H, H_{Ar}), 6.82 (bs, 1H, H_{Ar}), 6.64–6.55 (m, 2H, H_{Ar}), 6.20–6.28 (m, 1H, H_{Ar}), 6.19 (s, 1H, CH–N), 3.62 (bs, 1H, HCN of cyclohexyl), 2.39 (s, 3H, $H_{Me–Ar}$), 1.80–0.96 (m, 25H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.25, 172.63, 169.81, 138.96, 138.32, 134.85, 134.01, 133.71, 132.02, 130.83, 130.22, 129.79, 129.52, 128.45, 125.76, 62.49, 52.13, 51.14, 48.53, 32.68, 28.69, 26.10, 25.66, 25.15, 24.98, 24.61, 19.46. MS *m/z*: 563 (M^+ +4, 2.90), 561 (M^+ +2, 7.90), 559 (M^+, 6.97), 390 (14.68), 264 (90.45), 170 (100), 143 (40.18), 114 (18.16), 83 (23.05), 57 (98.60). Anal. Calcd for $C_{30}H_{39}Cl_2N_3O_3$: C, 64.28; H, 7.01; N, 7.50; found C, 64.19; H, 7.14; N, 7.39.

***N*^{1}-Cyclohexyl-*N*^{3}-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-*N*^{3}-(3,4-dichlorophenyl)-2,2-dimethylmalonamide** (**8h**) White powders: 497 mg, 87% yield; mp 135–137 °C. IR (ATR) cm^{-1}: 3305, 3069, 2926, 2852, 1659, 1626, 1536. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04 (bs, 2H, NH), 7.47 (bs, 1H, H_{Ar}), 7.17–7.13 (m, 3H, H_{Ar}), 6.97–6.89 (m, 3H, H_{Ar}), 6.68–6.55 (m, 1H, H_{Ar}), 6.00 (s, 1H, CH–N), 3.61–3.58 (m, 1H, HCN of cyclohexyl), 3.18–3.16 (m, 1H, HCN of cyclohexyl), 1.78–1.52 (m, 10H, $H_{Aliphatic}$), 1.30–0.95 (m, 16H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.83, 172.42, 169.07, 138.28, 135.54, 134.18, 130.84, 130.67, 129.26, 128.35, 65.54, 51.01, 49.06, 48.76, 48.41, 32.70, 32.59, 32.22, 32.07, 25.68, 25.25, 24.94. MS *m/z*: 524 (M^+—47, 0.41), 507 (10.97), 434 (48.18), 406 (30.75), 301 (38.08), 210 (100), 196 (37.00), 91 (44.55), 57 (34.57). Anal. Calcd for $C_{31}H_{39}Cl_2N_3O_3$: C, 65.03; H, 6.87; N, 7.34; found C, 65.17; H, 6.97; N, 7.19.

***N*^{1}-(1-(4-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*^{1}-(2-chlorobenzyl)-*N*^{3}-cyclohexyl-2,2-dimethylmalonamide** (**8i**) White powders: 529 mg, 84% yield; mp 217–218 °C. IR (ATR) cm^{-1}: 3243, 3067, 2926, 2845, 1662, 1626, 1544. ^{1}H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 8.00 (m, 1H, NH), 7.72 (m, 1H, NH), 7.38–7.05 (m, 8H, H_{Ar}), 5.61 (s, 0.4H, CH–N), 5.48 (s, 0.6H, CH–N), 4.71–4.65 (m, 0.3H, CH_2–N), 4.42–4.39 (m, 1.7H, CH_2–N), 3.71–3.52 (bs, 2H, HCN of cyclohexyl), 1.96–1.72 (m, 6H, $H_{Aliphatic}$), 1.53–1.13 (m, 20H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers) δ 174.96, 173.88, 173.30, 172.83, 169.13, 167.79, 135.84, 135.51, 135.12, 132.57, 131.55, 131.31, 131.02, 130.92, 129.12, 128.77, 128.50, 127.67, 126.46, 121.84, 121.49, 63.82, 62.94, 50.32, 50.22, 49.12, 47.96, 32.41, 26.95, 26.29, 25.64, 25.50, 25.26, 24.89, 23.87, 23.67. MS *m/z*: 633 (M^+ +4, 0.84), 631 (M^+ +2, 2.04), 629 (M^+, 1.41), 505 (8.10), 435 (13.78), 379 (24.87), 335 (64.59), 310 (54.18), 196 (100), 125 (63.27), 83 (94.34), 55 (80.46). Anal. Calcd for $C_{32}H_{41}BrClN_3O_3$: C, 60.91; H, 6.55; N, 6.66; found C, 60.69; H, 6.72; N, 6.76.

***N*^{1}-Benzyl-*N*^{1}-(2-(*tert*-butylamino)-2-oxo-1-(*o*-tolyl)ethyl)-*N*^{3}-cyclohexyl-2,2-dimethylmalonamide** (**8j**) White powders: 415 mg, 82% yield; mp 196–198 °C. IR (ATR) cm^{-1}: 3335, 3302, 2932, 2857, 1687, 1623, 1526. ^{1}H NMR (300 MHz, DMSO-d_6) δ: ^{1}H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 8.14–8.11 (m, 1H, NH), 7.84–7.82 (m, 1H, NH), 7.40 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.30–7.14 (m, 4H, H_{Ar}), 7.07–6.90 (m, 3H, H_{Ar}), 6.76–6.64 (m, 1H, H_{Ar}), 5.76 (s, 0.4H, CH–N), 5.34 (d, J = 17.0 Hz, 0.6H, CH_2–N), 5.18 (s, 0.6H, CH–N), 4.42 (d, J = 17.0 Hz, 0.4H, CH_2–N), 4.24–4.16 (m, 1H, CH_2–N), 3.80–3.77 (m, 0.6H, HCN of cyclohexyl), 3.60 (bs, 0.4H, HCN of cyclohexyl), 2.09 (s, 1.8H, $H_{Me–Ar}$), 2.00 (s, 1.2H, $H_{Me–Ar}$), 1.86–1.62 (m, 6H, $H_{Aliphatic}$), 1.45–1.05 (m, 13H, $H_{Aliphatic}$), 0.91–0.83 (m, 6H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers) δ 176.08, 175.27, 173.69, 172.79, 171.15, 165.94, 138.92, 138.05, 137.51, 137.01, 136.10, 133.57, 130.92, 129.99, 129.49, 128.40, 128.00, 127.78, 127.27, 126.70, 126.49, 126.37, 125.82, 63.94, 60.80, 51.10, 50.70, 50.60, 50.37, 49.90, 49.33, 48.76, 33.28, 32.41, 32.15, 28.71, 28.05, 27.94, 27.56, 25.83, 25.58, 25.46, 25.26, 24.15, 21.71, 19.81, 19.57. MS *m/z*: 505 (M^+, 0.13), 401 (11.13), 355 (12.24), 275 (100), 196 (15.13), 170 (59.51), 91 (53.42), 57 (28.22). Anal. Calcd for $C_{31}H_{43}N_3O_3$: C, 73.63; H, 8.57; N, 8.31; found C, 73.75; H, 8.69; N, 8.19.

***N*^{1}-Benzyl-*N*^{1}-(1-(4-bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*^{3}-cyclohexyl-2,2-dimethylmalonamide** (**8k**) White powders: 496 mg, 87% yield; mp 154 °C. IR (ATR) cm^{-1}: 3279, 3090, 2942, 2850, 1667, 1631, 1554. ^{1}H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 7.83–7.76 (m, 2H, NH), 7.66 (bs, 1H, H_{Ar}), 7.54–7.47 (m, 1H, H_{Ar}), 7.26 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.16–7.05 (m, 4H, H_{Ar}), 6.98 (d, J = 8.1 Hz, 1H, H_{Ar}), 6.91–6.88 (m, 1H, H_{Ar}), 5.37 (s, 0.5H, CH–N), 5.32 (s, 0.5H, CH–N), 4.71 (d, J = 16.5 Hz, 0.5H, CH_2–N), 4.52–4.36 (m, 1H, CH_2–N), 4.21 (d, J = 16.5 Hz, 0.5H, CH_2–N) 3.62 (bs, 1H, HCN of cyclohexyl), 1.84–1.59 (m, 5H, $H_{Aliphatic}$), 1.39–1.06 (m, 20H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers) δ 174.68, 174.57, 173.58, 172.93, 169.65, 167.27, 138.65, 137.85, 136.53, 134.89, 132.55, 131.35, 130.99, 130.78, 128.37, 127.81, 127.22, 126.99, 126.13, 121.42, 121.12, 64.50, 63.64, 51.01, 50.95, 50.30, 49.42, 49.03, 48.64, 32.66, 32.46, 32.15, 28.66, 28.15, 26.80, 25.74, 25.53, 25.21, 24.53, 24.32. MS *m/z*: 573 (M^+ +4, 1.26), 571 (M^+ +2, 1.55), 569 (M^+, 0.07), 418 (6.97), 376 (14.32), 250 (84.92), 196 (98.42), 169 (100), 83 (87.10), 55 (69.02). Anal. Calcd for $C_{30}H_{40}BrN_3O_3$: C, 63.15; H, 7.07; N, 7.36; found C, 63.29; H, 7.14; N, 7.23.

***N*^{1}-(1-(4-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*^{3}-(*tert*-butyl)-*N*^{1}-(2-chlorobenzyl)-2,2-dimethylmalonamide** (**8l**) White powders: 537 mg, 89%

yield; mp 197–198 °C. IR (ATR) cm^{-1}: 3282, 3080, 2850, 1667, 1639, 1547. ^1H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 8.06–8.00 (m, 2H, NH), 7.37 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 7.27 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.20–7.13 (m, 3H, H_{Ar}), 7.07–6.96 (m, 2H, H_{Ar}), 5.59 (s, 0.7H, CH–N), 5.41 (s, 0.3H, CH–N), 4.72–4.67 (m, 0.3H, CH_2–N), 4.49–4.32 (m, 1.7H, CH_2–N), 3.52 (bs, 1H, HCN of cyclohexyl), 1.69–1.54 (m, 5H, $H_{Aliphatic}$), 1.41–1.28 (m, 15H, $H_{Aliphatic}$), 1.23–0.94 (m, 5H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers) δ 175.17, 173.50, 173.24, 169.19, 135.65, 135.11, 133.89, 132.74, 131.68, 130.98, 130.91, 129.16, 129.08, 128.77, 128.45, 127.01, 126.48, 121.91, 121.43, 121.43, 63.77, 63.24, 51.60, 51.37, 50.88, 48.74, 48.38, 47.91, 32.48, 32.40, 28.91, 28.90, 28.56, 27.30, 25.63, 25.12, 24.93, 24.81, 23.47. MS *m/z*: 607 ($M^+ + 4$, 0.35), 605 ($M^+ + 2$, 0.88), 603 (M^+, 0.68), 435 (12.32), 353 (22.23), 309 (73.85), 170 (79.92), 125 (57.57), 83 (30.74), 57 (100). Calcd for $C_{30}H_{39}BrClN_3O_3$: C, 59.56; H, 6.50; N, 6.95; found C, 59.32; H, 6.38; N, 6.99.

***N*^{1}-Benzyl-*N*^{3}-cyclohexyl-*N*^{1}-(2-(cyclohexylamino)-2-oxo-1-(*o*-tolyl)ethyl)-2,2-dimethylmalonamide** (**8m**) White powders: 473 mg, 89% yield; mp 196–198 °C. IR (ATR) cm^{-1}: 3246, 3072, 2929, 2844, 1650, 1631, 1550. ^1H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 8.05–7.98 (m, 1H, NH), 7.80–7.73 (m, 1H, NH), 7.38–6.90 (m, 7H, H_{Ar}), 6.77–6.67 (m, 2H, H_{Ar}), 5.71 (s, 0.6H, CH–N), 5.31 (d, $J = 16.0$ Hz, 0.4H, CH_2–N), 5.21 (s, 0.4H, CH–N), 4.41 (d, $J = 16.0$ Hz, 0.6H, CH_2–N), 4.24–4.09 (m, 1H, CH_2–N), 3.77–3.70 (m, 0.5H, HCN of cyclohexyl), 3.60–3.36 (m, 1H, HCN of cyclohexyl), 2.90 (bs, 0.5H, HCN of cyclohexyl), 2.07 (s, 1.2H, $H_{Me–Ar}$), 1.99 (s, 1.8H, $H_{Me–Ar}$), 1.83–1.50 (m, 9H, $H_{Aliphatic}$), 1.37–0.90 (m, 17H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers) δ 175.90, 175.17, 173.72, 172.97, 170.30, 166.58, 138.76, 138.30, 137.62, 136.68, 136.00, 133.45, 131.03, 130.08, 129.68, 128.44, 127.95, 127.86, 127.55, 126.78, 126.59, 126.51, 125.82, 63.08, 60.73, 50.53, 50.43, 49.65, 49.28, 48.86, 48.50, 47.44, 47.42, 32.99, 32.50, 31.79, 30.71, 27.84, 27.36, 25.73, 25.53, 25.31, 25.11, 24.98, 24.47, 23.52, 22.06, 19.74, 19.44. MS *m/z*: 531 (M^+, 3.04), 405 (15.95), 335 (27.76), 301 (55.63), 210 (100), 196 (34.08), 91 (64.94), 83 (56.43), 55 (41.38). Calcd for $C_{33}H_{45}N_3O_3$: C, 74.54; H, 8.53; N, 7.90; found C, 74.42; H, 8.66; N, 7.78.

***N*^{1}-Benzyl-*N*^{3}-(*tert*-butyl)-*N*^{1}-(1-(cyclohexylamino)-1-oxopentan-2-yl)-2,2-dimethylmalonamide** (**8n**) White powders: 353 mg, 77% yield; mp 69–69 °C. IR (ATR) cm^{-1}: 3289, 2926, 2855, 1631, 1529. ^1H NMR (300 MHz, $CDCl_3$): (mixture of rotamers) δ 7.38–7.13 (m, 5H, H_{Ar}), 6.50–6.47 (m, 0.5H), 5.91 (bs, 0.6H), 5.74 (bs, 0.4H), 4.69–4.22 (m, 2H), 3.88–3.85 (m, 0.5H), 3.71–3.66 (m, 1H), 3.51–3.43 (m, 0.5H), 2.34–2.21 (m, 0.5H), 1.94–0.71 (m, 32H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$): (mixture of rotamers) δ 175.56, 174.76, 173.32, 172.28, 170.03, 167.44, 138.64, 136.22, 128.64, 128.06, 127.35, 126.49, 62.39, 60.25, 53.50, 51.84, 51.68, 50.99, 48.66, 48.30, 47.72, 34.65, 33.13, 32.80, 32.56, 32.27, 29.05, 28.82, 28.52, 27.91, 26.89, 26.07, 25.59, 25.26, 24.81, 24.45, 22.86, 20.89, 20.63, 14.07, 13.87. MS *m/z*: 457 (M^+, 6.01), 359 (43.43), 331 (39.79), 287 (45.86), 162 (100), 91 (59.28), 57 (61.75). Anal. Calcd for $C_{27}H_{43}N_3O_3$: C, 70.86; H, 9.47; N, 9.18; found C, 70.99; H, 9.43; N, 9.01.

***N*^{1}-(*tert*-Butyl)-*N*^{3}-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-*N*^{3}-(3,4-dichlorophenyl)-2,2-dimethylmalonamide** (**8o**) White powders: 475 mg, 87% yield; mp 183–185 °C. IR (ATR) cm^{-1}: 3323, 3057, 2924, 2842, 1636, 1552, 1526. ^1H NMR (300 MHz, DMSO-d_6): δ 8.14–8.12 (m, 1H, NH), 7.91 (bs, 1H, NH), 7.13–7.08 (m, 4H, H_{Ar}), 7.00–6.96 (m, 3H, H_{Ar}), 6.39–6.33 (m, 1H, H_{Ar}), 5.98 (s, 1H, CH–N), 3.60 (bs, 1H, HCN of cyclohexyl), 1.99–1.52 (m, 6H, $H_{Aliphatic}$), 1.26–0.99 (m, 19H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.10, 172.51, 169.24, 138.94, 135.32, 133.69, 130.89, 130.25, 129.54, 128.30, 66.14, 52.05, 51.16, 48.51, 32.64, 32.59, 28.69, 25.69, 25.07, 24.94. MS *m/z*: 549 ($M^+ + 4$, 0.48), 547 ($M^+ + 2$, 1.49), 545 (M^+, 1.54), 419 (3.93), 392 (6.48), 376 (13.96), 250 (81.74), 170 (80.50), 143 (60.34), 83 (23.78), 57 (100). Anal. Calcd for $C_{29}H_{37}Cl_2N_3O_3$: C, 63.73; H, 6.82; N, 7.69; found C, 63.51; H, 6.89; N, 7.79.

***N*^{1}-(2-Chlorobenzyl)-*N*^{3}-cyclohexyl-*N*^{1}-(2-(cyclohexylamino)-1-(3-methoxyphenyl)-2-oxoethyl)-2,2-dimethylmalonamide** (**8p**) White powders: 512 mg, 88% yield; mp 188–190 °C. IR (ATR) cm^{-1}: 3317, 3253, 2929, 2852, 1672, 1621, 1539. ^1H NMR (300 MHz, DMSO-d_6): (mixture of rotamers) δ 8.00–7.71 (m, 2H, NH), 7.24–7.03 (m, 5H, H_{Ar}), 6.83–6.65 (m, 3H, H_{Ar}), 5.61 (s, 0.6H, CH–N), 5.51 (s, 0.4H, CH–N), 4.73 (d, $J = 17.1$ Hz, 0.5H, CH_2–N), 4.44–4.38 (m, 1.5H, CH_2–N), 3.75–3.55 (m, 5H, HCN of cyclohexyl and O-CH_3), 1.85–1.55 (m, 10H, $H_{Aliphatic}$), 1.39–0.99 (m, 16H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (mixture of rotamers): δ 175.18, 173.86, 173.29, 172.89, 169.71, 168.19, 159.42, 159.15, 158.85, 137.85, 135.76, 135.57, 130.86, 129.44, 129.03, 128.65, 128.37, 127.54, 126.95, 122.74, 121.35, 115.40, 114.58, 113.90, 64.60, 63.47, 55.34, 50.28, 49.16, 48.77, 48.45, 48.33, 47.84, 32.43, 27.40, 26.65, 25.65, 25.25, 24.96, 23.28. MS *m/z*: 583 ($M^+ + 2$, 1.06), 581 (M^+, 3.04), 455 (8.81), 385 (15.95), 331 (39.96), 260 (100), 196 (35.63), 125 (41.34), 83 (53.46), 55 (39.55). Anal. Calcd for $C_{33}H_{44}ClN_3O_4$: C, 68.08; H, 7.62; N, 7.22; found C, 68.01; H, 7.71; N, 7.05.

***N*^{1}-Benzyl-*N*^{3}-(*tert*-butyl)-*N*^{1}-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-2,2-dimethylmalonamide** (**8q**) White powders: 428 mg, 87% yield; mp 224 °C. IR (ATR) cm^{-1}: 3284, 3082, 2929, 2852, 1651, 1626, 1552. ^1H NMR (300 MHz, DMSO-d_6): (major of rotamers) δ 7.83–7.81 (s, 2H, NH), 7.32 (bs, 1H, H_{Ar}), 7.21–7.00 (m, 7 H, H_{Ar}), 6.82–6.77 (m, 2H, H_{Ar}), 5.34 (s, 1H, CH–N), 4.49 (d,

$J = 17.5$ Hz, CH_2–N), 4.14 (d, $J = 17.5$ Hz, 1H, CH_2–N), 3.52 (bs, 1H, HCN of cyclohexyl), 1.76–0.92 (m, 25 H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, DMSO-d_6): (major rotamer) δ 175.19, 173.48, 169.71, 138.15, 134.69, 130.66, 128.36, 127.97, 127.11, 126.56, 64.97, 51.24, 50.82, 50.35, 48.23, 32.45, 28.72, 27.47, 25.65, 24.89, 24.75, 23.85. MS *m/z*: 491 (M^+, 3.91), 393 (13.91), 365 (17.39), 321 (27.08), 275 (95.40), 196 (100), 170 (50.64), 91 (78.43), 83 (22.72), 55 (29.59). Anal. Calcd for $C_{30}H_{41}N_3O_3$: C, 73.29; H, 8.41; N, 8.55; found C, 73.48; H, 8.56; N, 8.37.

***N*^{1}-Benzyl-*N*^{3}-(*tert*-butyl)-*N*^{1}-(2-(*tert*-butylamino)-1-(4-nitrophenyl)-2-oxoethyl)-2,2-dimethylmalonamide** (**8r**) Yellow powders: 383 mg, 75% yield; mp 88 °C. IR (ATR) cm^{-1}: 3310, 2975, 2934, 1659, 1644, 1513. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, NH), 7.92 (s, 1H, NH), 7.28–7.21 (m, 3H, H_{Ar}), 7.18–7.08 (m, 3H, H_{Ar}), 6.97–6.94 (m, 2H, H_{Ar}), 6.61 (bs, 1H, H_{Ar}), 5.60 (s, 1H, CH–N), 4.62 (d, $J = 16.0$ Hz, 1H, CH_2–N), 4.44 (d, $J = 16.0$ Hz, 1H, CH_2–N), 1.58–1.00 (m, 24H, $H_{Aliphatic}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.32, 172.91, 167.64, 147.25, 142.87, 135.68, 131.03, 128.50, 127.95, 127.76, 123.12, 77.32, 67.01, 54.29, 52.08, 51.76, 50.78, 28.55, 28.45, 25.84, 24.67. MS *m/z*: 510 (M^+, 0.78), 340 (12.23), 320 (23.55), 275 (36.96), 241 (20.47), 170 (62.04), 91 (72.58), 57 (100). Anal. Calcd for $C_{28}H_{38}N_4O_5$: C, 65.86; H, 7.50; N, 10.97; found C, 65.90; H, 7.65; N, 10.78.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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