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Synthesis of Functionalized β-Lactams and Pyrrolidine-2,5-diones through a Metal-Free Sequential Ugi-4CR/Cyclization Reaction

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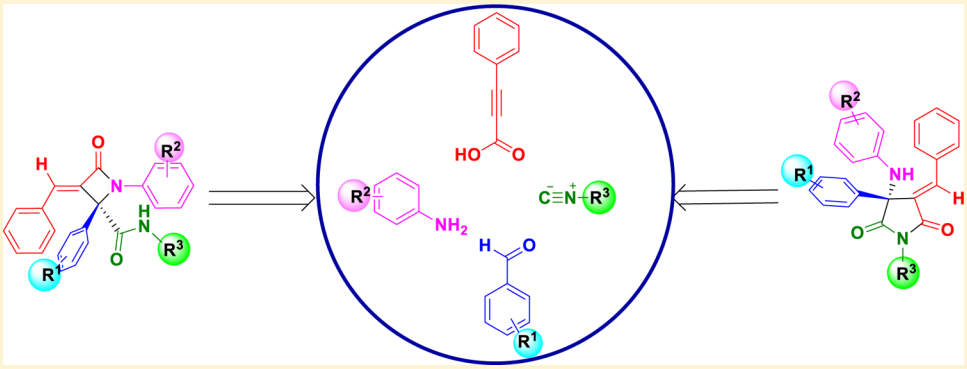
Supporting Information



ABSTRACT: An efficient approach for the synthesis of functionalized β-lactams and pyrrolidine-2,5-diones was achieved through a sequential Ugi-4CR/cyclization reaction. Diversity-oriented synthesis, good to high yields, easy workup, and short reaction times are advantages of this procedure.

INTRODUCTION

The synthesis of molecules with high diversity and complexity using readily available starting materials is an interesting approach in combinatorial chemistry and drug discovery. In this regard, combining the multicomponent reactions (MCRs) with post-MCR transformation has been used as an efficient method for the synthesis of highly functionalized compounds.[1] Among these sequential reactions, Ugi-4CR/post-transformation is the most powerful approach for the synthesis of polyfunctional compounds.[2]

N-substituted 2-alkynamides have proved to be valuable building blocks in organic synthesis.[3] In recent years, some functionalized N-substituted 2-alkynamides were synthesized through Ugi-4CR in our research group. These compounds were used for further post-transformation reactions such as nucleophilic addition and cyclization using suitable starting materials and palladium catalysts.[4] Recently, Van der Eycken used these starting materials to construct heterocyclic skeletons in the presence of different gold catalysts.[5] Meanwhile, palladium catalyst was used for the transition-metal-catalyzed cycloisomerization of alkynyl *N*-acyl enamines to access lactams.[6] Zhang et al. reported a highly enantioselective cycloisomerization approach to access functionalized lactams using Rh-based catalysts.[7] Due to the biological activities of lactams,[8] finding the new method that allows the formation of C−N bonds and stereoselective generation of functionalized lactams is an interesting subject in organic synthesis. In all of the reported cyclization reactions with these starting materials, use of a metal catalyst is necessary. However, development of a metal-free approach is an interesting challenge in organic synthesis.[9] Ugi/post-transformation has been reported for the synthesis of β-lactams, but the use of functionalized starting materials has an important role in the cyclization reaction process.[10]

In continuation of our previous research based on the cyclization reactions of functionalized N-substituted 2-alkynamides,[4] we were encouraged to investigate the cyclization products through these compounds under metal-free reaction conditions. Herein, we report a metal-free cyclization through a sequential Ugi-4CR/cyclization reaction for the synthesis of functionalized β-lactams and pyrrolidine-2,5-diones (Scheme 1).

RESULTS AND DISCUSSION

In the first step, Ugi-4CR of benzaldehyde, aniline, *tert*-butyl isocyanide, and phenylpropiolic acid was chosen as the model reaction. The N-substituted 2-alkynamide **5a** was precipitated and separated, followed by treatment with different bases and solvents. During the optimization of the reaction conditions, it was revealed that potassium carbonate (K_2CO_3) was the most effective base to provide cyclization products in comparison to

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Scheme 1. Synthesis of β-Lactams and Pyrrolidine-2,5-diones through a Metal-Free Sequential Ugi-4CR/Cyclization Reaction

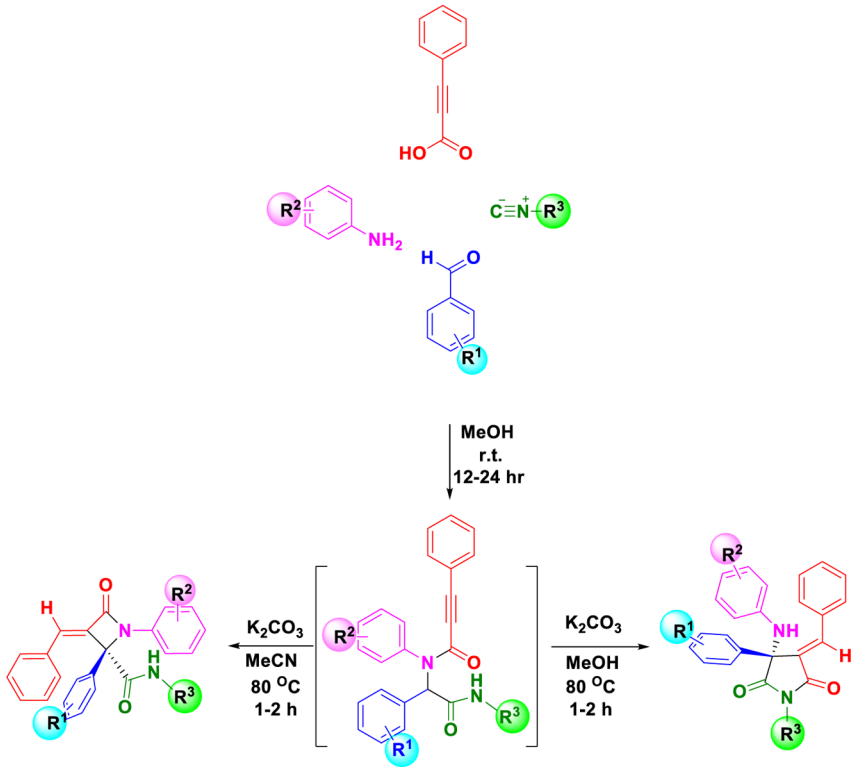
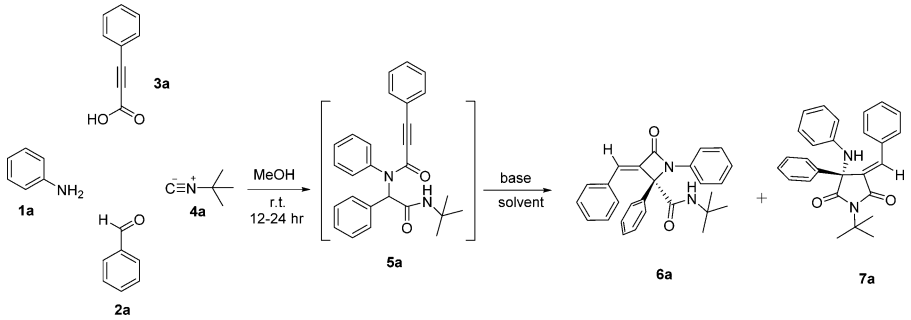


Table 1. Optimization of Reaction Conditions for the Synthesis of β-Lactam 6a and)Pyrrolidine-2,5-dione 7a[a]



entry	base	solvent	T (°C)	yield (%) 6a	yield (%) 7a
1	K_2CO_3	CH_2Cl_2	room temp		
2	K_2CO_3	MeCN	80	95	
3	K_2CO_3	DMF	120	75	25
4	K_2CO_3	THF	reflux		
5	K_2CO_3	H_2O	reflux		
6	K_2CO_3	toluene	reflux		
7	K_2CO_3	MeOH	reflux		94
8	Cs_2CO_3	MeOH	reflux		54
9	CsOAc	MeOH	reflux		
10	Et_3N	MeOH	reflux	trace	
11	DIEA	MeOH	reflux	10	

[a]The reaction was performed using **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), **4a** (1 mmol), the base (1 equiv), and 5 mL of solvent.

other bases (Table 1, entries 8−11). Carrying out the reaction in acetonitrile led to the synthesis of β-lactam **6a**, and in methanol the sole product was pyrrolidine-2,5-dione **7a** (Table 1). With our optimized reaction conditions in hand, carrying out the reaction in DMF led to a mixture of the two products **6a** and **7a** (75:25, respectively).

On the basis of this information and in order to explore the above reaction scope, different aldehydes, anilines, and isocyanides were used as starting materials. In all cases, β-lactam skeletons with some functional groups were produced in good to high yields. The results are summarized in Table 2. The products with β-lactam skeletons (**6a−n**) were obtained in 63−

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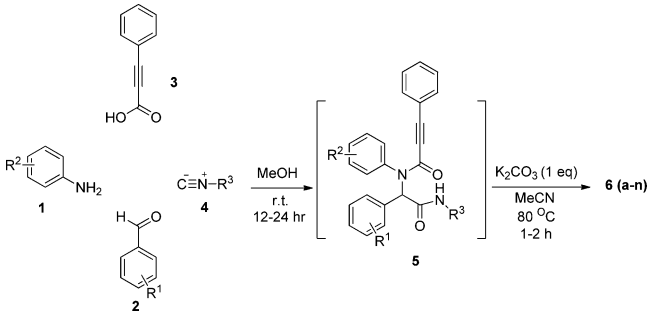
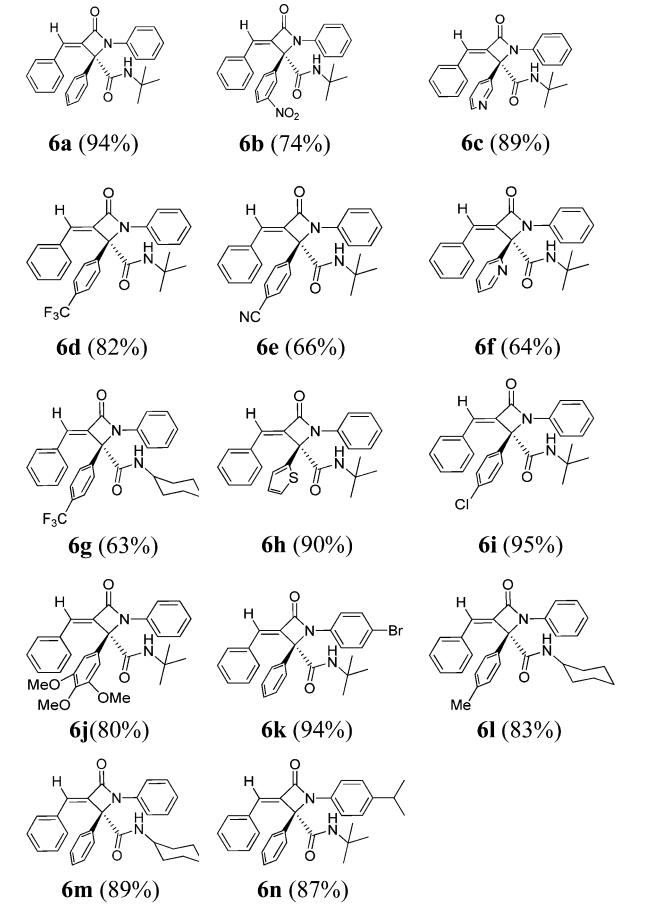
Table 2. Synthesis of Functionalized β-Lactams 6a−n through a Sequential Ugi 4-CR/Cyclization Reaction





95% yields. The lowest yield (63%) was obtained for compound **6g**, for which trifluoromethyl benzaldehyde was used as the aldehyde and cyclohexyl isocyanide as the isocyanide. A significant point in the formation of β-lactams is an *E* geometry for the double bond in all cases. It seems that the secondary interaction (π−π stacking) could affect the geometry of formed β-lactams.

X-ray crystallographic data could confirm the structure of **6i**. The double bond has an *E* configuration, and the orientation of the two aryl groups is suitable for π−π stacking (Figure 1).

After having the best reaction conditions in hand, we screened a range of N-substituted 2-alkynamides in a one-pot sequential Ugi-4CR/intramolecular nucleophilic cyclization in methanol. The results are summarized in Table 3. The obtained products were pyrrolidine-2,5-diones with regioselectivity **7a**−**o**, and the double bonds in the structures of products had an *E* configuration. The progress of the reactions was monitored by

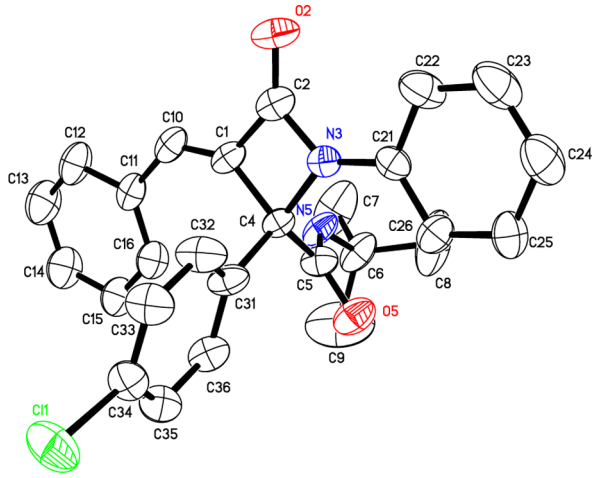


Figure 1. ORTEP structure of compound **6i**.

TLC, and comparison of data showed that the pyrrolidine-2,5-dione **7a** was produced through a β-lactam intermediate in high yield.

The structures of **6a**−**n** and **7a**−**o** were assigned by ^{1}H NMR and ^{13}C NMR spectroscopy and also proved by ESI-HRMS. There are two prominent differences in the NMR spectra of these two sets of compounds. The first is the highly characteristic peak at 4−5 ppm for NH in pyrrolidine-2,5-dione, which was not observed in β-lactam derivatives. The second is the difference in the chemical shift of the carbonyl amide in β-lactam (162−166 ppm) and pyrrolidine-2,5-dione (170−176 ppm). For the two compounds **7b**,**d** the ORTEP structure could confirm the products (Supporting Information). ^{1}H−^{1}H-COSY 2D NMR was used for determination of the structure of compounds. The 2D ^{1}H NMR spectra of the compounds **6n** and **7m** are provided in the Supporting Information.

In another try, the reaction was investigated using propiolic acid instead of phenylpropiolic acid. In this case, the intermediate **8** could not convert to the desired pyrrolidine-2,5-dione and MeOH was added to the triple bond (Scheme 2).

The same reaction was also checked with 2-butynoic acid and trimethylsilylpropiolic acid in methanol, and the desired products were not formed. The structure of the product was confirmed on the basis of the NMR spectra. According to the NMR data, when 2-butynoic acid was used, the reaction in methanol led to the methyl ether. The Ugi-4CR reaction was carried out using trimethylsilylpropiolic acid, and its reaction was studied in methanol in the presence of potassium carbonate, which led to the acetal **9** with the elimination of a trimethylsilyl group.

In the structures of functionalized N-substituted 2-alkynamides **5**, there are two amide moieties, a triple bond, and also a C−H bond. The C−H bond has an acidic character, which could be deprotonated using a suitable base to form the carbanion, which in turn could be added to the triple bond through intramolecular nucleophilic addition. A plausible mechanism for these cyclization reactions is depicted in Scheme 3. The reactions proceed via the formation of intermediate **5** through Ugi-4CR. There are two feasible pathways from **5** in different solvents. Initially, the carbanion is formed by the addition of the base (Scheme 3). It is reasonable to assume that the intramolecular nucleophilic addition of carbanion to a triple bond in Ugi product **5**, forms the β-lactam

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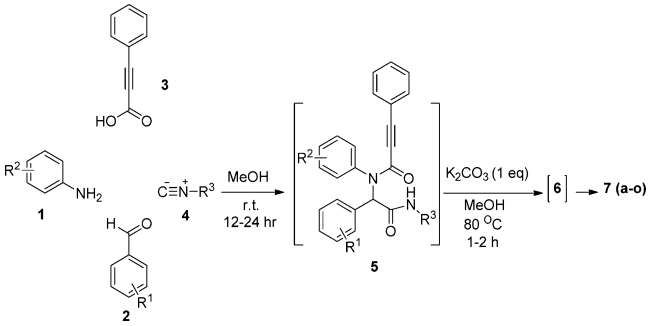
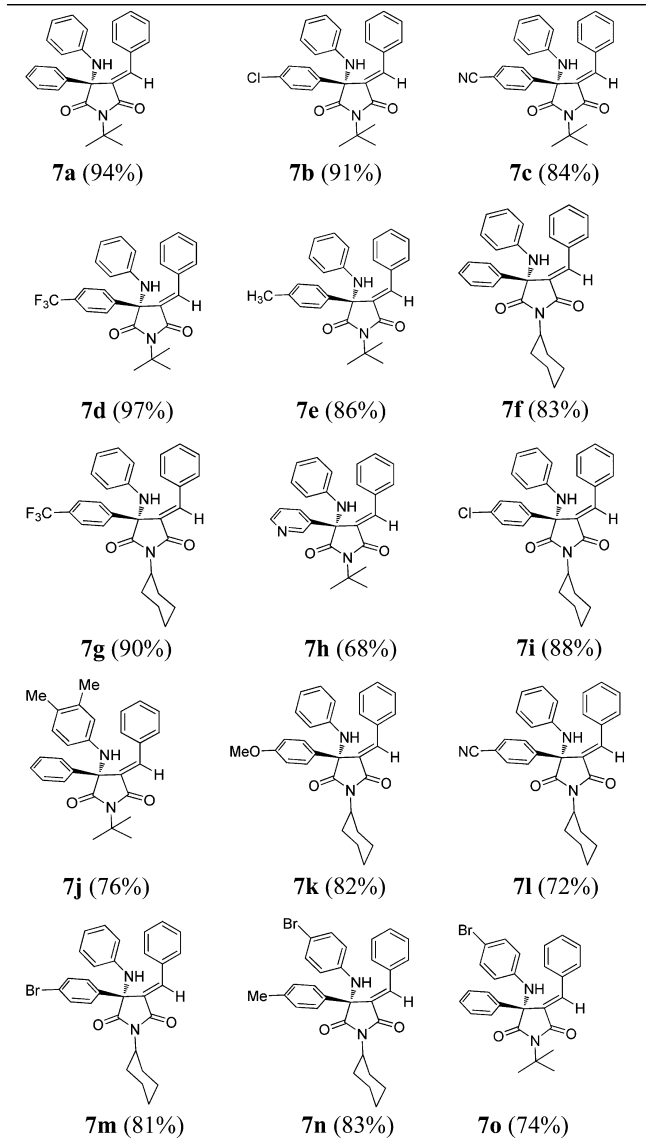
Table 3. Synthesis of Pyrrolidine-2,5-dione Derivatives 7a−o through a Sequential Ugi 4CR/Cyclization Reaction via the β-Lactam Intermediate 6





skeleton in both solvents. However, it can act as an intermediate in MeOH and the attack of methoxide at the carbonyl group in the β-lactam skeleton takes place immediately from one direction to afford the pyrrolidine-2,5-dione with regioselectivity.

The formation of different products in various solvents could be attributed to the basicity of K_2CO_3 in MeCN and MeOH. Potassium carbonate in MeCN could deprotonate the acidic C(sp^3)−H in the Ugi product, but in MeOH, methoxide anion is produced, which is a stronger nucleophile than K_2CO_3 and, in addition to the deprotonation of C−H, can activate the NH amide; thus, the second cyclization occurs.

In conclusion, we have developed a novel and efficient method for the synthesis of two distinct sets of functionalized β-lactams and pyrrolidine-2,5-dione from the same Ugi adducts **5** involving an Ugi-4CR/cyclization sequence under metal-free reaction conditions. Good to excellent yields, short reaction times, easy workup, high bond-forming efficiency, atom economy, and application of this approach to combinatorial chemistry are the advantages of this approach.

EXPERIMENTAL SECTION

General Information. High-resolution mass spectra were recorded on Mass-ESI-POS and Mass-ESI-NEG (FT-ICR) spectrometers.

General Procedure for the Synthesis of Polysubstituted β-Lactams 6a−n through a Sequential Ugi-4CR/Cyclization Reaction. To a solution of aldehyde **1** (1 mmol) in MeOH (5 mL) was added aniline as the primary amine **2** (1 mmol), and the reaction mixture was stirred at room temperature (25 °C) for 1 h. Then phenylacetylenecarboxylic acid **3** (1 mmol) was added and stirring was continued for 15 min, followed by addition of isocyanide **4** (1 mmol). The mixture was stirred for 24 h. The progress of the reaction was monitored using TLC (petroleum ether/EtOAc 3/1). After completion of the reaction, the N-substituted 2-alkynamide **5** was precipitated, separated, and transferred to a flask which contained 10 mL of MeCN. Then K_2CO_3 (1 equiv) was added to the mixture and the mixture was heated under reflux conditions for 1−2 h. The progress of the reaction was monitored using TLC (hexane/EtOAc 4/1). After the mixture was cooled to room temperature, the desired product was precipitated and the yellowish sediment was filtered.

*(E)-3-Benzylidene-N-(tert-butyl)-4-oxo-1,2-diphenylazetidine-2-carboxamide (**6a**):* white powder; 385 mg (94%); mp 172−173 °C; IR (KBr, cm^{-1}) ν 1670, 1749, 3343; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.22 (s, 9H, *t*-Bu), 6.09 (s, 1H, NH), 7.03 (td, *J* = 7.4, 0.9 Hz, 1H, H-Ar), 7.20−7.39 (m, 11H, H-Ar, C═CH), 7.52 (d, *J* = 8.1 Hz, 2H, H-Ar), 7.65 (dd, *J* = 7.2, 1.1 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.3, 52.0, 76.6, 118.3, 124.5, 126.5, 128.3, 128.7, 128.9, 128.9, 129.1, 130.2, 130.6, 131.9, 134.8, 136.7, 141.0, 163.0, 166.2; HR-MS (ESI-POS) calcd for $C_{27}H_{27}N_2O_2$ $[M + H]^+$ 411.20676, found 411.20670, calcd for $C_{27}H_{26}N_2NaO_2$ $[M + Na]^+$ 433.18871, found 433.18865.

*(E)-3-Benzylidene-N-(tert-butyl)-2-(3-nitrophenyl)-4-oxo-1-phenylazetidine-2-carboxamide (**6b**):* white powder; 337 mg (74%); mp 182−184 °C; IR (KBr, cm^{-1}) ν 1673, 1740, 3383; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.30 (s, 9H, *t*-Bu), 6.34 (s, 1H, NH), 7.08 (t, *J* = 7.3 Hz, 1H, H-Ar), 7.25−7.54 (m, 10H, H-Ar, C═CH), 7.97 (d, *J* = 7.8 Hz, 1H, H-Ar), 8.14 (d, *J* = 8.2 Hz, 1H, H-Ar), 8.60 (s, 1H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.4, 52.5, 74.6, 118.0, 123.9, 125.1, 128.1, 128.9, 129.4, 129.7, 130.7, 130.8, 131.1, 134.4, 136.0, 136.6, 139.6, 148.3, 162.5, 165.5; HR-MS (ESI-POS) calcd for $C_{27}H_{26}N_3O_4$ $[M + H]^+$ 456.19182, found 456.1917, calcd $C_{27}H_{25}N_3NaO_4$ $[M + Na]^+$ 478.17377, found 478.17373.

*(E)-3-Benzylidene-N-(tert-butyl)-4-oxo-1-phenyl-2-(pyridin-3-yl)-azetidine-2-carboxamide (**6c**):* white powder; 366 mg (89%); mp 161−162 °C; IR (KBr, cm^{-1}) ν 1675, 1744, 3339; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.27 (s, 9H, *t*-Bu), 6.25 (s, 1H, NH), 7.07 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.21−7.37 (m, 7H, H-Ar, C═CH), 7.44 (d, *J* = 6.5 Hz, 2H, H-Ar), 7.47 (d, *J* = 8.2 Hz, 2H, H-Ar), 7.95 (d, *J* = 9.3 Hz, 1H, H-Ar), 8.53 (d, *J* = 4.7 Hz, 1H, H-Ar), 8.93 (s, 1H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.3, 52.3, 74.3, 118.1, 123.3, 125.0, 127.8, 128.8, 129.2, 130.4, 130.6, 130.7, 131.3, 136.1, 136.2, 139.6, 149.9, 150.0, 162.6, 165.6; HR-MS (ESI-POS) calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.20195, found 412.20195, calcd $C_{26}H_{25}N_3NaO_2$ $[M + Na]^+$ 434.18391, found 434.18390.

*(E)-3-Benzylidene-N-(tert-butyl)-4-oxo-1-phenyl-2-(4-(trifluoromethyl)phenyl)azetidine-2-carboxamide (**6d**):* white pow-

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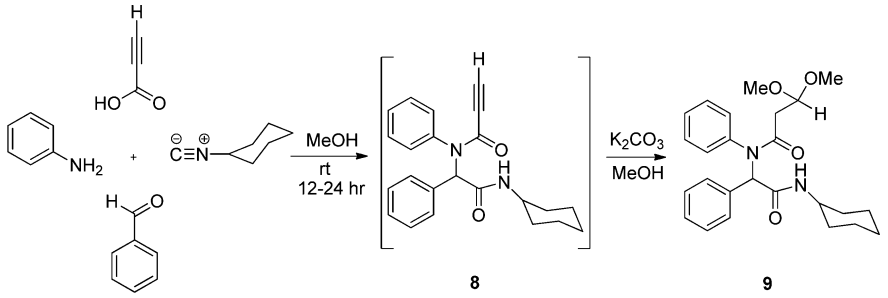
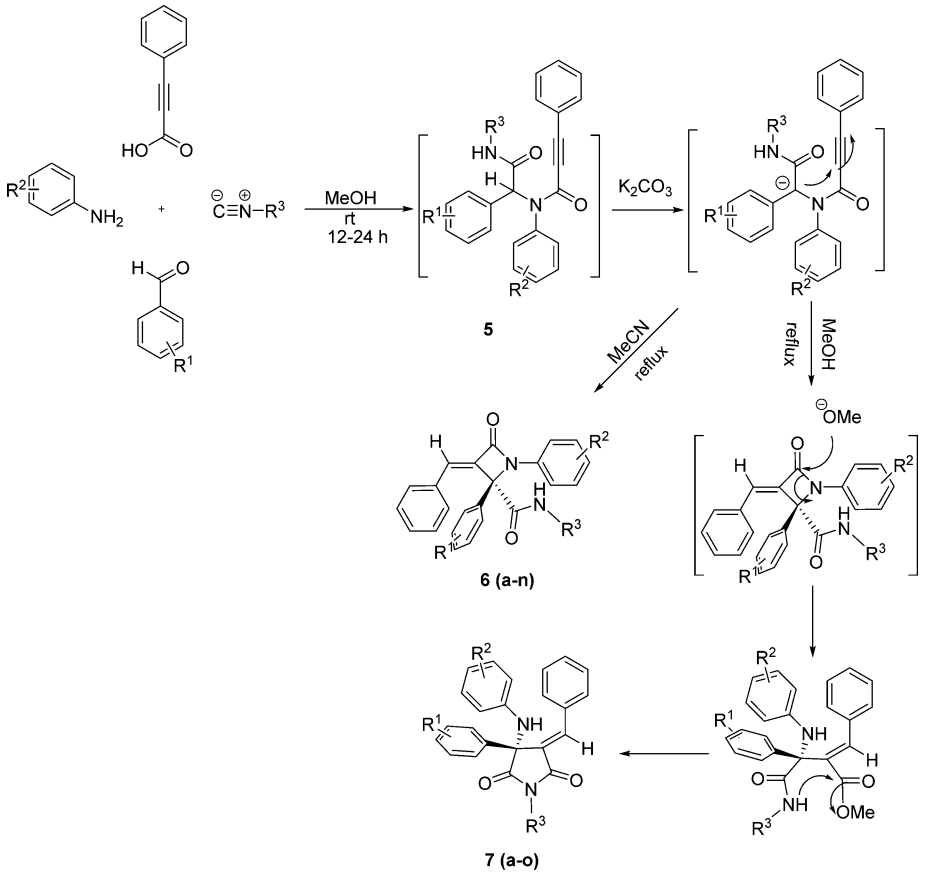
Scheme 2. Nucleophilic Addition of Methanol to N-Substituted 2-Alkynamide 8 and Formation of the Unexpected Product 9



Scheme 3. Plausible Mechanism for the Formation of β-Lactams 6a−n and Pyrrolidine-2,5-diones 7a−o in Methanol



der; 392 mg (82%); mp 164−166 °C; IR (KBr, cm^{-1}) ν 1670, 1751, 3349; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.27 (s, 9H, *t*-Bu), 6.23 (s, 1H, NH), 7.08 (t, *J* = 7.1 Hz, 1H, H-Ar), 7.24−7.34 (m, 6H, H-Ar, C═CH), 7.41 (d, *J* = 6.7 Hz, 2H, H-Ar), 7.48 (d, *J* = 8.4 Hz, 2H, H-Ar), 7.59 (d, *J* = 8.2 Hz, 2H, H-Ar), 7.80 (d, *J* = 8.2 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.3, 52.3, 75.4, 118.1, 124.9, 125.7, 127.5, 128.8, 128.9, 129.2, 130.6, 130.7, 131.2, 131.3, 136.2, 138.5, 140.0, 162.7, 165.7;HR-MS (ESI-POS) calcd for $C_{28}H_{26}F_3N_2O_2$ $[M + H]^+$ 479.19417, found 479.19409, calcd $C_{28}H_{25}F_3N_2NaO_2$ $[M + Na]^+$ 501.17613, found 501.17603.

*(E)-3-Benzylidene-N-(tert-butyl)-2-(4-cyanophenyl)-4-oxo-1-phenylazetidine-2-carboxamide (**6e**):* white powder; 287 mg (66%); mp 182−184 °C; IR (KBr, cm^{-1}) ν 1670, 1751, 3349; ^1H NMR ($CDCl_3$,300 MHz) δ (ppm) 1.27 (s, 9H, *t*-Bu), 6.25 (s, 1H, NH), 7.09 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.24−7.35 (m, 6H, H-Ar, C═CH), 7.42 (t, *J* = 7.7 Hz, 4H, H-Ar), 7.61 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.79 (d, *J* = 8.4 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.3, 52.4, 75.0, 112.8, 118.0, 118.2, 125.1, 127.9, 128.8, 129.3, 130.7, 130.8, 131.1, 132.4, 136.0, 139.6, 139.7, 162.6, 165.4; HR-MS (ESI-POS) calcd for $C_{28}H_{26}N_3O_2$ $[M + H]^+$ 436.20202, found 436.20195, calcd $C_{28}H_{25}N_3NaO_2$ $[M + Na]^+$ 458.18398, found 458.18390.

*(E)-3-Benzylidene-N-(tert-butyl)-4-oxo-1-phenyl-2-(pyridin-2-yl)-azetidine-2-carboxamide (**6f**):* white powder; 263 mg (64%); mp 159−161 °C; IR (KBr, cm^{-1}) ν 1673, 1755, 3214, 3429; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.35 (s, 9H, *t*-Bu), 7.02 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.13 (s, 1H, NH), 7.21−7.69 (m, 12H, H-Ar, H-pyrid, C═CH), 8.63 (d, *J* = 4.7 Hz, 1H, H-Ar), 9.67 (s, 1H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.5, 51.8, 73.2, 117.3, 123.4, 123.5, 124.1, 125.6, 128.4, 129.0, 129.8, 130.3, 132.1, 137.0, 138.2, 142.1, 147.7, 156.1, 162.7, 165.0; HR-MS (ESI-POS) calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.20195, found 412.20195, calcd for $C_{26}H_{25}N_3NaO_2$ $[M + Na]^+$ 434.18393, found 434.18390, calcd for $C_{26}H_{25}KN_3O_2$ $[M + K]^+$ 450.15787, found 450.15784.

*(E)-3-Benzylidene-N-cyclohexyl-4-oxo-1-phenyl-2-(4-(trifluoromethyl)phenyl)azetidine-2-carboxamide (**6g**):* white powder; 317 mg (63%); mp 166−168 °C; IR (KBr, cm^{-1}) ν 1668, 1750, 3342; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.00−1.88 (m, 10H, H-cyclohexyl), 3.85−3.95 (m, 1H, N−CH), 6.34 (d, *J* = 7.5, 1H, NH), 7.08 (t, *J* = 7.3 Hz, 1H, H-Ar), 7.24−7.46 (m, 10H, H-Ar, C═CH),

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7.58 (d, J = 8.2 Hz, 2H, H-Ar), 7.83 (d, J = 8.1 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 24.5, 25.2, 32.4, 32.6, 48.9, 74.9, 118.0, 124.9, 125.5, 125.7, 127.9, 128.7, 128.9, 129.3, 130.7, 130.9, 131.2, 136.1, 138.2, 139.6, 162.8, 165.5; HR-MS (ESI-POS) calcd for $C_{30}H_{28}F_3N_2O_2$ $[M + H]^+$ 505.20978, found 505.20974, calcd for $C_{30}H_{27}F_3N_2NaO_2$ $[M + Na]^+$ 527.19168, found 527.19168, calcd for $C_{30}H_{27}F_3KN_2O_2$ $[M + K]^+$ 543.16567, found 543.16562.

*(E)-3-Benzylidene-N-(tert-butyl)-4-oxo-1-phenyl-2-(thiophen-2-yl)azetidine-2-carboxamide (**6h**):* yellow powder; 374 mg (90%); mp 174−176 °C; IR (KBr, cm^{-1}) ν 1670, 1749, 3338; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.24 (s, 9H, *t*-Bu), 6.23 (s, 1H, NH), 6.92 (t, J = 4.6 Hz, 1H, H-thienyl), 7.08 (t, J = 7.5 Hz, 1H, H-Ar), 7.18 (s, 1H, =CH), 7.26−7.53 (m, 11H, H-Ar, H-thienyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.2, 52.2, 72.2, 117.9, 124.7, 126.6, 126.8, 128.2, 128.7, 128.8, 129.1, 130.4, 130.9, 131.5, 136.2, 136.3, 141.3, 162.6, 166.1; HR-MS (ESI-POS) calcd for $C_{25}H_{25}N_2O_2S$ $[M + H]^+$ 417.16319, found 417.16313, calcd $C_{25}H_{24}N_2NaO_2S$ $[M + Na]^+$ 439.14515, found 439.14507.

*(E)-3-Benzylidene-N-(tert-butyl)-2-(4-chlorophenyl)-4-oxo-1-phenylazetidine-2-carboxamide (**6i**):* white powder; 422 mg (95%); mp 184−185 °C; IR (KBr, cm^{-1}) ν 1671, 1747, 3341, 3341; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.24 (s, 9H, *t*-Bu), 6.17 (s, 1H, NH), 7.06 (t, J = 7.0 Hz, 1H, H-Ar), 7.21−7.35 (m, 8H, H-Ar, C=CH), 7.41 (d, J = 6.8 Hz, 2H, H-Ar), 7.48 (d, J = 7.9 Hz, 2H, H-Ar), 7.61 (d, J = 8.4 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.3, 52.2, 75.6, 118.2, 124.8, 127.1, 128.8, 129.0, 129.1, 129.8, 130.5, 130.7, 131.5, 133.1, 135.0, 136.3, 140.4, 162.8, 165.8; HR-MS (ESI-POS) calcd for $C_{27}H_{26}ClN_2O_2$ $[M + H]^+$ 445.16781, found 445.16773, calcd $C_{27}H_{25}ClN_2NaO_2$ $[M + Na]^+$ 467.14977, found 467.14968. Crystal data: colorless crystal (polyhedron), dimensions 0.170 × 0.110 × 0.110 mm^3, crystal system monoclinic, space group $C2/c$, Z = 8, a = 25.069(3) Å, b = 10.0489(12) Å, c = 20.245(2) Å, α = 90°, β =110.317(2)°, γ = 90°, V = 4782.8(10) Å^3, ρ = 1.236 g/cm^3, T = 200(2) K, θ_{max} = 25.027°, radiation Mo Kα, λ = 0.71073 Å, 0.5° ω scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 10.42 and a completeness of 99.9% to a resolution of 0.84 Å, 44807 reflections measured, 4210 unique (R(int) = 0.0469), 3255 observed ($I > 2\sigma(I)$), intensities corrected for Lorentz and polarization effects, empirical absorption correction applied using SADABS based on the Laue symmetry of the reciprocal space, μ = 0.19 mm^{-1}, T_{min} = 0.90, T_{max} = 0.99, structure refined against F^2 with a full-matrix least-squares algorithm using the SHELXL (version 2014-1) software, 407 parameters refined, hydrogen atoms treated using appropriate riding models, goodness of fit 1.14 for observed reflections, final residual values R1(F) = 0.057, wR(F^2) = 0.133 for observed reflections, residual electron density −0.23 to 0.24 e Å^{-3}. CCDC 991555 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*(E)-3-Benzylidene-N-(tert-butyl)-4-oxo-1-phenyl-2-(3,4,5-trimethoxyphenyl)azetidine-2-carboxamide (**6j**):* white powder; 400 mg (80%); mp 136−138 °C; IR (KBr, cm^{-1}) ν 3368, 3327, 1740, 1673; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.19 (s, 9H, *t*-Bu), 3.70 (s, 6H, OMe), 3.83 (s, 3H, OMe), 6.04 (s, 1H, NH), 6.82 (s, 2H, H-Ar), 7.06 (t, J = 7.3 Hz, 1H, H-Ar), 7.23−7.38 (m, 8H, H-Ar, C=CH), 7.54 (d, J = 8.2 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.2, 52.0, 56.1, 60.9, 105.4, 118.4, 124.7, 126.3, 128.8, 128.9, 130.2, 130.4, 132.1, 136.8, 138.4, 141.2, 153.3, 162.8, 166.4; HR-MS (ESI-POS) calcd for $C_{30}H_{33}N_2O_5$ $[M + H]^+$ 501.23807, found 501.23807, calcd $C_{30}H_{32}N_2NaO_5$ $[M + Na]^+$ 523.22021, found 523.22023, calcd $C_{30}H_{32}KN_2O_5$ $[M + K]^+$ 539.19422, found 539.19423.

*(E)-3-Benzylidene-1-(4-bromophenyl)-N-(tert-butyl)-4-oxo-2-phenylazetidine-2-carboxamide (**6k**):* white powder; 464 mg (95%); mp 212−214 °C; IR (KBr, cm^{-1}) ν 3337, 1750, 1674; ^{1}H NMR ($CDCl_3$,300 MHz) δ (ppm) 1.19 (s, 9H, *t*-Bu), 6.00 (s, 1H, NH), 7.26−7.30 (m, 6H, H-Ar, -C=CH), 7.32−7.33 (m, 2H, H-Ar), 7.36−7.41 (m, 3H, H-Ar), 7.43−7.47 (m, 2H, H-Ar), 7.59−7.63 (m, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 28.3, 52.1, 76.8, 117.2, 119.9, 126.6, 128.0, 128.9, 129.2, 129.4, 130.3, 130.4, 131.8, 134.8, 135.9, 141.3, 162.6, 165.9; HR-MS (ESI-POS) calcd for $C_{27}H_{26}{}^{79}BrN_2O_2$ $[M + H]^+$ 489.11721, found 489.11721.

*(E)-3-Benzylidene-N-cyclohexyl-4-oxo-1-phenyl-2-(p-tolyl)-azetidine-2-carboxamide (**6l**):* white powder; 373 mg (83%); mp 154−156 °C; IR (KBr, cm^{-1}) ν 3337, 1746, 1670; ^{1}H NMR ($CDCl_3$,300 MHz) δ (ppm) 0.95−1.07 (m, 3H, H-cyclohexyl), 1.25−1.32 (m, 2H, H-cyclohexyl), 1.50−1.52 (m, 3H, H-Ar), 1.75−1.84 (m, 2H, H-Ar), 2.30 (*s*, 1H, -Me), 3.83−3.92 (m, 1H, CH- cyclohexyl), 6.19 (d, J = 7.8, Hz, 1H, NH), 7.03 (t, J = 7.4 Hz, 1H, H-Ar), 7.14 (d, J = 8.1 Hz, 2H, H-Ar), 7.21−7.31 (m, 6H, H-Ar, C=CH), 7.44−7.56 (m, 6H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 21.2, 24.4, 25.3, 32.3, 32.6, 48.6, 76.1, 118.2, 124.5, 126.9, 128.2, 128.6, 129.0, 129.6, 130.2, 130.9, 131.2, 131.7, 136.6, 139.0, 140.5, 163.2, 166.2; HR-MS (ESI-POS) calcd for $C_{30}H_{31}N_2O_2$ $[M + H]^+$ 451.23834, found 451.23828, calcd $C_{30}H_{30}N_2NaO_2$ $[M + Na]^+$ 473.22036, found 473.22029, calcd $C_{30}H_{30}KN_2O_2$ $[M + K]^+$ 489.19436, found 489.19428.

*(E)-3-Benzylidene-N-cyclohexyl-4-oxo-1,2-diphenylazetidine-2-carboxamide (**6m**):* yellow powder; 388 mg (89%); mp 150−152 °C; IR (KBr, cm^{-1}) ν 3358, 1737, 1669; ^{1}H NMR ($CDCl_3$,300 MHz) δ (ppm) 0.87−1.12 (m, 3H, H-cyclohexyl), 1.27−1.36 (m, 2H, H-cyclohexyl), 1.51−1.53 (m, 3H, H-cyclohexyl), 1.78−1.86 (m, 2H, H-cyclohexyl), 3.83−3.95 (m, 1H, CH- cyclohexyl), 6.24 (d, J = 7.7, Hz, 1H, NH), 7.04 (t, J = 7.0 Hz, 1H, H-Ar), 7.18−7.29 (m, 6H, H-Ar), 7.31−7.38 (m, 3H, H-Ar, C=CH), 7.40 (d, J = 7.7 Hz, 2H, H-Ar), 7.49 (d, J = 8.4 Hz, 2H, H-Ar), 7.67 (d, J = 7.1 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 24.4, 25.3, 32.3, 32.6, 48.7, 76.1, 115.4, 118.2, 124.6, 127.2, 128.3, 128.6, 128.9, 129.0, 129.1, 129.5, 130.3, 130.9, 131.6, 134.3, 136.5, 140.3, 163.1, 166.1; HR-MS (ESI-POS) calcd for $C_{29}H_{29}N_2O_2$ $[M + H]^+$ 437.22209, found 437.22214, calcd $C_{29}H_{28}N_2NaO_2$ $[M + Na]$ + 459.20408, found 459.20412, calcd $C_{29}H_{28}KN_2O_2$ $[M + K]^+$ 475.17806, found 475.17809.

*(E)-3-Benzylidene-N-(tert-butyl)-1-(4-isopropylphenyl)-4-oxo-2-phenylazetidine-2-carboxamide (**6n**):* white powder; 393 mg (87%); mp 162−164 °C; IR (KBr, cm^{-1}) ν 3351, 1740, 1670; ^{1}H NMR ($CDCl_3$,300 MHz): 1.17 (d, J = 6.9 Hz, 6H, −CH3), 1.22 (s, 9H, *t*-Bu), 2.78−2.83 (m, 1H, −CH), 6.09 (s, 1H, NH), 7.08 (d, J = 8.5 Hz, 2H, H-Ar), 7.23−7.29 (m, 4H, H-Ar), 7.30−7.39 (m, 5H, H-Ar, C=CH), 7.42 (d, J = 8.5 Hz, 2H, H-Ar), 7.65 (d,, J = 6.2 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 23.8, 23.9 28.3, 33.6, 52.0, 118.4, 126.1, 126.9, 128.3, 128.7, 128.9, 129.0, 130.1, 130.5, 131.9, 134.4, 135.0, 141.1, 145.2, 162.8, 166.3; HR-MS (ESI-POS) calcd for $C_{30}H_{33}N_2O_2$ $[M + H]^+$ 453.25344, found 453.25348, calcd $C_{30}H_{32}N_2NaO_2$ $[M + Na]^+$ 475.23552, found 475.23553, calcd $C_{30}H_{32}KN_2O_2$ $[M + K]^+$ 491.20949, found 491.20950.

General Procedure for the Synthesis of Polysubstituted Pyrrolidine-2,5-diones through a One-Pot Ugi 4CR/Cyclization Reaction (7a−o). To a solution of aldehyde **1** (1 mmol) in MeOH (5 mL) was added aniline as the primary amine **2** (1 mmol), and the reaction mixture was stirred at room temperature (25 °C) for 1 h. Then phenylacetylenecarboxylic acid **3** (1 mmol) was added, and stirring was continued for 15 min, followed by addition of isocyanide **4** (1 mmol). The mixture was stirred for 24 h. The progress of the reaction was monitored using TLC (petroleum ether/EtOAc 3/1). After completion of the reaction, K_2CO_3 (1 equiv) was added to the mixture and then the mixture was heated under reflux for 1−2 h. The reaction progress was monitored using TLC (hexane/EtOAc 4/1). After the mixture was cooled to room temperature, the desired product was precipitated and the yellowish sediment was filtered.

*(R,E)-4-Benzylidene-1-(tert-butyl)-3-phenyl-3-(phenylamino)-pyrrolidine-2,5-dione (**7a**):* yellow powder; 385 mg (94%); mp 171−173 °C; IR (KBr, cm^{-1}) ν 3389, 1763, 1698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H, *t*-Bu), 4.45 (s, 1H, −NH), 6.28 (d, 2H, J = 8.3 Hz, H-Ar), 6.72 (t, 1H, J = 7.0 Hz, H-Ar), 7.17 (t, 2H, J = 7.4 Hz, H-Ar), 7.23−7.28 (m, 1H, H-Ar), 7.33 (d, 2H, J = 7.3 Hz, H-Ar), 7.40−7.47 (m, 3H, H-Ar), 7.73 (d, 2H, J = 8.1 Hz, H-Ar), 7,93 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 59.1, 67.2, 116.4, 120.0, 126.3, 128.1, 128.6, 128.7, 129.1, 129.4, 129.9, 131.0, 133.1, 138.2, 138.5, 144.1, 170.6, 176.5; HR-MS (ESI-POS) calcd for $C_{27}H_{27}N_2O_2$

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[M + H]+ 411.20700, found 411.20694, calcd for $C_{27}H_{26}N_2NaO_2$ [M + Na]$^+$ 433.18908, found 433.18900, calcd for $C_{27}H_{26}KN_2O_2$ [M + K]$^+$ 449.16301, found 449.16293.

*(R,E)-4-Benzylidene-1-(tert-butyl)-3-(4-chlorophenyl)-3-(phenylamino)pyrrolidine-2,5-dione (**7b**):* yellow powder; 404 mg (91%); mp 197−199 °C; IR (KBr, cm^{-1}) ν 1705, 1768, 3424; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 9H, *t*-Bu), 4.36 (s, 1H, −NH), 6.29 (d, 2H, *J* = 8.0 Hz, H-Ar), 6.74 (t, 1H, *J* = 7.3 Hz, H-Ar), 6.98 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.20 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.27 (d, 1H, *J* = 5.6 Hz, H-Ar), 7.33 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.39 (d, 2H, *J* = 8.5 Hz, H-Ar), 7.64 (d, 2H, *J* = 8.5 Hz, H-Ar), 7.91 (s, 1H, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 59.2, 66.8, 116.9, 120.5, 127.8, 128.2, 128.8, 129.5, 130.1, 131.0, 132.9, 135.2, 137.0, 138.6, 143.8, 170.4, 176.2; HR-MS (ESI-NEG): calcd for $C_{27}H_{26}ClN_2O_2$ [M + H]$^+$ 445.16745, found 445.16750, calcd for $C_{27}H_{25}ClKN_2O_2$ [M + K]+ 483.12336, found 483.12340. Crystal data: yellow crystal (polyhedron), dimensions 0.18 × 0.10 × 0.10 mm^3, crystal system monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 12.8190(6) Å, *b* = 10.5217(5) Å, *c* = 18.1283(8) Å, α = 90°, β =106.9487(12)°, γ = 90°, *V* = 2338.90(19) Å^3, ρ = 1.264 g/cm^3, *T* = 200(2) K, θ_{max} = 25.106°, radiation Mo Kα, λ = 0.71073 Å, 0.5° ω scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 6.74 and a completeness of 99.5% to a resolution of 0.84 Å, 28777 reflections measured, 4154 unique (*R*(int) = 0.0445), 3053 observed ($I > 2\sigma(I)$), intensities corrected for Lorentz and polarization effects, empirical absorption correction applied using SADABS based on the Laue symmetry of the reciprocal space, μ = 0.19 mm^{-1}, T_{min} = 0.89, T_{max} = 0.96, structure refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL (Version 2014−1) software, 292 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.06 for observed reflections, final residual values R1(F)=0.064, wR(F^2)=0.155 for observed reflections, residual electron density −0.30 to 0.58 e Å^{-3}. CCDC 991554 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*(R,E)-4-(4-Benzylidene-1-(tert-butyl)-2,5-dioxo-3-(phenylamino)-pyrrolidin-3-yl)benzonitrile (**7c**):* yellow powder; 365 mg (84%); mp 235−237 °C; IR (KBr, cm^{-1}) ν 3385, 1766, 1704,; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9H, *t*-Bu), 4.45 (s, 1H, −NH), 6.45 (d, 2H, *J* = 7.9 Hz, H-Ar), 6.84 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.04 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.21 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.26−7.32 (m, 1H, H-Ar), 7.40 (d, 2H, *J* = 7.3 Hz, H-Ar), 7.67 (d, 2H, *J* = 8.4 Hz, H-Ar), 7.77 (d, 2H, *J* = 8.4 Hz, H-Ar), 7,94 (s, 1H, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 59.5, 67.4, 112.9, 118.1, 118.5, 121.7, 127.3, 128.0, 128.3, 128.9, 130.4, 131.1, 132.6, 132.8, 139.4, 143.3, 143.4, 170.2, 176.0; HR-MS (ESI-POS) calcd for $C_{28}H_{26}N_3O_2$ [M + H]$^+$ 436.20262, found 436.20250, calcd for $C_{28}H_{25}N_3NaO_2$ [M + Na]$^+$ 458.18468, found 458.18454.

*(R,E)-4-Benzylidene-1-(tert-butyl)-3-(phenylamino)-3-(4-trifluoromethyl)phenyl)pyrrolidine-2,5-dione (**7d**):* yellow powder; 464 mg (97%); mp 175−177 °C; IR (KBr, cm^{-1}) ν 3438, 1772, 1705; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 9H, *t*-Bu), 4.44 (s, 1H, −NH), 6.38 (d, 2H, *J* = 7.9 Hz, H-Ar), 6.79 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.02 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.20 (t, 2H, *J* = 7.34 Hz, H-Ar), 7.29 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.37 (d, 2H, *J* = 7.2 Hz, H-Ar), 7.67 (d, 2H, *J* = 8.4 Hz, H-Ar), 7.82 (d, 2H, *J* = 8.3 Hz, H-Ar), 7.95 (s, 1H, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 59.3, 67.2, 117.6, 121.1, 126.1 (CF_3), 126.9, 128.1, 128.3, 128.8, 130.2, 130.9, 131.1, 131.3, 132.7, 139.0, 142.2, 143.6, 170.3, 176.1; HR-MS (ESI-NEG): calcd for $C_{28}H_{24}F_3N_2O_2$ [M + H]$^-$ 477.17984, found 477.17979. Crystal data: yellow crystal (polyhedron), dimensions 0.290 × 0.180 × 0.120 mm^3, crystal system triclinic, space group $P\bar{1}$, *Z* = 2, *a* = 10.7819(15) Å, *b* = 11.2776(18) Å, *c* = 12.123(3) Å, α = 114.810(4)°, β = 97.625(4)°, γ = 108.463(3)°, *V* = 1207.3(4) Å^3, ρ = 1.316 g/cm^3, *T* = 200(2) K, θ_{max} = 24.854°, radiation Mo Kα, λ = 0.71073 Å, 0.5° ω scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 3.36 and a completeness of 99.0% to a resolution of 0.85 Å, 14048 reflections measured, 4147 unique (*R*(int) = 0.0280), 3168 observed ($I > 2\sigma(I)$), intensities corrected for Lorentz and polarization effects, empirical absorption correction applied using SADABS based on the Laue symmetry of the reciprocal space, μ = 0.10 mm^{-1}, T_{min} = 0.91, T_{max} = 0.96, structure refined against F^2 with a full-matrix least-squares algorithm using the SHELXL (version 2013-4) software, 347 parameters refined, hydrogen atoms treated using appropriate riding models, goodness of fit 1.05 for observed reflections, final residual values R1(*F*) = 0.043, wR(F^2) = 0.096 for observed reflections, residual electron density −0.22 to 0.32 e Å^{-3}. CCDC 991553 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*(R,E)-4-Benzylidene-1-(tert-butyl)-3-(phenylamino)-3-(p-tolyl)-pyrrolidine-2,5-dione (**7e**):* yellow powder; 365 mg (86%); mp 153−155 °C; IR (KBr, cm^{-1}): ν 3054, 1768, 1704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H, *t*-Bu), 2.38 (s, 3H, −CH3), 4.40 (s, 1H, −NH), 6.24 (d, 2H, *J* = 7.9 Hz, H-Ar), 6.69 (t, 1H, *J* = 7.3 Hz, H-Ar), 6.96 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.17 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.22−7.27 (m, 3H, H-Ar), 7.32 (d, 2H, *J* = 7.2 Hz, H-Ar), 7.60 (d, 2H, *J* = 8.2 Hz, H-Ar), 7.91 (s, 1H, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 28.3, 59.0, 66.9, 116.1, 119.8, 126.2, 128.0, 128.7, 129.7, 130.0, 131.0, 133.1, 135.6, 137.9, 139.0, 144.1, 170.6, 176.5; HR-MS (ESI-POS) calcd for $C_{28}H_{29}N_2O_2$ [M + H]$^+$ 425.22272, found 425.22265, calcd for $C_{28}H_{28}N_2NaO_2$ [M + Na]$^+$ 447.20475, found 447.20467, calcd for $C_{28}H_{28}KN_2O_2$ [M + K]$^+$ 463.17870, found 463.17862.

*(R,E)-4-Benzylidene-1-cyclohexyl-3-phenyl-3-(phenylamino)-pyrrolidine-2,5-dione (**7f**):* yellow powder; 362 mg (83%); mp 197−199 °C; IR (KBr, cm^{-1}) ν 3290, 1757, 1696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19−1.33 (m, 3H, H-cyclohexyl), 1.52−1.67 (m, 3H, H-cyclohexyl), 1.79−1.82 (m, 2H, H-cyclohexyl), 2.08−2.21 (m, 2H, H-cyclohexyl), 4.05−4.13 (m, 1H, N−CH), 4.45 (s, 1H, −NH), 6.29 (d, 2H, *J* = 7.9 Hz, H-Ar), 6.73 (t, 1H, *J* = 7.3 Hz, H-Ar), 6.97 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.19 (t, 2H, *J* = 7.3 Hz, H-Ar), 7.25−7.30 (m, 1H, H-Ar), 7.34 (d, 2H, *J* = 7.4 Hz, H-Ar), 7.40−7.43 (m, 3H, H-Ar), 7.72(d, 2H, *J* = 6.2 Hz, H-Ar), 7.94 (s, 1H, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.7, 25.8, 28.6, 28.7, 52.2, 67.2, 116.6, 120.3, 126.3, 128.2, 128.7, 128.8, 129.1, 129.3, 130.0, 131.1, 131.4, 133.0, 138.4, 138.7, 144.1, 169.7, 175.8; HR-MS (ESI-POS) calcd for $C_{29}H_{29}N_2O_2$ [M + H]$^+$ 437.22204, found 437.22210, calcd for $C_{29}H_{28}N_2NaO_2$ [M + Na]$^+$ 459.20406, found 459.20410, calcd for $C_{29}H_{28}KN_2O_2$ [M + K]$^+$ 475.17794, found 475.17799.

*(R,E)-4-Benzylidene-1-cyclohexyl-3-(phenylamino)-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione (**7g**):* yellow powder; 454 mg (90%); mp 200−203 °C; IR (KBr, cm^{-1}) ν 3410, 1769, 1708; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23−1.33 (m, 3H, H-cyclohexyl), 1.52−1.67 (m, 3H, H-cyclohexyl), 1.80−1.83 (m, 2H, H-cyclohexyl), 2.05−2.18 (m, 2H, H-cyclohexyl), 4.03−4.12 (m, 1H, N−CH), 4.45 (s, 1H, −NH), 6.38 (d, 2H, *J* = 8.1 Hz, H-Ar), 6.80 (t, 1H, *J* = 7.3 Hz, H-Ar), 7.01 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.23 (t, 1H, *J* = 7.2 Hz, H-Ar), 7.25 (t, 1H, *J* = 7.2 Hz, H-Ar), 7.31 (t, 1H, *J* = 7.2 Hz, H-Ar), 7.39 (d, 2H, *J* = 7.1 Hz, H-Ar), 7.66 (d, 1H, *J* = 8.4 Hz, H-Ar), 7.83 (d, 2H, *J* = 8.4 Hz, H-Ar), 7.947 (s, 1H, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.6, 25.7, 28.6, 28.7, 52.4, 67.3, 117.8, 121.3, 121.9, 126.2 (CF3), 126.9, 128.1, 128.4, 128.9, 130.4, 131.1, 132.7, 139.6, 142.1, 143.6, 169.4, 175.4; HR-MS (ESI-POS) calcd for $C_{30}H_{28}F_3N_2O_2$ [M + H]$^+$ 505.20942, found 505.20947, calcd for $C_{30}H_{27}F_3N_2NaO_2$ [M + Na]$^+$ 527.19170, found 527.19170, calcd for $C_{30}H_{27}F_3KN_2O_2$ [M + K]$^+$ 543.16568, found 543.16567.

*(R,E)-4-Benzylidene-1-(tert-butyl)-3-(phenylamino)-3-(pyridin-3-yl)pyrrolidine-2,5-dione (**7h**):* yellow powder; 279 mg (68%); mp 128−130 °C; IR (KBr, cm^{-1}) ν 3390, 1761, 1702; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H, *t*-Bu), 5.0 (*brs*, 1H, −NH), 6.47 (d, 2H, *J* = 7.8 Hz, H-Ar), 6.81 (t, 1H, *J* = 7.2 Hz, H-Ar), 7.02 (t, 2H, *J* = 7.7 Hz, H-Ar), 7.08−7.28 (m, 4H, H-Ar), 7.36−7.47 (m, 3H, H-Ar), 7.84−7.99 (m, 3H, H-Ar, ═CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 36.5, 59.4, 116.0, 118.5, 120.1, 121.6, 127.6, 128.1, 128.3, 128.9, 129.1, 130.4, 131.3, 132.5, 135.0, 139.6, 143.5, 170.1, 176.3; HR-MS (ESI-POS) calcd for $C_{26}H_{26}N_3O_2$ [M + H]$^+$ 412.20166, found 412.20166, calcd for $C_{26}H_{25}N_3NaO_2$ [M + Na]$^+$ 434.18381, found 434.18383, calcd for $C_{26}H_{25}KN_3O_2$ [M + K]$^+$ 450.15770, found 450.15772.

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*(R,E)-4-Benzylidene-3-(4-chlorophenyl)-1-cyclohexyl-3-(phenylamino)pyrrolidine-2,5-dione (**7i**):* yellow powder; 414 mg (88%); mp 185−187 °C; IR (KBr, cm^{-1}) ν 3504, 1762, 1701; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22−1.26 (m, 3H, H-cyclohexyl), 1.53−1.79 (m, 5H, H-cyclohexyl), 2.06−2.18 (m, 2H, H-cyclohexyl), 3.68−3.75 (m, 1H, N−CH), 4.38 (s, 1H, −NH), 6.30 (d, 2H, J = 7.5 Hz, H-Ar), 6.75 (t, 1H, J = 7.0 Hz, H-Ar), 6.98 (t, 2H, J = 7.3 Hz, H-Ar), 7.21−7.45 (m, 7H, H-Ar), 7.64 (d, 2H, J = 8.2 Hz, H-Ar), 7.93 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 25.7, 25.8, 28.6, 28.7, 52.3, 66.9, 117.1, 120.8, 127.9, 128.2, 128.3, 128.8, 129.5, 130.2, 131.1, 132.8, 135.2, 136.8, 139.2, 143.8, 169.5, 175.6; HR-MS (ESI-POS) calcd for $C_{29}H_{28}ClN_2O_2$ $[M + H]^+$ 471.18383, found 471.18375, calcd for $C_{29}H_{27}ClN_2NaO_2$ $[M + Na]^+$ 493.16562, found 493.16557, calcd for $C_{29}H_{27}ClKN_2O_2$ $[M + K]^+$ 509.13969, found 509.13962.

*(R,E)-4-Benzylidene-1-(tert-butyl)-3-((3,4-dimethylphenyl)-amino)-3-phenylpyrrolidine-2,5-dione (**7j**):* yellow powder; 333 mg (76%); mp 150−152 °C; IR (KBr, cm^{-1}) ν 3394, 1761 1698; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H, *t*-Bu), 2.04 (s, 3H, $-CH_3$), 2.08 (s, 3H, $-CH_3$), 4.3 (br s, 1H, −NH), 6.10 (d, 1H, J = 8.0 Hz, H-Ar), 6.15 (s, 1H, H-Ar), 6.75 (d, 1H, J = 8.0 Hz, H-Ar), 7.18−7.30 (m, 3H, H-Ar), 7.39−7.41 (m, 5H, H-Ar), 7.69 (d, 2H, J = 6.9 Hz, H-Ar), 7.91 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 19.9, 28.3, 59.0, 67.4, 114.6, 118.9, 126.3, 128.1, 128.6, 128.9, 129.2, 129.3, 129.8, 131.2, 131.4, 133.2, 136.8, 138.0, 138.6, 142.1, 170.9, 176.9; HR-MS (ESI-POS) calcd for $C_{29}H_{31}N_2O_2$ $[M + H]^+$ 439.23843, found 439.23835, calcd for $C_{29}H_{30}N_2NaO_2$ $[M + Na]^+$ 461.22063, found 461.22051, calcd for $C_{29}H_{30}KN_2O_2$ $[M + K]^+$ 477.19453, found 477.19442.

*(R,E)-4-Benzylidene-1-cyclohexyl-3-(4-methoxyphenyl)-3-(phenylamino)pyrrolidine-2,5-dione (**7k**):* yellow powder; 382 mg (82%); mp 156−158 °C; IR (KBr, cm^{-1}) ν 3386, 1766, 1703; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19−1.27 (m, 3H, H-cyclohexyl), 1.53−1.80 (m, 5H, H-cyclohexyl), 2.09−2.22 (m, 2H, H-cyclohexyl), 3.82 (s, 1H, -OMe), 4.09 (t, 1H, J = 11.5 Hz, N−CH), 4.40 (s, 1H, −NH), 6.23 (d, 2H, J = 7.6 Hz, H-Ar), 6.70 (t, 1H, J = 7.2 Hz, H-Ar), 6.93−6.98 (m, 4H, H-Ar), 7.20 (t, 2H, J = 7.0 Hz, H-Ar), 7.28 (t, 1H, J = 7.0 Hz, H-Ar), 7.34 (d, 2H, J = 7.4 Hz, H-Ar), 7.66 (d, 1H, J = 7.3 Hz, H-Ar), 7.90 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.7, 25.8, 28.6, 28.8, 52.1, 55.3, 66.6, 114.7, 116.1, 120.0, 127.8, 128.2, 128.7, 129.9, 130.3, 131.1, 133.0, 138.5, 144.2, 160.1, 169.7, 176.0; HR-MS (ESI-POS) calcd for $C_{30}H_{31}N_2O_3$ $[M + H]^+$ 467.23276, found 467.23279, calcd for $C_{30}H_{30}N_2NaO_3$ $[M + Na]^+$ 489.21470, found 489.21473.

*(R,E)-4-(4-Benzylidene-1-cyclohexyl-2,5-dioxo-3-(phenylamino)-pyrrolidin-3-yl)benzonitrile (**7l**):* yellow powder; 332 mg (72%); mp 225−22 7 °C; IR (KBr, cm^{-1}) ν 3393, 1771, 1705; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17−1.32 (m, 3H, H-cyclohexyl), 1.49−1.82 (m, 5H, H-cyclohexyl), 2.02−2.15 (m, 2H, H-cyclohexyl), 4.05 (*tt*, 1H, J = 12.3, 3.6 Hz, N−CH), 4.45 (s, 1H, −NH), 6.44 (d, 2H, J = 7.8 Hz, H-Ar), 6.84 (t, 1H, J = 7.3 Hz, H-Ar), 7.04 (t, 2H, J = 7.7 Hz, H-Ar), 7.24 (t, 2H, J = 7.4 Hz, H-Ar), 7.33 (t, 1H, J = 7.2 Hz, H-Ar), 7.42 (d, 2H, J = 7.3 Hz, H-Ar), 7.67 (d, 2H, J = 8.4 Hz, H-Ar), 7.79 (d, 2H, J = 8.4 Hz, H-Ar), 7.96 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.6, 25.7, 28.6, 28.7, 52.4, 67.5, 113.0, 118.1, 118.6, 122.0, 127.3, 127.9, 128.4, 129.0, 129.2, 130.6, 131.2, 132.5, 132.8, 139.9, 143.1, 143.4, 169.2, 175.2; HR-MS (ESI-POS) calcd for $C_{30}H_{28}N_3O_2$ $[M + H]^+$ 462.21785, found 462.21781.

*(R,E)-4-Benzylidene-3-(4-bromophenyl)-1-cyclohexyl-3-(phenylamino)pyrrolidine-2,5-dione (**7m**):* yellow powder; 412 mg (81%); mp 217−219 °C; IR (KBr, cm^{-1}) ν 3330, 3056, 1764, 1701; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17−1.24 (m, 3H, H-cyclohexyl), 1.52−1.81 (m, 5H, H-cyclohexyl), 2.01−2.22 (m, 2H, H-cyclohexyl), 4.02−4.1 (m, 1H, N−CH), 4.39 (s, 1H, −NH), 6.29 (d, 2H, J = 7.7 Hz, H-Ar), 6.84 (t, 1H, J = 7.3 Hz, H-Ar), 7.04 (t, 2H, J = 7.7 Hz, H-Ar), 7.24 (t, 2H, J = 7.4 Hz, H-Ar), 6.75 (t, 1H, J = 7.1 Hz, H-Ar), 6.97 (d, 2H, J = 7.4 Hz, H-Ar), 7.20−7.30 (m, 3H, H-Ar), 7.35 (d, 2H, J = 7.3 Hz, H-Ar), 7.53 (d, 2H, J = 8.3 Hz, H-Ar), 7.58 (d, 2H, J = 8.3 Hz, H-Ar), 7.93 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.6, 25.7, 28.6, 28.7, 52.3, 66.9, 117.1, 120.8, 123.5, 128.1, 128.2, 128.3, 128.8, 130.3, 131.1, 132.4, 132.8, 137.3, 139.3, 143.8, 169.5, 175.5; HR-MS (ESI-POS) calcd for $C_{29}H_{28}BrN_2O_2$ $[M + H]^+$ 515.13343, found 515.13334, calcd for $C_{29}H_{27}BrKN_2O_2$ $[M + K]^+$ 553.08932, found 553.08923.

*(R,E)-4-Benzylidene-3-((4-bromophenyl)amino)-1-cyclohexyl-3-(p-tolyl)pyrrolidine-2,5-dione (**7n**):* yellow powder; 439 mg (83%); mp 152−154 °C; IR (KBr, cm^{-1}) ν 3310, 3401, 1764, 1702; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17−1.27 (m, 3H, H-cyclohexyl), 1.51−1.79 (m, 5H, H-cyclohexyl), 2.02−2.23 (m, 2H, H-cyclohexyl), 2.36 (s, 3H, $-CH_3$), 4.09 (m, 1H, N−CH), 4.43 (s, 1H, −NH), 6.06 (d, 2H, J = 8.4 Hz, H-Ar), 7.02 (d, 2H, J = 8.4 Hz, H-Ar), 7.16−7.28 (m, 7H, H-Ar), 7.58 (d, 2H, J = 7.9 Hz, H-Ar), 7.91 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 25.0, 25.6, 25.7, 28.6, 28.8, 52.2, 66.8, 111.9, 117.3, 126.2, 128.1, 128.2, 130.1, 130.2, 130.9, 131.5, 132.8, 135.2, 138.7, 139.4, 143.2, 169.5, 175.6; HR-MS (ESI-POS) calcd for $C_{30}H_{30}{}^{79}BrN_2O_2$ $[M + H]^+$ 529.14932, found 529.14919.

*(R,E)-4-Benzylidene-3-((4-bromophenyl)amino)-1-(tert-butyl)-3-phenylpyrrolidine-2,5-dione (**7o**):* yellow powder; 361 mg (74%); mp 152−154 °C; IR (KBr, cm^{-1}) ν 3310, 3060, 1762, 1698; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H, *t*-Bu), 4.42 (s, 1H, −NH), 6.08 (d, 2H, J = 8.2 Hz, H-Ar), 7.05 (d, 2H, J = 8.2 Hz, H-Ar), 7.17 (t, 1H, J = 7.5 Hz, H-Ar), 7.18 (d, 1H, J = 6.8 Hz, H-Ar), 7.19−7.30 (m, 3H, H-Ar), 7.43−7.45 (m, 3H, H-Ar), 7.70 (d, 2H, J = 5.5 Hz, H-Ar), 7.92 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 59.2, 67.1, 111.8, 117.3, 126.3, 127.9, 128.2, 129.4, 129.5, 130.0, 130.8, 131.5, 132.9, 138.3, 143.1, 170.3, 176.0; HR-MS (ESI-POS) calcd for $C_{27}H_{26}{}^{79}BrN_2O_2$ $[M + H]^+$ 489.11867, found 489.11867, calcd for $C_{27}H_{25}{}^{79}BrN_2NaO_2$ $[M + Na]^+$ 511.10132, found 511.10097, calcd for $C_{27}H_{25}{}^{79}BrKN_2O_2$ $[M + K]^+$ 527.07544, found 527.07507.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, tables, and CIF files giving ^1H NMR, ^{13}C NMR, $^1H-^1H$-COSY 2D NMR, IR, and HRMS spectra for compounds **6a−n** and **7a−o** and X-ray crystal data for compounds **6i** and **7b,d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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