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# Multicomponent Approach to a Library of *N*-Substituted γ-Lactams

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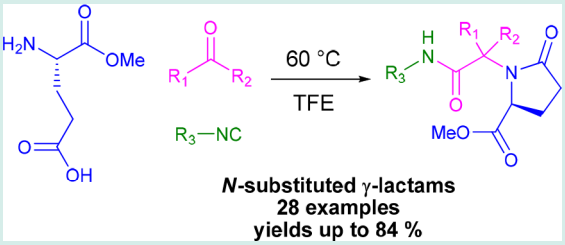
Supporting Information

**ABSTRACT:** The γ-lactam motif is often found in naturally occurring compounds with diverse biological activities. We prepared a 28-member library of *N*-substituted γ-lactams following a single-pot, three-component Ugi reaction comprising bifunctional building block, L-glutamic acid methyl ester. The reaction tolerates structurally diverse carbonyl and isocyanide components providing a robust access to functionalized γ-lactams. Antimicrobial susceptibility testing, including agar well diffusion assay, serial microdilution broth assay, and antibiofilm activity testing, identified a potent compound with antibiofilm activity against *Staphylococcus aureus* ATCC 6538.




**KEYWORDS:** *γ-lactams, multicomponent reactions, Ugi reaction, antibiofilm activity*



## INTRODUCTION

The pyrrolidin-2-one, also known as γ-lactam ring, is the core structure of a large number of natural and non-natural compounds covering a broad spectrum of biological activities.[1] The synthesis of substituted γ-lactams is an important goal, because of their use as key intermediates in the synthesis of biologically and pharmaceutically relevant molecules.[2] Important examples of these γ-lactams include the proteasome inhibitor lactacystin (**I**),[3] (−)-clausenamide (**II**) for the treatment of Alzheimer's disease,[4] and (−)-dysibetaine (**III**) and anantine (**IV**), which exhibit cytotoxic, antitumor, and anti-inflammatory activities,[5,6] while (±)-rolipram (**V**) is a selective inhibitor of phosphodiesterase type IV, anti-inflammatory agent, and antidepressant (Figure 1).[7] Compounds containing γ-lactams have direct applications in the treatment of epilepsy,[8] HIV,[9] neurodegenerative diseases, and depression.[10,11] Many approaches have been developed for the preparation of γ-lactam structures. The most widely used method is cyclization by amide formation between a carboxylic group and an amine or its precursor. Cyclization can also be performed by intramolecular *N*-alkylation of an amide or by C−C bond formation.[12] In addition to these cyclization strategies, several (3 + 2) and (4 + 1) cycloaddition/annulation reactions leading to the γ-lactam structure have also been designed.[13]

Furthermore, recognizing the potential for discovery of novel bioactive small molecules based upon the γ-lactam core structure, several research groups have presented interesting multicomponent or cascade approaches toward functionalized γ-lactams.[14−16] Multicomponent reactions (MCRs) were found to be an excellent tool to rapidly access a large and versatile drug-like chemical space to address the corresponding biological space.[17]

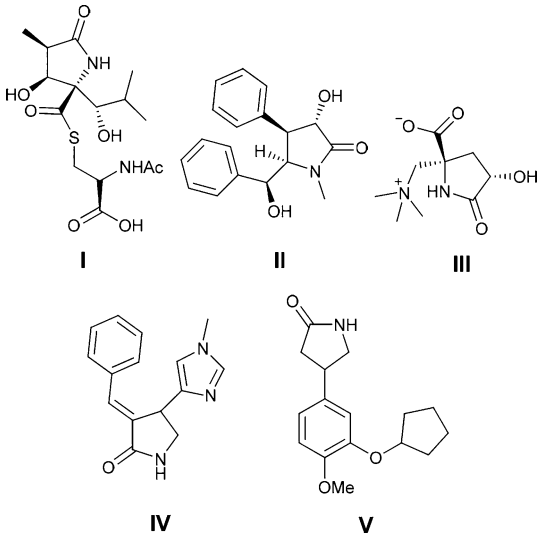



**Figure 1.** Biologically active γ-lactam structures.

Among these reactions, isocyanide based multicomponent reactions (IMCRs), like Passerini and Ugi reaction, are particularly popular due to the carbenic reactivity of isocyanides, wide substrate scope and mild reaction conditions.[18] The classical Ugi reaction combines four components; an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide, in a one-pot manner to produce an α-acylaminoamide. This process, known as the Ugi four-component reaction (U-4CR), has found widespread application in both, diversity and target oriented organic syntheses.[19]

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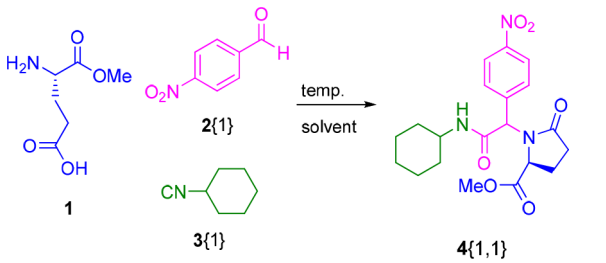
In 1996, Ugi reported an effective variation of the U-4CR as a 5-center 4-component reaction (U-5C-4CR) with very high yields and excellent stereoselectivity.[20] α-Amino acids serve as bifunctional starting materials in the U-5C-4CR instead of the amine and acid components in the familiar U-4CR. They react with equimolar amounts of aldehyde and isocyanide as well as with the alcohol that also serves as a solvent.[20,21] The main advantage of bifunctional substrates in IMCRs is a smooth access to novel, functionalized cyclic scaffolds.[22] A convenient and versatile synthesis of *N*-substituted γ-lactams using convergent Ugi reaction was exploited by several groups.[23−25] Gunawan et al. described solid-phase synthesis of *N*-substituted γ-lactams utilizing resin-bound glutamic acid, but with very limited substrate scope.[25] In this Research Article, we used C-terminal protected L-glutamic acid as a bifunctional building block in the 4-center 3-component Ugi reaction (U-4C-3CR) with various carbonyls and isocyano-components. The advantage of this approach is that only three components are involved in one reaction step, thus enabling a smooth access to a library of diverse *N*-substituted γ-lactams.

## RESULTS AND DISCUSSION

**Chemical Synthesis.** Our initial reaction was conducted with L-glutamic acid methyl ester (**1**), *p*-nitro benzaldehyde **2**{*1*}, and cyclohexyl isocyanide **3**{*1*}. First reaction performed in dichloromethane did not give a corresponding product, probably because of poor solubility of the reactants (Table 1, entry 1). The same reaction performed in dichloromethane/methanol (10:1, v/v) mixture gave, after 48 h, desired *N*-substituted γ-lactam product **4**{*1,1*}, although in low yield (28%, entry 2). Encouraged by this result, we tested different polar solvents, commonly used for the Ugi reaction (Table 1, entries 3−8). Running the reaction in methanol afforded the product in a disappointing yield (22%, entry 3), while heating up the reaction mixture at 60 °C for 24 h improved the yield to 47% (entry 4). Next, we tested trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) as solvents at the room temperature and at elevated temperature for 24 and 72 h. Both, TFE and HFIP at 60 °C proved to be suitable for this type of the Ugi reaction (75% and 84%, respectively, after 24 h; entries 6 and 8). For economic reasons, the less expensive TFE was used in all further reactions.

**Table 1. Screening of Reaction Conditions for the Ugi 3-Component Reaction**




| entry | solvent | *T* (°C) | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | DCM | RT | 24 | |
| 2 | DCM/MeOH (10:1) | RT | 48 | 28 |
| 3 | MeOH | RT | 24 | 22 |
| 4 | MeOH | 60 | 48 | 47 |
| 5 | TFE | RT | 24/72 | 68/70 |
| 6 | TFE | 60 | 24/72 | 75/83 |
| 7 | HFIP | RT | 24 | 80 |
| 8 | HFIP | 60 | 24 | 84 |

[a]Reactions were performed with 0.17 mmol of *p*-nitrobenzaldehyde, 0.19 mmol of H-Glu-OMe, and 0.19 mmol of cyclohexyl isocyanide. [b]Isolated yields.

With the optimized conditions in hand, we set out to test the scope of the protocol by utilizing different carbonyl components (chemset **1**, Figure 2) and isocyanides (chemset **2**, Figure 2). First batch of Ugi-3CR was conducted with L-glutamic acid methyl ester, *p*-nitrobenzaldehyde, and different commercially available and synthesized isocyanides (see Supporting Information), and results are summarized at Figure 3.

Reactions performed with commercially available isocyanides **3**{*2−4*} afforded corresponding products in good to very good yields (53−83%, products **4**{*1,2−4*}). Next, we tested aromatic isocyanides **3**{*5−7*} and obtained γ-lactams in fair yield (57% and 54% for compounds **4**{*1,6*}, and **4**{*1,7*}, respectively), with the exception of compound **4**{*1,5*}, obtained in only 24% yield. Possible explanation for this result can be observed low stability of the corresponding isocyanide. Finally, we examined amino acid-derived racemic isocyanides **3**{*8−10*} and obtained γ-lactam scaffolds embedded into the tripeptide structures, in satisfactory yields (57−80% for compounds **4**{*1,8−10*}, Figure 3). Since the best yield is achieved in the reaction with 1,1,3,3-tetramethylbutyl isocyanide **3**{*3*} (Figure 3, product **4**{*1,3*}), it was used in the second batch of Ugi-3CR during the screening of different carbonyl components.

Comparison of the Ugi reactions performed with benzaldehyde **2**{*2*} (product **4**{*2,3*}), *p*-Cl benzaldehyde **2**{*3*} (product **4**{*3,3*}), and *p*-OMe benzaldehyde **2**{*4*} (product **4**{*4,3*}), revealed that unsubstituted aromatic aldehyde and an aldehyde bearing electron withdrawing substituent furnished corresponding Ugi products in very good yields (82%), compared to aromatic aldehyde bearing electron donating substituents (40%, Figure 3). Additionally, aliphatic aldehydes, 2-methylpentanal **2**{*5*}, and cyclohexylcarboxaldehyde **2**{*6*} furnished corresponding products in satisfactory yields (62−89%, products **4**{*5−6,3*} and **4**{*6,8*}). Finally, three ketones were used in the Ugi reaction; product **4**{*7,3*} was obtained with acetone **2**{*7*} in rather low yield (24%), while acetophenone **2**{*8*} failed to give the expected product **4**{*8,3*} presumably due to steric reasons. Contrary to that, reaction with cyclohexanone **2**{*8*} gave the desired product **4**{*9,3*} in very good yield (74%). Furthermore, we used chiral *N*-terminally protected amino aldehydes derived from valine **2**{*10*}, leucine **2**{*11*}, phenylalanine **2**{*12*}, and proline **2**{*13*} to introduce additional functionality into the Ugi product. As presented at the Figure 2, all performed reactions furnished corresponding Ugi products in moderate to very good yields (22−84%, products **4**{*10−13,3*} and **4**{*13,1*}). Comparison of obtained results revealed that steric hindrance of the amino aldehyde have impact on the yield of the Ugi reaction. Nice examples are Ugi products **4**{*10,3*} (39%) and **4**{*13,3*} (22%) with branched β carbon atoms in comparison with sterically less demanding **4**{*11,3*} (75%) and **4**{*12,3*} (84%). However, the influence of isocyanide cannot be neglected, as apparent by comparing product **4**{*13,3*} (22%) and **4**{*13,1*} (58%), differing in the nature of isocyano component. Finally, we introduced Garner's aldehyde **2**{*14*}[26] and obtained Ugi product **4**{*14,3*} in fair yield (41%), while a 63% yield was achieved in the reaction with cyclohexyl isocyanide, **4**{*14,1*}.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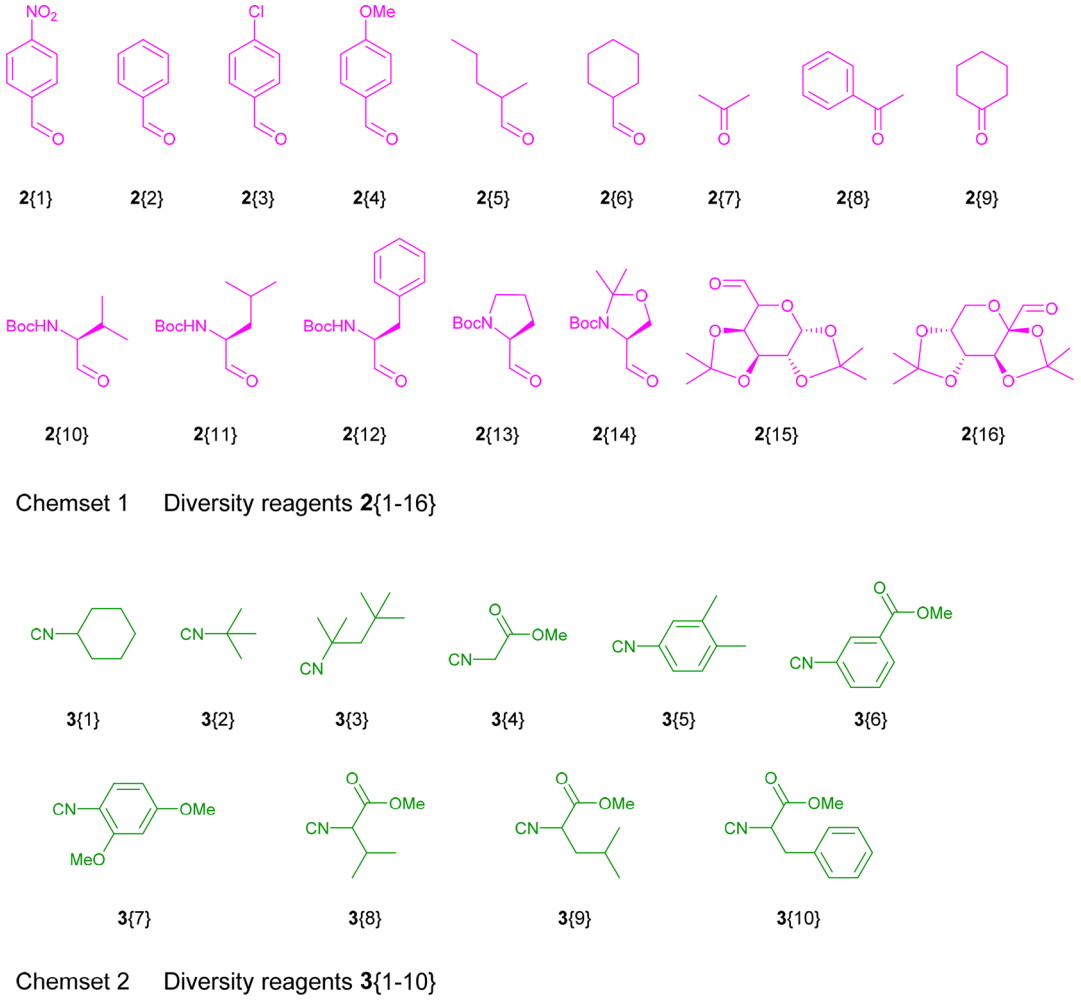


**Figure 2.** Chemsets selected for the library of *N*-substituted γ-lactam products: carbonyl components (chemset **1**) and isocyanides (chemset **2**).

To further widen substrate scope of carbonyl compounds, we performed two reactions with sugar derived aldehydes. Bis-isopropylidene protected D-galactose-derived aldehyde **2**{*15*} gave Ugi product **4**{*15,3*} in very good yield (72%), while bis-isopropylidene protected D-fructose-derived aldehyde **2**{*16*} furnished Ugi product **4**{*16,3*} in somewhat lower, but satisfactory yield (59%).

The formation of new stereocenter is inherent to the Ugi reaction, and is generally accepted that the nature of amine component dictates the stereoselectivity of the reaction.[27] Since amine and acid component are the same in all Ugi reactions performed within this work, any differences in stereoselectivity of the reaction can be attributed to the carbonyl and isocyanide components. All Ugi products are isolated as inseparable mixture of diastereoisomers, and the inspection of the NMR spectra revealed that there is virtually no diastereoselectivity or is very modest. The best result, 77:23 *d.r.* is obtained with the Ugi product **4**{*1,1*}. Although it is expected that chiral aldehydes can induce some stereoselectivity, their influence is generally not significant under the conditions performed in this work.

The currently accepted mechanism of the U-4C-3CR starts with condensation of the amino acid with the carbonyl component to form the corresponding protonated Schiff's base **I**. Addition of the isocyanide then produces the cyclic *O*-acylimide **II**. Final step is the Mumm rearrangement to form the five-membered ring **III** (Scheme 1).[28]

**Biological Screening.** With a library of *N*-substituted γ-lactams in-hand and having in mind that γ-lactams cover a broad spectrum of biological activities, we decided to test antimicrobial activity of selected compounds and thus performed an agar well diffusion assay, a serial microdilution broth assay and antibiofilm activity testing. Along with compounds prepared by the 3-component Ugi reaction, we also included compounds **5**-**8** (Figure 4) obtained by acid hydrolysis of compounds **4**{*11,3*}, **4**{*12,3*}, **4**{*13,1*}, and **4**{*14,1*}, respectively. Altogether, 28 compounds were investigated, except for compounds **4**{*1,5*}, **4**{*1,7*}, **4**{*7,3*}, and **4**{*8,3*}, which were unstable or not obtained. Results of all performed assays were calculated as the mean of three independent experiments. No antimicrobial activity was observed in an agar well diffusion assay and a serial microdilution broth assay in tested concentrations (Table S1). Within the initial antibiofilm screening, activity was observed for compound **4**{*13,1*} (inhibition less than 50%, data not shown), so its activity during biofilm formation was investigated in more details (Table 2). The $MBFIC_{50}$ and $MBFIC_{90}$ values represent the lowest compound dilution at which bacterial growth during biofilm formation was inhibited for 50% and 90%, in comparison to untreated control. It turned out that compound **4**{*13,1*} shows potent antibiofilm


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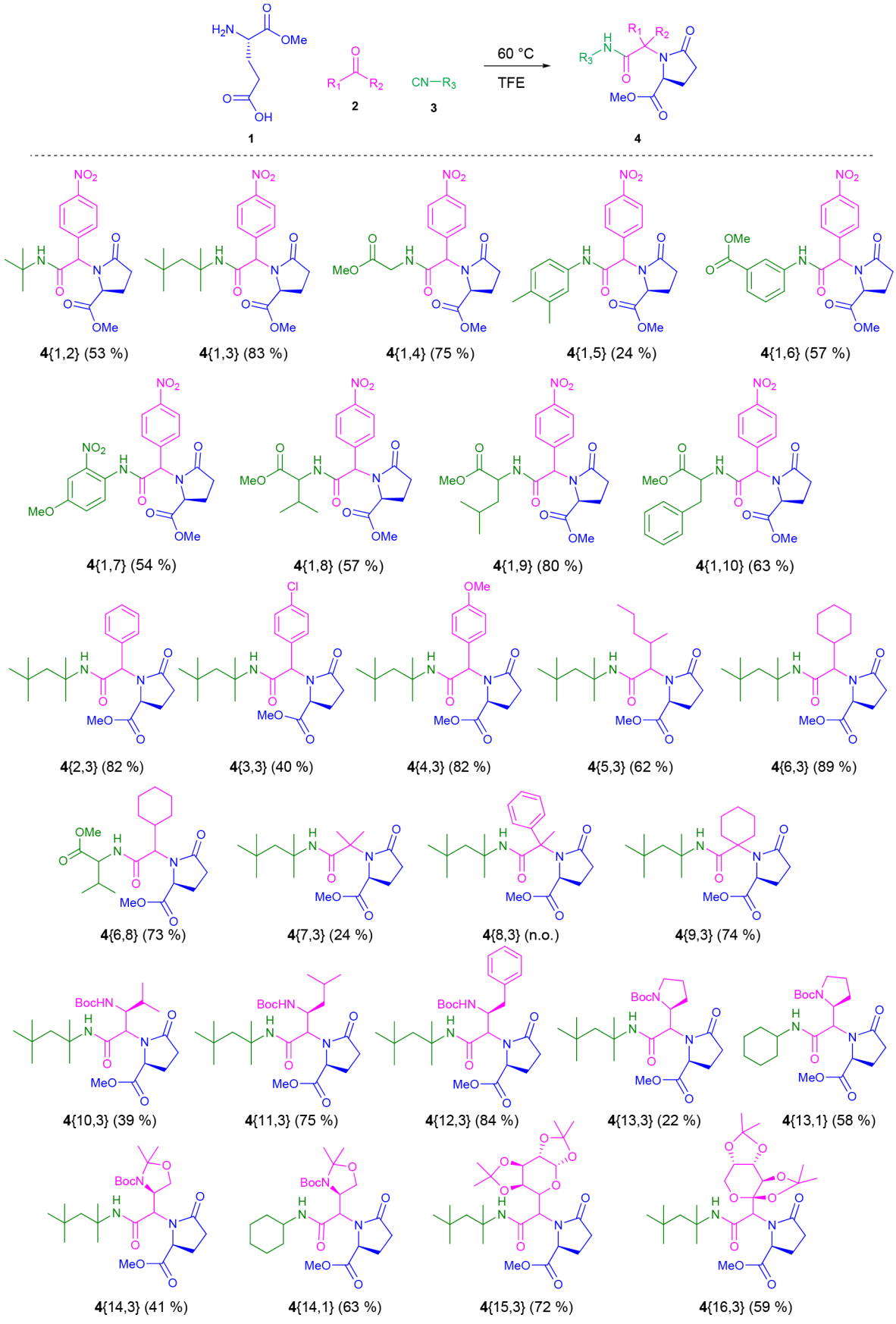


**Figure 3.** Scope of the Ugi reaction with different isocyanides and oxo-compounds.



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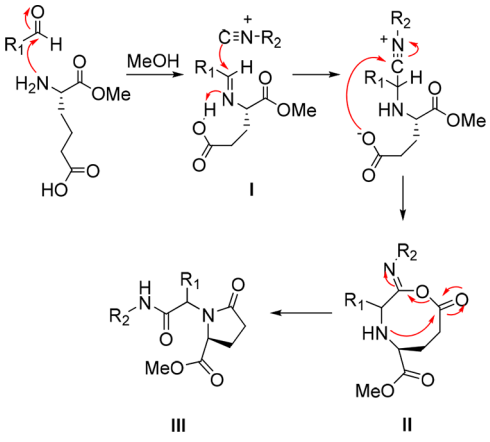
**Scheme 1. Proposed Mechanism of the U-4C-3CR**



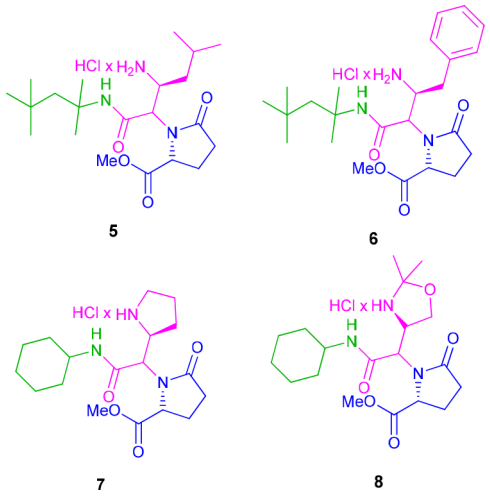




**Figure 4.** Compounds obtained by acid hydrolysis of compounds 4{*11,3*}, 4{*12,3*}, 4{*13,1*}, and 4{*14,1*}.

**Table 2. Antibiofilm Activity of Compound 4{*13,1*} on *S. aureus* ATCC 6538**

| compound code or control | $MBIFC_{50}$ [a] ($\mu$g/mL) | $MBFIC_{90}$ [a] ($\mu$g/mL) | $MMBIC_{50}$ [b] ($\mu$g/mL) | $MMBIC_{90}$ [b] ($\mu$g/mL) |
|---|---|---|---|---|
| 4{*13,1*} | 1.906 | 484.172 | >1250 | >1250 |
| gentamicin sulfate | 0.114 | 7.998 | 386.367 | 6280.584 |

[a]MBFIC= minimal biofilm-forming inhibition concentration. [b]MMBIC= minimal mature-biofilm inhibition.

formation activity against *S. aureus* ATCC 6538 with $MBFIC_{50}$ = 1.906 $\mu$g/mL and $MBFIC_{90}$ = 484.172 $\mu$g/mL (Figure 5).

Biofilms are defined as aggregated microorganism communities attached to surfaces and embedded in a self-produced matrix.[29] In this, actually defensive state, bacteria exhibit slowed metabolism and display up to 1000-fold enhanced resistance to antibiotic treatment. According to National Institutes of Health, bacterial biofilms are responsible for over 80% of infections found in the human body.[30] Naturally occurring biofilm inhibitors act as sources of inspiration in the design of small molecules with potential antibiofilm formation activity. Libraries of 2-aminoimidazoles, benzimidazoles, or indole−triazole-amide analogs, along with brominated furanone analogs, *N*-acyl homoserine lactone analogs and peptide-based compounds have been prepared and

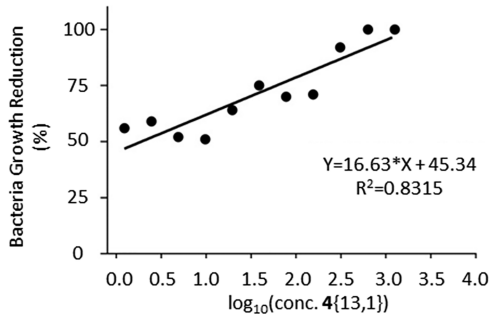



**Figure 5.** Compound 4{*13,1*} shows potent antibiofilm formation activity against *S. aureus* ATCC 6538 (MBFIC50 = 1.906 $\mu$g/mL and MBFIC90 = 484.172 $\mu$g/mL).

tested.[29,31,32] Based of these findings, our understanding of underlying molecular mechanisms of bacterial biofilm formation has increased, but to date, no antibiofilm drug has been registered and is in clinical use. This significantly hampered the treatment of biofilm-related infections especially in health-related environments. According to a recent study, three different $\gamma$-alkylidene-$\gamma$-lactams showed biofilm inhibition on *Streptococcus mutans*, *Enterococcus faecalis*, and *Candida glabrata*.[33] It therefore seems meaningful to further explore the potential of *N*-substituted $\gamma$-lactams to modulate bacterial virulence, through biofilm eradication. So, our next step is to design and develop a focused library of compounds based on structure of 4{*13,1*}, where proline-derived aldehyde will be replaced by its analogous along with different isocyanides.

## CONCLUSIONS

We have prepared a diverse selection of *N*-substituted $\gamma$-lactams in an efficient single-step procedure, utilizing a bifunctional $\alpha$-carboxy protected L-glutamic acid with diverse isocyanides and aldehydes or ketones. Functionalized $\gamma$-lactones are obtained in up to 84% yield and their antimicrobial activity was tested. Even though no antibacterial activity was shown within the agar well diffusion assay and serial 2-fold microdilution broth assay, the observed antibiofilm formation potency of compound 4{*13,1*} for *S. aureus* ATCC 6538 gives impetus for further antibiofilm investigations, especially regarding Gram-positive bacteria.

## EXPERIMENTAL PROCEDURES

**General Procedure for the Ugi-5-Center-4-Component Reaction.** To a glass vial containing 1 M solution of H-Glu-OMe (**1**) (0.19 mmol; 1,1 equiv) in TFE were added oxo-compound (0.17 mmol) and the isocyanide (0.19 mmol; 1,1 equiv). With all reactants added, the solution was allowed to stir at 60 °C for 24 h. The reactions were concentrated under reduced pressure and reaction mixtures were purified by flash column chromatography.

**Representative Example of the Ugi Product.** *(2R)-Methyl 1-(1-(4-nitrophenyl)-2-oxo-2-(2,4,4-trimethylpentan-2-ylamino)ethyl)-5-oxo pyrrolidine-2-carboxylate 4{1,3}.* Colorless oil (68 mg; 83%); dr 58:42. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$/ppm 8.20−8.18 (Har, Ph, 3a, 3b, m, 2H), 7.62−7.60 (Har, Ph, 3a, m, 1H), 7.58−7.56 (Har, Ph, 3b, m, 1H), 5.68 (H1, 3a, s, 1H), 5.57 (H1, 3b, s, 1H), 4.68−4.65 (H2, 3a, m, 1H), 4.28 (H2, 3b, m, 1H), 3.74 (OMe, 3a, s, 3H), 3.36 (OMe, 3b, s, 3H), 2.59 (H4, 3a, m, 1H), 2.50−2.19 (H3, 3a, 3b, m, 2H), 2.12−1.98 (H4, 3b, m, 1H), 1.44 (H8, H9, 3a, m,



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4H), 1.41 (H8, H9, 3b, m, 4H), 1.39 (H6, 3a, 3b, m, 2H), 0.96 ($CH_3$, *t*-Bu, 3a, s, 9H), 0.92 ($CH_3$, *t*-Bu, 3b, s, 9H).

$^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$/ppm 176.1 (CO, 3a), 175.6 (CO, 3b), 172.8 (CO, 3a), 172.6 (CO, 3b), 166.6 (CO, 3a), 165.9 (CO, 3b), 147.9 (Car, 3a), 147.8 (Car, 3b), 142.8 (Car, 3a), 141.1 (Car, 3b), 130.8, 129.2, 123.8, 123.6 (CHar, 3a, 3b), 59.9 (C1, 3a), 59.4 (C1, 3b), 58.8 (C2, 3a), 58.7 (C2, 3b), 56.0 (C6, 3a), 55.9 (C6, 3b), 52.5 (OMe, 3a), 52.2 (OMe, 3b), 52.2 (C5, 3a), 51.9 (C5, 3b), 31.6 (C7, 3a), 31.6 (C7, 3b), 31.6, 31.5, 31.4, 31.4, 30.9, 30.9 ($CH_3$, *t*-Bu, 3a, 3b), 29.2 (C4, 3a), 29.1 (C4, 3b), 28.8, 28.6, 28.5, 28.4 (C8, C9, 3a, 3b), 24.6 (C3, 3a), 24.2 (C3, 3b).

MS-ESI: *m/z* 432.0 $[M-H]^-$; *m/z* 434.3 $[M + H]^+$; *m/z* 456.3 $[M + Na]^+$; *m/z* 889.5 $[2M+Na]^+$. HRMS: calcd for $C_{22}H_{31}N_3O_6$ $[M + H]^+$ 434.2291, found 434.2307.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.8b00147.

General methods, synthetic procedures, characterization data, and copies of $^1H$, $^{13}C$, and HRMS spectra, antimicrobial susceptibility testing, and antibiofilm activity screening (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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