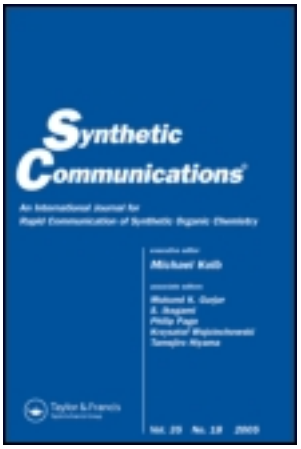

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Efficient Synthesis of Urea Derivatives via a Sequential One-Pot Nucleophilic Addition/Ugi Five-Component Reaction Under Solvent-Free Conditions

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EFFICIENT SYNTHESIS OF UREA DERIVATIVES VIA A SEQUENTIAL ONE-POT NUCLEOPHILIC ADDITION/UGI FIVE-COMPONENT REACTION UNDER SOLVENT-FREE CONDITIONS

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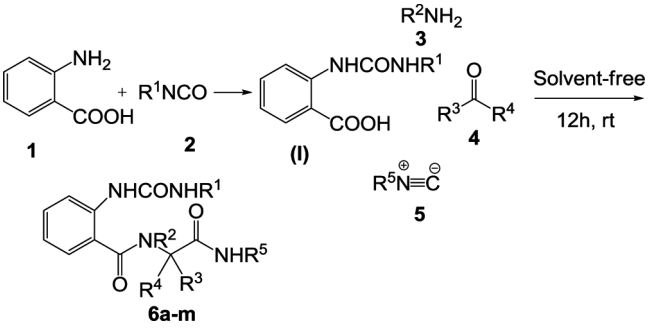
GRAPHICAL ABSTRACT



Abstract *Urea polyfunctional derivatives were successfully synthesized via a one-pot, five-component nucleophilic addition/Ugi reaction sequence. Simplicity, solvent-free conditions, and good yields of products are advantages of this method.*

Keywords Five-component reaction; nucleophilic addition; one-pot; solvent-free; Ugi reaction; urea derivatives

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INTRODUCTION

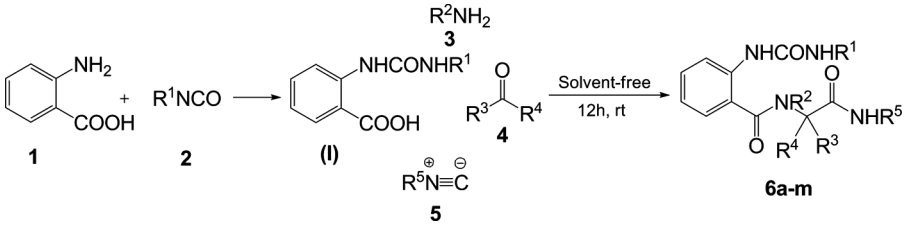
The synthesis of new biologically active molecules is an important challenge in the development of improved and innovative drugs. Finding a suitable route with fewer reaction steps for the synthesis of pharmaceutical scaffolds is very interesting. It has been well established that urea derivatives have a significant place in modern medicinal chemistry.[1–3] Because of the broad pharmacological interest in urea derivatives, their synthesis has been of widespread interest. For example, in the past years, a large variety of urea derivatives were reported to possess potent inhibiting effects on HIV protease enzyme,[4] receptor tyrosine kinases (RTKs),[5] nicotinamide adenine dinucleotide hydrate (NADH) oxidase,[6] and acyl-coenzyme A-cholesterol acyltransferase (ACAT).[7] Various methods have been developed for the syntheses of these compounds.[8,9] Drawbacks of these methods include harsh thermal conditions, long reaction times, modest yields, use of expensive reagents, multistep reactions, and use of organic solvents. Therefore, the further development of synthetic methods to produce a variety of these templates remains an important task.

In this field, multicomponent condensation reactions based on isocyanides have been utilized efficiently in conjunction with combinatorial chemistry to prepare polyfunctional compounds in short reaction sequences.[10,11] One of the best-known multicomponent reactions is the Ugi four-component coupling (4CC) reaction.[12] In this reaction, an isocyanide, an amine, a carboxylic acid, and an oxo compound spontaneously are condensed to yield an acylaminocarboxamide.

Herein we report an efficient and convenient procedure for the synthesis of urea derivatives under solvent-free conditions at room temperature. Thus, one-pot, five-component reaction of 2-amino benzoic acid **1**, phenyl isocyanate **2**, primary amines **3**, oxo compound **4**, and isocyanides **5** leading to the urea derivatives is shown in Scheme 1. The intermediate **I** contains functional groups that are suitable for further reactions. The reaction proceeds without any catalyst and separation of intermediate **I** (Scheme 1).

RESULTS AND DISCUSSION

Generally, the Ugi 4CR was performed in organic solvents such as methanol or tetrahydrofuran (THF) at room temperature for 1–2 days.[13] Although this Ugi 4CR was carried out successfully in methanol at room temperature to afford the desired compounds, there are some drawbacks in Ugi reaction such as long reaction times and use of methanol as solvent, leading to side reactions. More recently, Shaabani

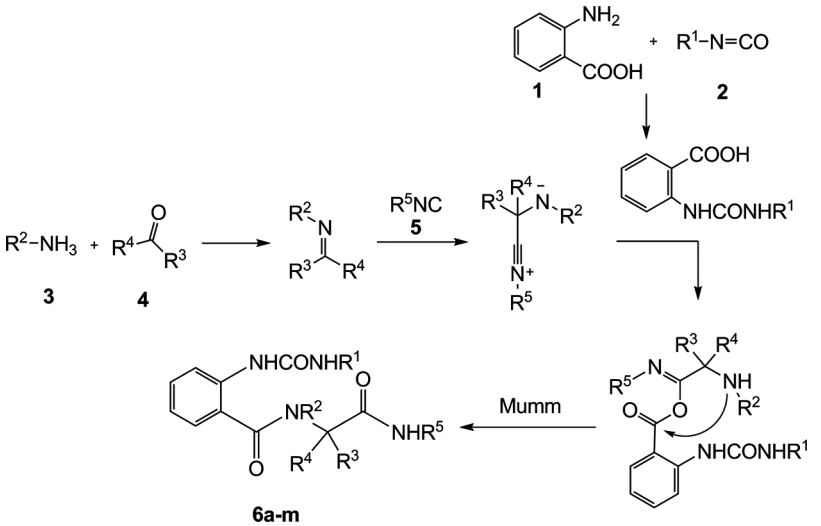


Scheme 1. Synthesis of urea derivatives *via* a five-component reaction.

et al. studied the reaction of carboxylic acids and isocyanides in methanol at ambient temperature carefully. Aryl amides were obtained in good yield after 24 h. They also proved that methanol took part in this reaction and converted to methylformate.[14] Furthermore, it also has been reported that methanol took part in the reaction to form unintended by-products. For example, Mitchell et al. demonstrated that under the Ugi reaction conditions, the iminium cation underwent another competing reaction involving the reaction solvent (methanol) to give an undesired by-product.[15] These studies have shown that the utility of methanol as solvent led inevitably to the formation of some undesired side products. Organic syntheses involving multicomponent reactions (MCRs) under solvent-free conditions have been receiving much attention.[16] As part of our continuing interest in developing more efficient and practical methods in organic synthesis, we explored the possibility of obtaining the products **6a–m** by the Ugi 5CR under solvent-free conditions.

We have developed a one-pot, two-step reaction for the synthesis of urea derivatives under solvent-free conditions. Using this novel approach, all five starting materials were mixed in one pot within short intervals to maximize bond formation for complexity generation and diversification. The addition of three components (amine, isonitrile, carbonyl compound) took place a half hour after mixing the two starting materials (benzoic acid and phenyl isocyanate), which led to the formation of the product as a precipitate. Compared to the original Ugi reactions, which take 1–2 days, it would appear that this approach has more favorable reaction and purification conditions such as less than 12 h to complete the two-step reaction and no need for the double scavenging step. Although the mechanism of the reaction has not been established experimentally, a possible explanation is proposed in Scheme 2.

In Fig. 1, the structures of compounds were characterized by IR, mass, ^{1}H NMR, and ^{13}C NMR spectral data. The mass spectra of compounds **6a–6m** displayed molecular ion peaks at appropriate m/z values. The IR and ^{1}H NMR



Scheme 2. Proposed mechanism for the formation of compounds.

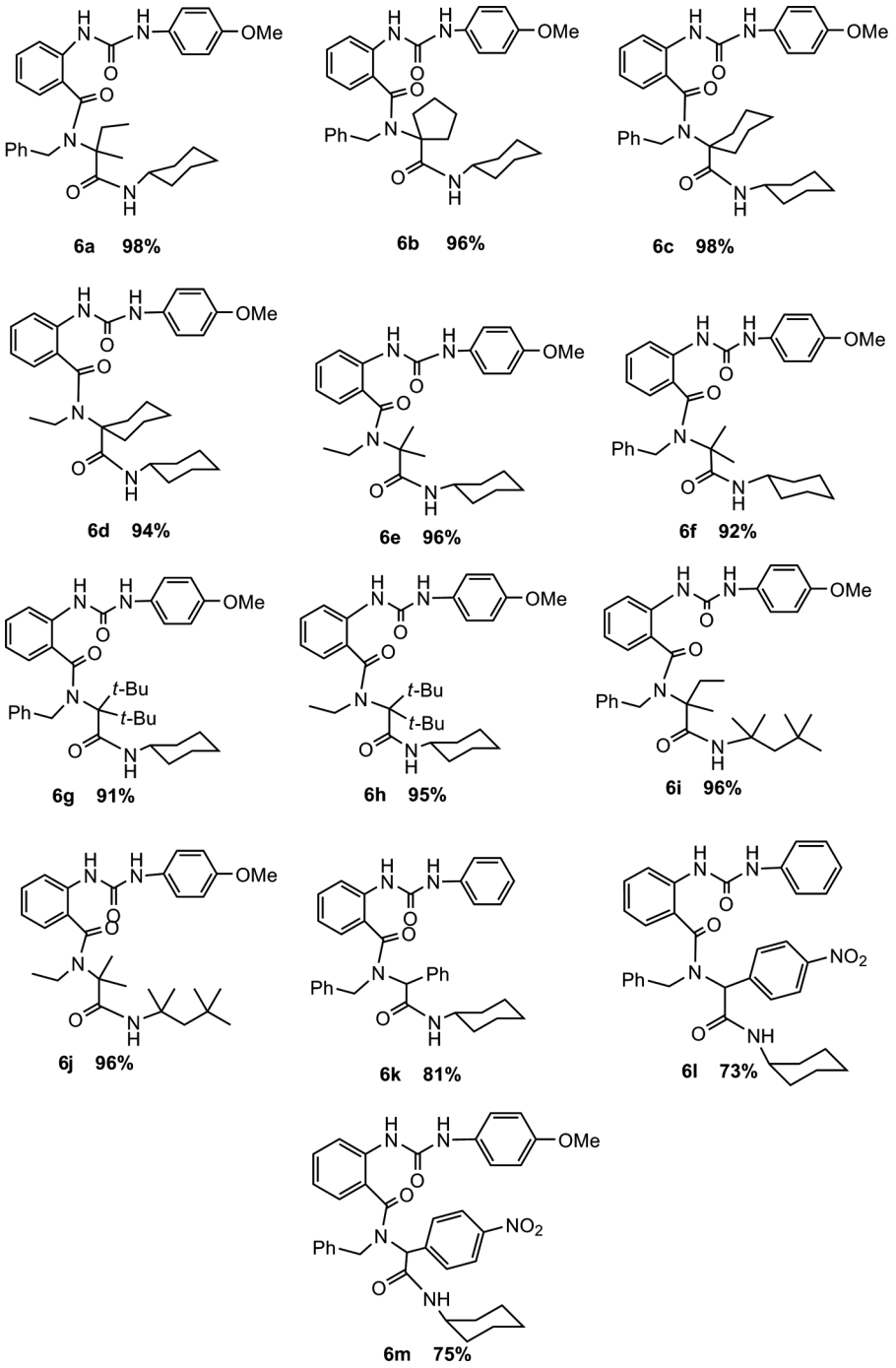


Figure 1. Results of the nucleophilic addition/Ugi MCR reaction.

spectra of **6a–6m** exhibited three characteristic peaks for the NH moieties. The ^{1}H-decoupled ^{13}C NMR spectra of **6a–6m** showed three distinct resonances for C=O. Compounds **6a, 6i**, and **6k–m** possess stereogenic centers and can exist as doublets of doublet for CH_2 benzyl amine in the NMR spectra. It should be noted that Passerini-type reactions were not detected in these reactions, even in the reactions that gave the desired products in moderate yields. The results confirm the versatility and efficiency of this method for the preparation of urea derivatives.

CONCLUSION

In conclusion, we have described an efficient method for the synthesis of urea derivatives in good yields via a one-pot, five-component reaction under mild and solvent-free conditions. Reaction times were dramatically reduced and yields were generally improved by this new method. The reaction scope is broad, which permits the use of four points of diversity in the starting materials. Because of the well-recognized utility of urea derivatives, many libraries of compounds can be prepared using this method as structural scaffolds for further diversification.

EXPERIMENTAL

Materials were purchased from Merck and Fluka companies. Melting points were obtained using an Electrothermal-9100 apparatus and are uncorrected IR spectra were recorded with a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX-300 Avance instrument using $CDCl_3$ as the deuterated solvent containing tetramethylsilane as internal standard, at 300 and 75 MHz, respectively (δ in parts per million, J in hertz). Electron-impact mass spectrometry (EIMS) (70 eV): Mass spectra were obtained with a Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses (C, H, N) were obtained with a Heraeus CHN-O- Rapid analyzer.

General Procedure for the Synthesis of Urea Derivatives 6a–m

2-Amino benzoic acid **1** (1 mmol) was added to phenyl isocyanate **2** (1 mmol), and the mixture was stirred at room temperature for 0.5 h. Then, primary amine **3** (1 mmol) and oxo compound **4** (1.2 mmol) were added and stirred for 15 min, followed by addition of isocyanide **5** (1 mmol). The reaction was detected by TLC (*n*-hexane–EtOAc, 3/1) and completed after 11 h. The evaporable compounds were removed under reduced pressure, and the residue was dissolved in EtOAc (20 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (2×20 mL) and dried on Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2; hexane/EtOAc 3/1) to afford quite pure title compounds.

1-(2-(N-(2-(Cyclohexylcarbamoyl)butan-2-yl)-N-benzylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6a)

Yield: 0.54 g (98%), white powder, mp 94–96 °C. IR (KBr) (ν_{max}/cm^{-1}); 3460, 3430, 3290, 1664, 1635, 1602 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, $J = 7.4$,

3H), 1.12–1.92 (m, 10H), 1.54 (s, 3H), 1.99 (q, $J = 7.4$, 2H), 3.74 (s, 3H), 3.82 (m, 1H), 4.55 (d, $J = 16.8$, 1H), 4.70 (d, $J = 16.8$, 1H), 5.90 (br s, 1H), 6.92 (d, $J = 9.0$, 2H), 7.20 (m, 3H), 7.30 (m, 5H), 7.45 (d, $J = 9.0$, 2H), 7.96 (s, 1H), 8.32 (d, $J = 8.1$, 1H), 8.69 (s, 1H) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 9.4 (CH_3), 25.1 (CH_2), 25.2 (CH_3), 25.9 ($2CH_2$), 32.9 ($2CH_2$), 33.2 (CH_2), 49.8 (CH_2), 50.1 (C−N), 55.9 (MeO), 67.1 (C), 114.5 (2CH), 119.7 (CH), 121.0 (2CH), 122.3 (CH), 126.0 (CH), 126.1 (CH), 127.3 (2CH), 127.9 (CH), 129.1 (2CH), 130.4 (C), 133.1 (C), 136.9 (C), 138.3 (C), 153.6 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O) ppm. MS (EI, 70 eV): m/z (%): 556 (M^+, 4), 307 (12), 281 (100), 162 (94), 134 (15), 120 (87), 106 (21), 91 (40), 78 (12). Anal. calcd. for $C_{33}H_{40}N_4O_4$ (556.69): C, 71.20; H, 7.24; N, 10.06. Found: C, 71.33; H, 7.30; N, 10.24.

1-(2-(N-(1-(Cyclohexylcarbamoyl)cyclopentyl)-N-benzylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6b)

Yield: 0.55 g (96%), white powder, mp 90–92 °C. IR (KBr) (ν_{max}/cm^{-1}); 3360, 3330, 3290, 1654, 1635, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.12–1.39 (m, 8H), 1.53–1.78 (m, 10H), 3.74 (s, 3H), 3.82 (m, 1H), 4.70 (s, 2H), 5.90 (br, 1H), 6.88 (d, $J = 9$, 2H), 7.19 (m, 3H), 7.30(m, 5H), 7.45 (d, $J = 9$, 2H), 8.02 (s, 1H), 8.36 (d, $J = 9$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 23.8 ($2CH_2$), 25.0 ($2CH_2$), 25.8 (CH_2), 32.8 ($2CH_2$), 36.5 ($2CH_2$), 50.1 (C−N), 52.5 (CH_2), 55.9 (MeO), 69.1 (C), 114.5 (2CH), 119.7 (CH), 120.8 (2CH), 122.1 (CH), 125.7 (CH), 125.8 (CH), 126.4 (2CH), 127.7 (CH), 129.2 (2CH), 130.3 (C), 133.1 (C), 136.8 (C), 138.8 (C), 153.6 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O) ppm; MS (EI, 70 eV): m/z (%): 568 (M^+, 5), 320 (20), 291 (100), 172 (90), 103 (70), 91 (50). Anal. calcd. for $C_{34}H_{40}N_4O_4$ (568.70): C, 71.33; H, 7.30; N, 10.94. Found: C, 71.81; H, 7.09; N, 9.85.

1-(2-(N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-N-benzylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6c)

Yield: 0.57 g (98%), white powder, mp 89–91 °C. IR (KBr) (ν_{max}/cm^{-1}); 3390, 3365, 3290, 1674, 1645, 1588 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16–1.48 (m, 10H), 1.87–2.30 (m, 10H), 3.70 (s, 3H), 3.80 (m, 1H), 4.80 (s, 2H), 6.50 (br, 1H), 6.78 (d, $J = 9$, 2H), 7.19 (m, 3H), 7.30 (m, 5H), 7.45 (d, $J = 9$, 2H), 8.02 (br, 1H), 8.36 (d, $J = 9$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 23.6 ($2CH_2$), 24.2 ($2CH_2$), 25.5 (CH_2), 33.8 (CH_2), 34.5 ($2CH_2$), 36.2 ($2CH_2$), 50.3 (C−N), 52.9 (CH_2), 55.8 (OMe), 67.1 (C), 114.6 (2CH), 120.1 (CH), 120.9 (2CH), 122.8 (CH), 125.2 (CH), 126.1 (CH), 126.6 (2CH), 127.7 (CH), 129.7 (2CH), 130.3 (C), 133.1 (C), 136.8 (C), 138.8 (C), 152.6 (C), 156.6 (C=O), 172.6 (C=O), 174.2 (C=O) ppm; MS (EI, 70 eV): m/z (%): 582 (M^+, 4), 334 (17), 306 (100), 188 (87), 105 (67), 91 (50). Anal. calcd. for $C_{35}H_{42}N_4O_4$ (582.73): C, 72.14; H, 7.26; N, 9.61. Found: C, 72.33; H, 7.30; N, 10.04.

1-(2-(N-(1-(Cyclohexylcarbamoyl)cyclohexyl)-N-ethylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6d)

Yield: 0.49 g (94%), white powder, mp 98–100 °C. IR (KBr) (ν_{max}/cm^{-1}); 3490, 3435, 3265, 1674, 1623, 1611 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.09 (t, $J = 9$,

3H), 1.16–1.48 (m, 10H), 1.87–2.30 (m, 10H), 3.40 (q, $J=9$, 2H), 3.80 (s, 3H), 3.86 (m, 1H), 6.13 (br, 1H), 6.85 (d, $J=9.14$, 2H), 6.99 (t, $J=6$, 1H), 7.14 (d, $J=9.14$, 1H) 7.34 (t, $J=6$, 1H), 7.42 (d, $J=9$, 2H), 8.02 (s, 2H), 8.30 (d, $J=9.14$, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 17.4 (CH_3), 23.4 (CH_2), 25.1 ($2CH_2$), 25.9 ($2CH_2$), 26.0 ($2CH_2$), 32.9 ($2CH_2$), 33.0 (CH_2), 40.7 (CH_2), 50.3 (C−N), 55.9 (MeO), 66.4 (C), 114.5 (2CH), 120.0 (CH), 121.0 (2CH), 122.2 (CH), 125.3 (CH), 126.8 (CH), 130.1 (C), 134.2 (C), 136.6 (C), 153.6 (C),155.6 (C=O), 171.9 (C=O), 175.5 (C=O) ppm; MS (EI, 70 eV) m/z (%): 520 (M^+, 6), 272 (16), 244 (100), 126 (77), 43 (67), 29 (40). Anal. calcd. for $C_{30}H_{40}N_4O_4$ (520.66): C, 69.20; H, 7.74; N, 10.76. Found: C, 70.33; H, 7.90; N, 10.04.

1-(2-(N-(2-(Cyclohexylcarbamoyl)propan-2-yl)-N-ethylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6e)

Yield: 0.46 g (96%), white powder, mp 87–89 °C. IR (KBr) (ν_{max}/cm^{-1}): 3467, 3425, 3265, 1674, 1623, 1611 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.02 (t, $J=10.8$, 3H), 1.46–2.08 (m, 10H), 1.87 (s, 6H), 3.40 (q, $J=10.8$, 2H), 3.80 (s, 3H), 3.86 (m, 1H), 6.41 (br, 1H), 6.85 (d, $J=9$, 2H), 6.99 (t, $J=6$, 1H), 7.14 (t, $J=9$, 1H), 7.34 (t, $J=6$, 1H), 7.42 (d, $J=9$, 2H), 8.02 (s, 2H), 8.30 (d, $J=9$, 1H), ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 15.4 (CH_3), 23.4 ($2CH_3$), 25.1 ($2CH_2$), 29.9 ($2CH_2$), 33.0 (CH_2), 40.76 (CH_2), 50.3 (C−N), 55.6 (MeO), 66.1 (C), 114.5 (2CH), 120.0 (CH), 121.0 (2CH), 122.2 (CH), 125.3 (CH), 126.8 (CH), 131.1 (C), 133.2 (C), 136.6 (C), 153.6 (C), 155.6 (C=O), 170.9 (C=O), 174.5 (C=O) ppm; MS (EI, 70 eV) m/z (%): 480 (M^+, 6), 232 (20), 204 (100), 86 (84), 43 (67), 29 (40). Anal. calcd. for $C_{27}H_{36}N_4O_4$ (480.59): C, 67.48; H, 7.55; N, 11.66. Found: C, 66.93; H, 7.90; N, 11.04.

1-(2-(N-(2-(Cyclohexylcarbamoyl)propan-2-yl)-N-benzylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6f)

Yield: 0.49 g (92%), white powder, mp 89–91 °C. IR (KBr) (ν_{max}/cm^{-1}); 3460, 3430, 3290, 1664, 1635, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (s, 6H), 1.27–2.17 (m, 10H), 3.70 (s, 3H), 3.80 (m, 1H), 4.80 (s, 2H), 6.50 (br, 1H), 6.78 (d, $J=9$, 2H), 7.19 (m, 3H), 7.30 (m, 5H), 7.45 (d, $J=9$, 2H), 8.02 (s, 1H), 8.36 (d, $J=9$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 20.9 ($2CH_3$), 23.6 ($2CH_2$), 25.5 (CH_2), 34.5 ($2CH_2$), 50.3 (C−N), 52.9 (CH_2), 55.8 (MeO), 67.1 (C), 114.6 (2CH), 120.1 (CH), 120.9 (2CH), 122.8 (CH), 125.2 (CH), 126.1 (CH), 126.6 (2CH), 127.7 (CH), 129.7 (2CH), 130.3 (C), 133.1 (C), 136.8 (C), 138.8 (C), 152.6 (C), 156.6 (C=O), 172.6 (C=O), 174.2 (C=O) ppm; MS (EI, 70 eV): m/z (%): 542 (M^+, 5), 294 (17), 266 (100), 148 (87), 133 (67),119 (43), 105 (56), 91 (50), 78 (32). Anal. calcd. for $C_{32}H_{38}N_4O_4$ (542.66): C, 70.82; H, 7.06; N, 10.32. Found: C, 71.33; H, 7.30; N, 10.04.

1-(2-(N-(3-(Cyclohexylcarbamoyl)-2,2,4,4-tetramethylpentan-3-yl)-N-benzylcarb amoyl)phenyl)-3-(4-methoxyphenyl)urea (6g)

Yield: 0.57 g (91%), white powder, mp 99–101 °C. IR (KBr) (ν_{max}/cm^{-1}): 3487, 3328, 3290, 1654, 1635, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.01 (s, 18H), 1.27–2.17 (m, 10H), 3.70 (s, 3H), 3.80 (m, 1H), 4.80 (s, 2H), 6.50 (br, 1H), 6.78 (d,

$J = 8.7$, 2H), 7.19 (m, 3H), 7.30 (m, 5H), 7.45 (d, $J = 8.7$, 2H), 8.02 (s, 1H), 8.36 (d, $J = 8.7$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 21.99 ($6CH_3$), 24.6 ($2CH_2$), 25.7 (2C), 25.9 (CH_2), 34.5 ($2CH_2$), 51.3 (C−N), 52.9 (CH_2), 55.8 (OMe), 78.1 (C), 114.7 (2CH), 120.8 (CH), 121.9 (2CH), 123.8 (CH), 126.2 (CH), 127.1 (CH), 127.6 (2CH), 128.5 (CH), 129.7 (2CH), 131.8 (C), 133.1 (C), 136.8 (C), 138.8 (C), 152.6 (C), 156.6 (C=O) 172.6 (C=O), 174.2 (C=O) ppm; MS (EI, 70 eV) m/z (%): 626 (M^+, 6), 378 (17), 350 (100), 232 (77), 175 (68), 119 (43), 105 (56), 91 (50), 78 (42). Anal. calcd. for $C_{38}H_{50}N_4O_4$ (626.82): C, 72.81; H, 8.04; N, 8.94. Found: C, 71.83; H, 7.69; N, 8.04.

1-(2-(N-(3-(Cyclohexylcarbamoyl)-2,2,4,4-tetramethylpentan-3-yl)-N-ethylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6h)

Yield: 0.57 g (91%), white powder, mp 100–102 °C. IR (KBr) (ν_{max}/cm^{-1}): 3413, 3363, 3310, 1664, 1635, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 (t, $J = 9$, 3H), 1.02 (s, 18H), 1.27–2.07 (m, 10H), 3.52 (q, $J = 9$, 2H), 3.70 (s, 3H), 3.80 (m, 1H), 6.50 (br, 1H), 6.85 (d, $J = 9.3$, 2H), 6.99 (t, $J = 6$, 1H), 7.14 (t, $J = 9$, 1H), 7.34 (t, $J = 6$, 1H), 7.42 (d, $J = 9.3$, 2H), 8.02 (s, 2H), 8.30 (d, $J = 9.3$, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 15.7 (CH_3), 21.5 ($6CH_3$), 24.2 ($2CH_2$), 24.9 (2C), 25.1 (CH_2), 33.5 ($2CH_2$), 44.8 (CH_2), 51.3 (C−N), 55.8 (OMe), 78.1 (C), 114.5 (2CH), 120.0 (CH), 121.0 (2CH), 122.2 (CH), 125.3 (CH), 126.8 (CH), 131.1 (C), 133.2 (C), 136.6 (C), 153.6 (C), 155.6 (C=O), 170.9 (C=O), 174.5 (C=O) ppm; MS (EI, 70 eV): m/z (%): 564 (M^+, 6), 317 (20), 288 (100), 170 (81), 113 (58),57 (43), 29 (16). Anal. calcd. for $C_{33}H_{48}N_4O_4$ (564.75): C, 70.18; H, 8.57; N, 9.92. Found: C, 70.83; H, 8.69; N, 9.04.

1-(2-(N-(2-(2,4,4-Trimethylpentan-2-ylcarbamoyl)butan-2-yl)-N-benzylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6i)

Yield: 0.56 g (91%), white powder, mp 94–96 °C. IR (KBr) (ν_{max}/cm^{-1}); 3345, 3397, 3278, 1667, 1624, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (t, $J = 7.3$, 3H), 1.05 (s, 9H), 1.37 (s, 3H), 1.41 (s, 3H), 1.52 (s, 2H), 1.61 (s, 3H), 1.99 (q, $J = 7.3$, 2H), 3.74 (s, 3H), 4.55 (d, $J = 16.8$, 1H), 4.70 (d, $J = 16.8$, 1H), 5.90 (br, 1H), 6.92 (d, $J = 9$, 2H), 7.20 (m, 3H), 7.30 (m, 5H), 7.45 (d, $J = 9$, 2H),7.96 (s, 1H), 8.32 (d, $J = 8.1$, 1H), 8.69 (s,1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 9.4 (CH_3), 25.8 (C), 28.9 ($3CH_3$), 30.9 (CH_3), 31.9 (CH_3), 33.2 (CH_3), 35.8 (CH_2), 51.1 (CH_2), 51.8 (C-N), 55.9 (MeO), 63.1 (C), 114.5 (2CH), 119.7 (CH), 121.0 (2CH), 122.3 (CH), 126.0 (CH), 126.1 (CH), 127.3 (2CH), 127.9 (CH), 129.1 (2CH), 130.4 (C), 133.1 (C), 136.9 (C), 138.3 (C), 153.6 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O), ppm; MS (EI, 70 eV) m/z (%): 586 (M^+, 4), 309 (12), 280 (100), 162 (94), 133 (15), 119 (87), 105 (21), 91 (40), 78 (12). Anal. calcd. for $C_{35}H_{46}N_4O_4$ (586.76): C, 71.64; H, 7.90, N, 9.55. Found: C, 71.33; H, 7.30; N, 10.04.

1-(2-(N-(2-(2,4,4-Trimethylpentan-2-ylcarbamoyl)propan-2-yl)-N-ethylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6j)

Yield: 0.48 g (96%), white powder, mp 101–103 °C. IR (KBr) (ν_{max}/cm^{-1}); 3460, 3330, 3270, 1654, 1645, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.05 (t,

$J = 7.35$, 3H), 1.23 (s, 9H), 1.37 (s, 6H), 1.44 (s, 6H), 1.54 (s, 2H), 3.49 (q, $J = 7.35$, 2H), 3.80 (s, 3H), 5.90 (br, 1H), 6.78 (d, $J = 9$, 2H), 7.19 (m, 3H), 7.45 (d, $J = 9$, 2H), 8.02 (s, 1H), 8.36 (d, $J = 9$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 18.7 (CH_3), 24.5 ($3CH_3$), 25.8 (C), 26.4 ($2CH_3$), 28.9 ($2CH_3$), 33.2 (CH_2), 37.9 (C), 49.8 (CH_2), 55.9 (MeO), 63.1 (C), 114.5 (2CH), 119.7 (CH), 120.8 (2CH), 122.1 (CH), 125.7 (CH), 127.7 (CH), 130.3 (C), 133.1 (C), 136.8 (C), 153.6 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O) ppm; MS (EI, 70 eV) m/z (%): 510 (M^+, 7), 233 (15), 204 (100), 119 (94), 85 (15), 71 (87), 57 (21), 43 (40), 29 (12). Anal. calcd. for $C_{29}H_{42}N_4O_4$ (510.66): C, 68.21; H, 8.29; N, 10.97. Found: C, 69.33; H, 7.98; N, 10.04.

1-(2-(N-((Cyclohexylcarbamoyl)(phenyl)methyl)-N-benzylcarbamoyl)phenyl)-3-phenylurea (6k)

Yield: 0.54 g (81%), white powder, mp 130–132 °C. IR (KBr) (ν_{max}/cm^{-1}): 3494, 3437, 3310, 1654, 1635, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15–1.99 (m, 10H), 3.82 (m, 1H), 4.55 (d, $J = 16.8$, 1H), 4.70 (d, $J = 16.8$, 1H), 5.90 (br, 1H), 6.34 (s, 1H), 7.14 (m, 5H), 7.33 (m, 5H), 7.63 (m, 4H), 7.94 (m, 4H), 8.02 (s, 1H), 8.36 (d, $J = 9$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 24.5 ($2CH_2$), 25.8 (CH), 33.2 ($2CH_2$), 49.8 (CH_2), 51.1 (C-N), 68.1 (CH), 121.5 ($2CH_2$), 121.8 (CH), 122.3 (CH), 123.9 (C), 124.1 (CH), 125 (CH), 127.7 ($2CH_2$), 128.1 ($2CH_2$), 128.9 ($2CH_2$), 129.4 ($2CH_2$), 130.3 (CH), 130.2 (CH), 131.0 ($2CH_2$), 131.8 (CH), 133.1 (C), 135.5 (C), 136.1 (C), 136.9 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O) ppm; MS (EI, 70 eV): m/z (%): 560 (M^+, 4), 342 (15), 314 (100), 196 (94), 119 (64), 105 (15), 91 (51). Anal. calcd. for $C_{35}H_{36}N_4O_3$ (560.27): C, 74.98; H, 6.47, N, 9.99. Found: C, 74.33; H, 7.01; N, 10.04.

1-(2-(N-((Cyclohexylcarbamoyl)(4-nitrophenyl)methyl)-N-benzylcarbamoyl)phenyl)-3-phenylurea (6l)

Yield: 0.53 g (73%), white powder, mp 128–130 °C. IR (KBr) (ν_{max}/cm^{-1}): 3434, 3937, 3387, 1654, 1615, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15–1.99 (m, 10H), 3.82 (m, 1H), 4.55 (d, $J = 16.8$, 1H), 4.70 (d, $J = 16.8$, 1H), 5.90 (br, 1H), 6.34 (s, 1H), 7.14 (m, 5H), 7.22 (d, $J = 9$, 2H), 7.33 (m, 5H), 7.43 (m, 3H), 7.98 (d, $J = 9$, 2H), 8.02 (s, 1H), 8.36 (d, $J = 9$, 1H), 8.58 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 24.5 ($2CH_2$), 25.8 (CH), 33.2 ($2CH_2$), 49.8 (CH_2), 51.1 (C-N), 68.1 (CH), 121.5 ($2CH_2$), 122.3 (CH), 123.9 (C), 124.1 (CH), 127.7 ($2CH_2$), 128.1 ($2CH_2$), 128.5 (CH), 128.9 ($2CH_2$), 129.4 ($2CH_2$), 130.3 (CH), 130.6 (CH), 131.0 ($2CH_2$), 131.8 (CH), 133.1 (C), 135.5 (C), 136.6 (C), 138.1 (C), 149.9 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O) ppm; MS (EI, 70 eV) m/z (%): 605 (M^+, 5), 387 (15), 359 (100), 241 (94), 119 (64), 105 (15), 91 (51). Anal. calcd. for $C_{35}H_{35}N_5O_5$ (605.68): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.33; H, 5.01; N, 11.04.

1-(2-(N-((Cyclohexylcarbamoyl)(4-nitrophenyl)methyl)-N-benzylcarbamoyl)phenyl)-3-(4-methoxyphenyl)urea (6m)

Yield: 0.54 g (75%), white powder, mp 131–133 °C. IR (KBr) (ν_{max}/cm^{-1}): 3494, 3437, 3310, 1634, 1625, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15–2.09 (m,

10H), 3.82 (m, 1H), 4.55 (d, $J = 16.8$, 1H), 3.87 (s, 3H), 4.70 (d, $J = 16.8$, 1H), 5.90 (br, 1H), 6.34 (s, 1H), 6.92 (d, $J = 9$, 2H), 7.20 (m, 3H), 7.30 (m, 5H), 7.32 (d, $J = 9$, 2H), 7.55 (d, $J = 9$, 2H), 7.95 (d, $J = 9$, 2H), 8.01 (s, 1H), 8.32 (d, $J = 8.1$, 1H), 8.69 (s, 1H) ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 24.5 ($2CH_2$), 25.8 (CH), 33.2 ($2CH_2$), 49.8 (CH_2), 51.1 (C-N), 55.9 (OMe), 68.1 (CH), 114.5 (2CH), 119.7 (CH), 121.0 (2CH), 122.3 (CH), 123 (2CH), 125 (CH), 126.0 (CH), 126.1 (CH), 127.3 (2CH), 127.9 (CH), 129.1 (2CH), 130.4 (C), 131 (CH), 133.1 (C), 136.9 (C), 138.3 (C), 142 (C), 147 (C), 153.6 (C), 155.6 (C=O), 172.6 (C=O), 176.2 (C=O) ppm; MS (EI, 70 eV) m/z (%): 635 (M^+, 5), 485 (15), 387 (100), 359 (94), 241 (64), 119 (23), 105 (15), 91 (51). Anal. calcd. for $C_{36}H_{37}N_5O_6$ (635.70): C, 68.02; H, 5.87; N, 11.02. Found: C, 68.33; H, 5.01; N, 11.04.

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