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Ugi Four-Center Three-Component Reaction as a Direct Approach to Racetams

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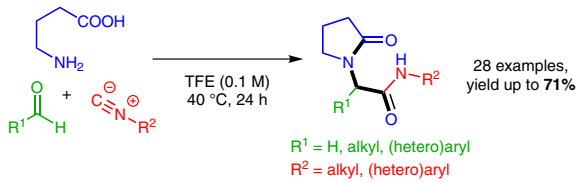

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Abstract We report the synthesis of racetams, a diverse class of small molecule drugs, by means of the Ugi four-center three-component reaction (U4C-3CR). For the first time, γ-aminobutyric acid is employed as bifunctional input in the Ugi reaction. This protocol is simple, general, and allows one-pot access to a range of drugs and bioactive small molecules.

Key words multicomponent reactions, racetams, pyrrolidones, medicinal chemistry, Ugi reaction

Racetams are a broad class of drugs that feature a pyrrolidone ring. Of particular importance are the 2-oxo-1-pyrrolidino acetamide derivatives (Figure 1), which find widespread use in the treatment of various medical conditions such as epilepsy, dementia, depression, anxiety, and hypoxia.[1] Despite more than 50 years of clinical significance, the 2-oxo-1-pyrrolidino acetamide remains an interesting pharmacophore for medicinal chemistry and novel applications of racetam derivatives continue to be developed.[2]

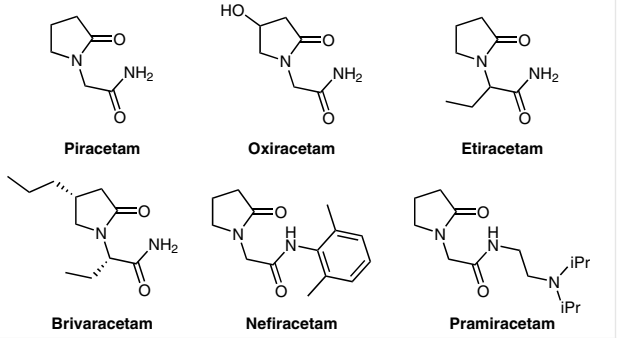
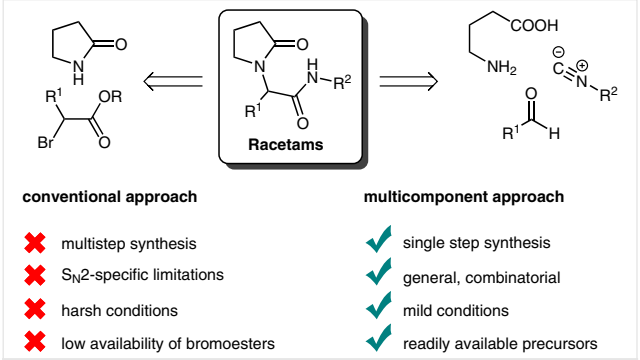


Figure 1 Commercial drugs of the racetam class

Structurally, the bioactive 2-oxo-1-pyrrolidino acetamides are relatively simple small molecules; their synthesis is straightforward and invariably relies on an S_N2 reaction with pyrrolidone to introduce the γ-lactam unit (Scheme 1). In the context of drug design, this approach, although reliable and robust, has certain drawbacks: it is time-consuming (linear, multistep synthesis), it is accompanied by a reduced variability at the α-position of the acetamide (due to the limited availability of precursors), and it features S_N2-specific scope limitations (base-sensitive functionalities, additional electrophilic centers, and bulky substituents are incompatible). Therefore, a chemoselective convergent/multicomponent approach would be more suitable for the combinatorial synthesis of novel racetam analogues.



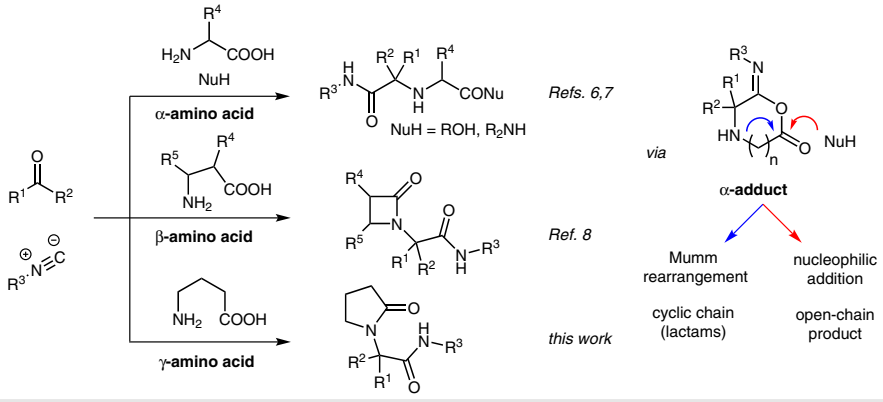
Scheme 1 Conventional versus multicomponent synthesis of racetams

Recognizing the general 2-oxo-1-pyrrolidino acetamide structure as an Ugi scaffold,[3] we envisaged the construction of racetam derivatives via this multicomponent condensation. Ugi approaches towards racetam derivatives have been previously reported, but these methods graft the pyrrolidone core indirectly by subsequent manipulation (i.e.,

xanthate cyclization,[4] olefin metathesis[5]) of Ugi adducts with appropriate functionalization handles. In a more direct approach toward the 2-oxo-1-pyrrolidino acetamide scaffold, we decided to pursue the direct synthesis from γ-aminobutyric acid, a carbonyl compound, and an isocyanide to provide the target scaffold in a single operation.

Amino acids have been intensively applied in Ugi chemistry (Scheme 2). In the case of α-amino acids, the typical Mumm rearrangement is kinetically blocked and the α-adduct undergoes reactions with external nucleophiles (alcohols,[6] amines[7]) or internal nucleophiles (e.g., alcohols[8]) instead. On the other hand, β-amino acids, unless sterically constrained,[9] do follow the complete Ugi pathway, including the final rearrangement, leading to β-lactam derivatives.[10] Remarkably, the use of γ-amino acids and higher homologues[11] has not been thoroughly investigated in the Ugi reaction. Extrapolating the behavior of the first members of the series, it is expected that γ-amino acids would react in an Ugi condensation by the contraction of the eight-membered ring α-adduct to a pyrrolidone derivative upon Mumm rearrangement. This hypothesis was only recently validated by Darehkordi et al., who showed that 2-(1-aminomethyl)cyclohexylacetic acid (gabapentin) can be successfully applied in Ugi type three-component condensations;[12] however, this bifunctional input is strongly biased toward cyclization by the Thorpe–Ingold effect and one should be cautious when generalizing this reactivity to linear, unbranched amino acids. Ugi type reactions of glutamic acid derivatives have also been reported.[13] Although deceptively simple, the use of γ-amino acids in the Ugi reaction involves a number of challenges. The formation of the α-adduct, an eight-membered ring, is plausibly a slow process;[14] competition with the intermolecular Ugi reaction is anticipated. Furthermore, the lactamization of γ-aminobutyric acid (possibly isocyanide-mediated[15]) is also a kinetically relevant transformation, particularly at high temperatures. Finally, the ring contraction transannulation (the Mumm rearrangement) in this medium-sized ring may also be problematic and lead to undesired side reactions (solvolysis, addition of other, external nucleophiles). Indeed, when performing the reaction between γ-aminobutyric acid, *tert*-butyl isocyanide, and an aldehyde (aliphatic or aromatic) under typical Ugi conditions (MeOH, 1 M, room temperature) the yield of the desired product was very low because the anticipated side reactions also occurred. Extensive optimization efforts[16] were rewarded with a significantly improved selectivity and a satisfactory yield for the expected 2-oxo-1-pyrrolidino acetamide derivative using 2,2,2-trifluoroethanol (TFE) as solvent at relatively high dilution.[17]

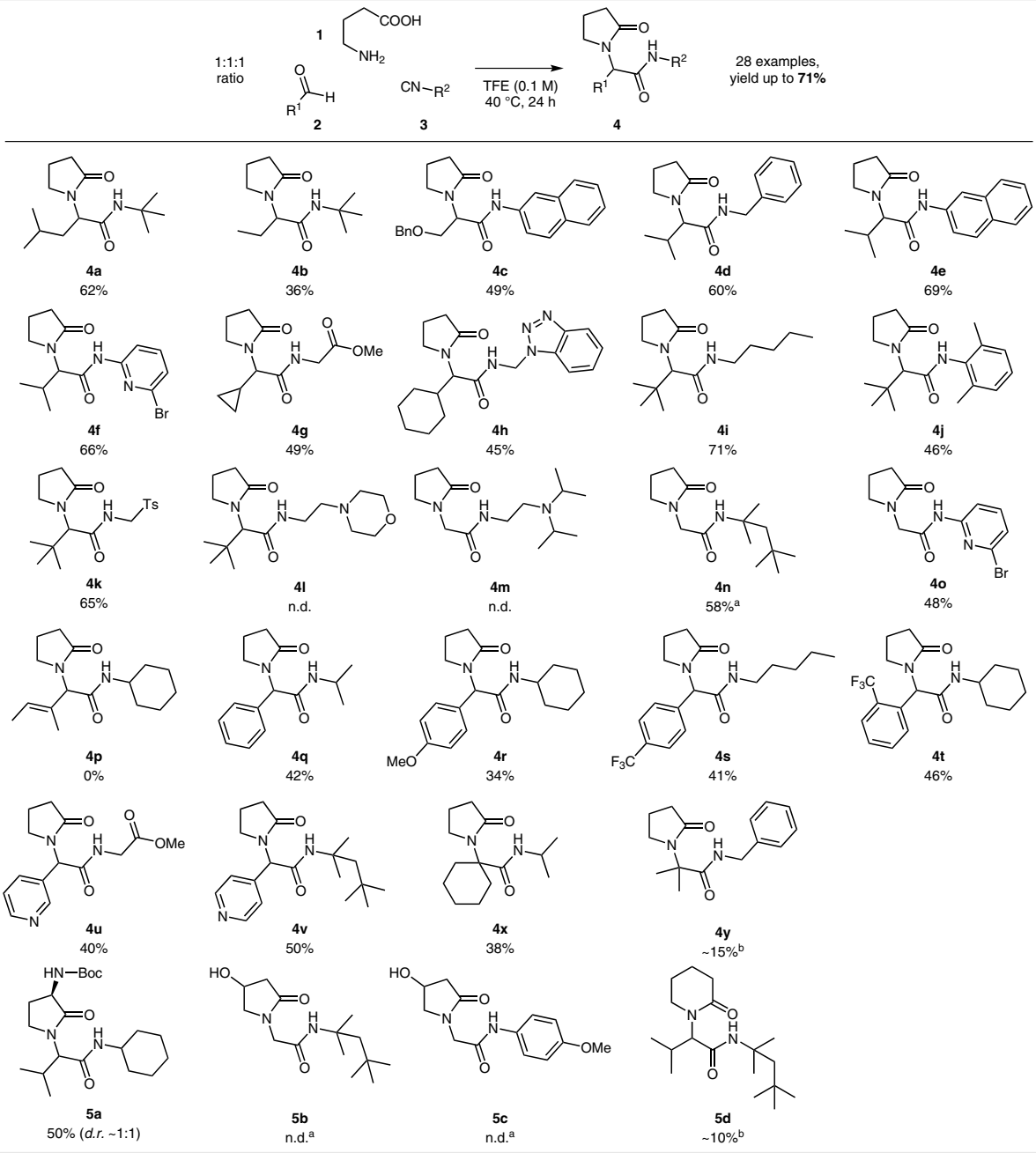
With the optimized protocol in hand, we set out to explore the scope of this reaction (Scheme 3). The key (and rate-determining) step in Ugi type reactions is believed to be the addition of the isocyanide to the iminium ion.[18] Indeed, we observed that the yield of the product in this reaction generally correlates well with the relevant reactivity parameters of the inputs; namely, aldehyde electrophilicity and isocyanide nucleophilicity (except in specific cases that will be outlined below). The aldehyde scope proved to be broad, including both aliphatic and aromatic inputs, with the former generally performing better than the latter (i.e., giving products **4i** vs. **4s**); α,β-unsaturated tiglic aldehyde gave no conversion due to reduced electrophilicity (expected product **4p**). In the series of aliphatic aldehydes, the yield was slightly higher for branched inputs (products **4d–f** vs. **4a–c**), possibly due to side reactions initiated by enamine formation in the case of linear aldehydes; in this respect, pivalic aldehyde appears to perform the best (**4i**, **4k**). This feature of our method nicely complements the conventional approach toward racetams, for which the introduction of bulky substituents at this position in the molecule is challenging (neopentylic halides are generally very poor S_N2 electrophiles). Formaldehyde, on the other hand, did not follow the general trend: the yield was somewhat lower than expected (formaldehyde is the most electrophilic aldehyde considering both electronic and steric properties, and does not enolize) but can be improved by performing the reaction at reflux (as shown for **4n**).[19] Furthermore, (hete-



Scheme 2 Ugi reactions with amino acids

ro)aromatic aldehydes could also be employed (**4q–v**), although the yield was slightly lower than for aliphatic homologues (the decrease was particularly significant for electron-rich anisaldehyde, product **4r**). Finally, (relatively reactive) ketones were also found to be suitable carbonyl components in this reaction (**4x**); again, this is an important complementary feature to conventional methods based on S_N2 substitution, which would require here a tertiary halide electrophile.

The reaction was found to be quite flexible regarding the isocyanide scope, without notable reactivity differences between various isocyanides (Scheme 3). Aliphatic (linear or branched, products **4a**, **4d**, **4h**, **4i**, **4n**, **4p**, **4q**), aromatic (**4c**, **4f**), and α-acidic isocyanides (**4g**, **4k**) were all well tolerated in the reaction. To our delight, the convertible reagent 2-bromo-6-isocyanopyridine,[20] which is somewhat less nucleophilic than most other isocyanides, could also be employed in this transformation (**4f**, **4o**). On the other



Scheme 3 *Reagents and conditions*: γ-aminobutyric acid (1 mmol), aldehyde (1 mmol) and isocyanide (1 mmol) in TFE (10 mL) at 40 °C for 24 h; isolated yields; n.d. = not determined, complex reaction mixture. [a] Performed at reflux. [b] Based on ^{1}H NMR analysis of the crude mixture, product not isolated.

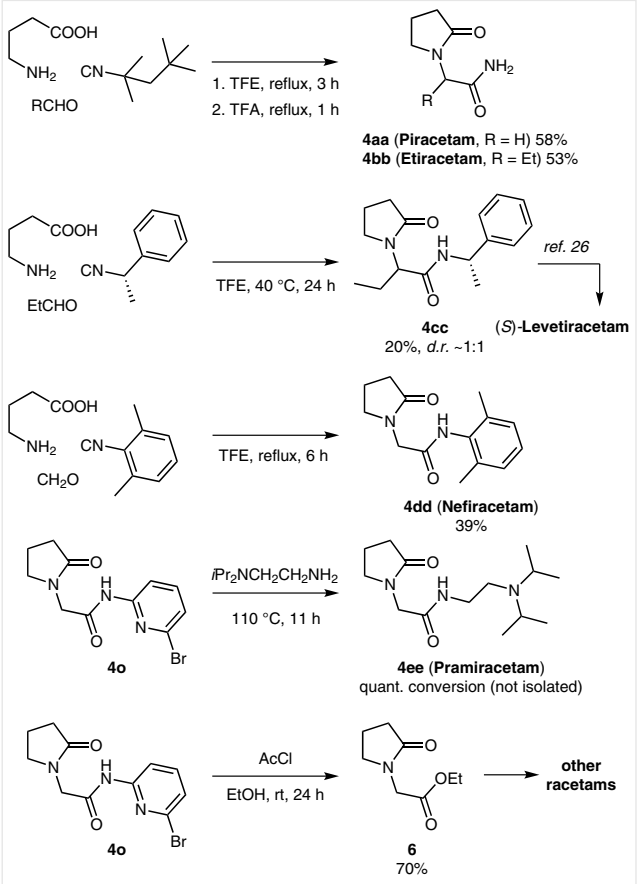
hand, 2-morpholinoethyl isocyanide [and the related 2-(diisopropyl-amino)ethyl isocyanide, envisaged for the synthesis of **4m**] most likely displayed peptide coupling reactivity rather than Ugi addition;[21] in these two examples, the desired products were formed in low yields at best.[22]

Although γ-aminobutyric acid is the component relevant to the family of racetams, we also investigated the amino acid scope of our reaction. Thus, product **5a** was obtained in good yield (as a ~1:1 mixture of diastereoisomers[23] starting from N_α-Boc-protected α,γ-diaminobutyric acid [Boc-Dab-OH]). On the other hand, the introduction of a 3-hydroxyl group on the amino acid proved to be a problematic variation, as a complex mixture resulted from the attempted synthesis of oxiracetam derivatives **5b** and **5c**.[24] A similar result was obtained when 5-aminovaleric acid was employed,[25] providing the desired product **5d** in only ~10% yield. It thus seems that this protocol is restricted to the formation of γ-lactam derivatives and we decided not to further pursue the exploration of the lactam space accessible via this Ugi type reaction.

We then probed the utility of this novel Ugi reaction in the synthesis of clinically important racetam derivatives (Scheme 4). Piracetam **4aa** and etiracetam **4bb** were prepared in good yields by one-pot Ugi condensation using 1,1,3,3-tetramethylbutyl isocyanide and subsequent acid-mediated dealkylation to the primary amide. Etiracetam enriched in the bioactive stereoisomer ((*S*)-levetiracetam, Keppra) can be obtained by a crystallization-induced dynamic resolution of the diastereoisomeric mixture of Ugi adduct **4cc**,[26] which was obtained in a relatively low yield (typical for enolizable linear aldehydes, in this case propionaldehyde). Another racetam drug, nefiracetam (**4dd**), can be obtained directly via the multicomponent condensation although the yield was moderate, plausibly due to the utilization of a less nucleophilic isocyanide (2,6-dimethylphenyl isocyanide, see also **4j** vs. **4i** in Scheme 3).

Finally, this Ugi type reaction was exploited to synthesize racetams in combination with the convertible isocyanide 2-bromo-6-isocyanopyridine:[20] Pramiracetam **4ee** could be obtained by heating Ugi product **4o** with the requisite primary amine,[27] whereas ester **6**, the general intermediate in the preparation of racetams, was accessed by acid-mediated solvolysis of **4o**.[2c] Given the high versatility of the conversion of Ugi products derived from the convertible isocyanide,[20] this approach provides rapid access to a large number of racetam derivatives, allowing extensive variation at the α-position of the 2-oxo-pyrrolidino acetamide as well as the primary amide side (see also **4f**, Scheme 3).

In summary, we have developed a novel, direct multicomponent synthesis of racetam derivatives. The Ugi 4C-3CR condensation with γ-aminobutyric acid is a simple, resource-efficient, and general way to access clinically relevant small molecules in a single step or through short reaction sequences. Typical problems of the conventional route are avoided, allowing the generation of a broad range of racetam derivatives, including examples that are challenging using traditional methods.



Scheme 4 Synthesis of clinically important racetams

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Cyclohexane was distilled prior to use. 2,2,2-Trifluoroethanol was flushed with nitrogen upon storing. Reactions were performed under nitrogen atmosphere. Melting points were recorded with a Büchi M-565 melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance 500 (125.78 MHz for ^{13}C) or Bruker Avance 400 (100.62 MHz for ^{13}C) using the residual solvent as internal standard (^1H: δ = 7.26 ppm, $^{13}C\{^1H\}$: δ = 77.16 ppm for $CDCl_3$, ^1H: δ = 2.50 ppm, $^{13}C\{^1H\}$: δ = 39.52 ppm for DMSO-d_6 and ^1H: δ = 3.31 ppm, $^{13}C\{^1H\}$: δ = 49.00 ppm for CD_3OD). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), br (broad), and m (multiplet) or combinations thereof. IR spectra were recorded neat with a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. Electrospray ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out with a Bruker microTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on

Silicycle Silia-P Flash Silica Gel (particle size 40–63 μm, pore diameter 60 Å) using the indicated eluent. Thin-layer chromatography (TLC) was performed using TLC plates from Merck (SiO_2, Kieselgel 60 F_{254} neutral, on aluminum with fluorescence indicator). *N*-[2-(Diisopropylamino)ethyl]formamide was synthesized by reacting *N*,*N*-diisopropylethane-1,2-diamine with ethyl formate; *N*-(2-isocyanoethyl)-*N*-isopropylpropan-2-amine was synthesized by dehydrating the corresponding formamide with $POCl_3$/NEt_3. 2-Bromo-6-isocyanopyridine was prepared as described previously.[20]

General Procedure A

To a solution of γ-aminobutyric acid (1.0 mmol, 1 equiv) in 2,2,2-trifluoroethanol (10 mL) were added the aldehyde (1.0 mmol, 1 equiv) and the isocyanide (1.0 mmol, 1 equiv). Unless otherwise indicated, the mixture was stirred and heated at 40 °C for 24 h. The solution was then concentrated in vacuo and the product was isolated by column chromatography on silica gel.

General Procedure B

To a solution of γ-aminobutyric acid (1.0 mmol, 1 equiv) in 2,2,2-trifluoroethanol (10 mL) were added the aldehyde (1.0 mmol, 1 equiv) and the isocyanide (1.0 mmol, 1 equiv). The mixture was heated at reflux for 3 h, then concentrated and redissolved in trifluoroacetic acid (3 mL). This solution was heated at reflux for 1 h. The reaction mixture was then concentrated in vacuo and the product was isolated by column chromatography on silica gel.

N-(*tert*-Butyl)-4-methyl-2-(2-oxopyrrolidin-1-yl)pentanamide (4a)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), 3-methylbutanal (86 mg, 1.0 mmol, 1 equiv) and *tert*-butyl isocyanide (83 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1 to 1:1).

Yield: 167 mg (0.621 mmol, 62%); white solid; mp 148–151 °C; R_f = 0.29 (cyclohexane/EtOAc, 1:1).

IR (neat): 3300 (s), 2952 (m), 2871 (m), 2362 (m), 1651 (s), 1552 (s), 1444 (s), 1388 (s), 1290 (s), 1224 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.00 (br, 1 H), 4.45 (dd, *J* = 9.1, 6.6 Hz, 1 H), 3.43–3.27 (m, 2 H), 2.41–2.26 (m, 2 H), 2.02–1.87 (m, 2 H), 1.66–1.50 (m, 2 H), 1.43–1.32 (m, 1 H), 1.24 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (C), 169.5 (C), 53.7 (CH), 51.2 (C), 43.8 (CH_2), 36.6 (CH_2), 31.3 (CH_2), 28.7 (CH_3), 24.8 (CH), 23.0 (CH_3), 22.0 (CH_3), 18.3 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}N_2NaO_2$: 277.1886; found: 277.1873.

N-(*tert*-Butyl)-2-(2-oxopyrrolidin-1-yl)butanamide (4b)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), propionaldehyde (58 mg, 1.0 mmol, 1 equiv) and *tert*-butyl isocyanide (83 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1 to 100% EtOAc).

Yield: 80 mg (0.355 mmol, 36%); white solid; mp 99–104 °C; R_f = 0.19 (cyclohexane/EtOAc, 1:1).

IR (neat): 3294 (s), 3074 (m), 2958 (s), 2360 (m), 1649 (s), 1550 (s), 1444 (s), 1390 (s), 1357 (s), 1303 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.06 (br, 1 H), 4.25 (dd, *J* = 8.5, 6.9 Hz, 1 H), 3.44–3.37 (m, 1 H), 3.36–3.29 (m, 1 H), 2.41–2.27 (m, 2 H), 2.01–1.90 (m, 2 H), 1.89–1.79 (m, 1 H), 1.63–1.52 (m, 1 H), 1.24 (s, 9 H), 0.80 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (C), 169.3 (C), 57.1 (CH), 51.2 (C), 43.8 (CH_2), 31.2 (CH_2), 28.7 (CH_3), 21.3 (CH_2), 18.3 (CH_2), 10.6 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{22}N_2NaO_2$: 249.1573; found: 249.1563.

3-(Benzyloxy)-*N*-(naphthalen-2-yl)-2-(2-oxopyrrolidin-1-yl)propanamide (4c)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), benzyloxyacetaldehyde (150 mg, 1.0 mmol, 1 equiv) and 2-naphthyl isocyanide (156 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1 to 100% EtOAc).

Yield: 191 mg (0.492 mmol, 49%); brown solid; mp 101–111 °C; R_f = 0.30 (cyclohexane/EtOAc, 1:1).

IR (neat): 3263 (m), 2900 (m), 2868 (m), 2358 (s), 1666 (s), 1631 (s), 1585 (s), 1544 (s), 1502 (s), 1433 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 8.31 (d, *J* = 2.0 Hz, 1 H), 7.80–7.71 (m, 3 H), 7.53 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.48–7.27 (m, 7 H), 5.25 (dd, *J* = 8.2, 6.0 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.03–3.92 (m, 2 H), 3.76–3.68 (m, 1 H), 3.53–3.45 (m, 1 H), 2.52–2.45 (m, 2 H), 2.14–1.96 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7 (C), 167.1 (C), 137.4 (C), 135.4 (C), 133.7 (C), 130.5 (C), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 126.4 (CH), 124.9 (CH), 120.0 (CH), 116.7 (CH), 73.1 (CH_2), 66.8 (CH_2), 55.2 (CH), 44.8 (CH_2), 31.0 (CH_2), 18.2 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{24}N_2NaO_3$: 411.1679; found: 411.1665.

N-Benzyl-3-methyl-2-(2-oxopyrrolidin-1-yl)butanamide (4d)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), isobutyraldehyde (72 mg, 1.0 mmol, 1 equiv) and benzyl isocyanide (117 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:4; R_f = 0.33).

Yield: 165 mg (0.60 mmol, 60%); colorless oil.

IR (neat): 3300 (w), 2968 (w), 1657 (s), 1529 (s), 1229 (m), 698 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.10 (m, 6 H), 4.48 (dd, *J* = 15.0, 6.0 Hz, 1 H), 4.32 (dd, *J* = 15.0, 6.0 Hz, 1 H), 4.15 (d, *J* = 11.0 Hz, 1 H), 3.56 (q, *J* = 7.5 Hz, 1 H), 3.41 (q, *J* = 7.5 Hz, 1 H), 2.39–2.18 (m, 3 H), 1.98 (quint, *J* = 7.0 Hz, 2 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (C), 169.4 (C), 138.3 (C), 128.6 (CH), 127.7 (CH), 127.4 (CH), 62.0 (CH), 44.4 (CH_2), 43.3 (CH_2), 31.1 (CH_2), 26.5 (CH), 19.5 (CH_3), 18.9 (CH_3), 18.3 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{22}N_2NaO_2$: 297.1573; found: 297.1565.

3-Methyl-*N*-(naphthalen-2-yl)-2-(2-oxopyrrolidin-1-yl)butanamide (4e)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), isobutyraldehyde (72 mg, 1.0 mmol, 1 equiv) and 2-naphthyl isocyanide (153 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1 to 100% EtOAc).

Yield: 213 mg (0.686 mmol, 69%); mp 160–165 °C; brown solid; R_f = 0.36 (cyclohexane/EtOAc, 1:1).

IR (neat): 3265 (s), 2958 (s), 2364 (m), 1658 (s), 1631 (s), 1585 (s), 1552 (s), 1502 (s), 1434 (s), 1350 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.68 (br, 1 H), 8.37 (s, 1 H), 7.85–7.69 (m, 3 H), 7.58 (d, *J* = 8.2 Hz, 1 H), 7.44 (t, *J* = 6.9 Hz, 1 H), 7.38 (t, *J* = 6.9 Hz, 1 H), 4.56 (d, *J* = 11.0 Hz, 1 H), 3.83–3.73 (m, 1 H), 3.59–3.50 (m, 1 H), 2.57–2.40 (m, 3 H), 2.13–1.98 (m, 2 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.0 (C), 168.4 (C), 135.8 (C), 133.8 (C), 130.6 (C), 128.5 (CH), 127.7 (CH), 127.5 (CH), 126.4 (CH), 124.9 (CH), 120.1 (CH), 116.7 (CH), 63.0 (CH), 44.8 (CH_2), 31.4 (CH_2), 27.1 (CH), 19.5 (CH_3), 19.1 (CH_3), 18.4 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{22}N_2NaO_2$: 333.1573; found: 333.1573.

N-(6-Bromopyridin-2-yl)-3-methyl-2-(2-oxopyrrolidin-1-yl)butanamide (4f)

Prepared from γ-aminobutyric acid (52 mg, 0.5 mmol, 1 equiv), isobutyraldehyde (36 mg, 0.5 mmol, 1 equiv) and 2-bromo-6-isocyanopyridine (92 mg, 0.5 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 2:1; R_f = 0.25).

Yield: 112 mg (0.329 mmol, 66%); green solid; mp 147–152 °C.

IR (neat): 3209 (w), 2964 (w), 1650 (s), 1568 (s), 1529 (s), 1427 (s), 1388 (s), 1124 (s), 784 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.51 (s, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 4.51 (d, *J* = 11.0 Hz, 1 H), 3.71–3.60 (m, 1 H), 3.53–3.39 (m, 1 H), 2.62–2.43 (m, 2 H), 2.42–2.27 (m, 1 H), 2.14–1.95 (m, 2 H), 1.04 (d, *J* = 6.0 Hz, 3 H), 0.92 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6 (C), 168.9 (C), 151.5 (C), 140.3 (CH), 139.5 (C), 123.6 (CH), 112.5 (CH), 62.6 (CH), 44.5 (CH_2), 31.3 (CH_2), 26.9 (CH), 19.6 (CH_3), 19.0 (CH_3), 18.5 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}BrN_3NaO_2$: 362.0475; found: 362.0469.

Methyl [2-Cyclopropyl-2-(2-oxopyrrolidin-1-yl)acetyl]glycinate (4g)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), cyclopropanecarboxaldehyde (70 mg, 1.0 mmol, 1 equiv) and methyl isocyanoacetate (99 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:1 to EtOAc/MeOH 9:1).

Yield: 126 mg (0.494 mmol, 49%); orange solid; mp 104–115 °C; R_f = 0.38 (EtOAc/MeOH, 9:1).

IR (neat): 3186 (m), 2939 (s), 2362 (s), 1753 (s), 1651 (s), 1546 (s), 1440 (s), 1400 (s), 1359 (s), 1309 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.02 (t, *J* = 4.7 Hz, 1 H), 3.99 (dd, *J* = 18.0, 5.7 Hz, 1 H), 3.88 (dd, *J* = 18.0, 5.7 Hz, 1 H), 3.75 (d, *J* = 10.4 Hz, 1 H), 3.66 (s, 3 H), 3.58–3.53 (m, 2 H), 2.36 (t, *J* = 7.9 Hz, 2 H), 2.08–1.93 (m, 2 H), 1.36–1.24 (m, 1 H), 0.74–0.66 (m, 1 H), 0.55–0.42 (m, 2 H), 0.26–0.19 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (C), 170.2 (C), 190.1 (C), 59.8 (CH_3), 52.3 (CH), 44.5 (CH_2), 41.0 (CH_2), 30.9 (CH_2), 18.1 (CH_2), 10.2 (CH), 5.3 (CH_2), 2.9 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}N_2NaO_4$: 277.1159; found: 277.1150.

N-{(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl}-2-cyclohexyl-2-(2-oxopyrrolidin-1-yl)acetamide (4h)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), cyclohexanecarboxaldehyde (112 mg, 1.0 mmol, 1 equiv) and 1*H*-benzotriazol-1-ylmethyl isocyanide (159 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:2 to EtOAc/MeOH, 9:1).

Yield: 158 mg (0.445 mmol, 45%); yellow solid; mp 88–93 °C; R_f = 0.13 (cyclohexane/EtOAc, 1:2).

IR (neat): 3271 (m), 2923 (s), 2850 (s), 2362 (s), 1658 (s), 1546 (s), 1492 (s), 1421 (s), 1286 (s), 1271 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.99 (t, *J* = 6.3 Hz, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 8.5 Hz, 1 H), 7.45–7.40 (m, 1 H), 7.34–7.29 (m, 1 H), 6.09 (dd, *J* = 13.9, 6.9 Hz, 1 H), 5.95 (dd, *J* = 13.9, 6.9 Hz, 1 H), 4.29 (d, *J* = 11.0 Hz, 1 H), 3.46–3.38 (m, 1 H), 3.35–3.28 (m, 1 H), 2.37–2.28 (m, 1 H), 2.24–2.15 (m, 1 H), 1.97–1.78 (m, 3 H), 1.63–1.43 (m, 3 H), 1.42–1.32 (m, 2 H), 1.15–1.04 (m, 2 H), 1.03–0.92 (m, 1 H), 0.79–0.65 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.1 (C), 170.3 (C), 146.0 (C), 132.2 (C), 127.6 (CH), 124.2 (CH), 119.6 (CH), 110.7 (CH), 60.0 (CH), 50.9 (CH_2), 44.4 (CH_2), 35.3 (CH), 31.0 (CH_2), 29.6 (CH_2), 29.0 (CH_2), 26.1 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 18.2 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{25}N_5NaO_2$: 378.1900; found: 378.1885.

3,3-Dimethyl-2-(2-oxopyrrolidin-1-yl)-*N*-pentylbutanamide (4i)

Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), pivalaldehyde (86 mg, 1.0 mmol, 1 equiv) and 1-pentyl isocyanide (97 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 20:1 to 1:1).

Yield: 189 mg (0.705 mmol, 71%); white solid; mp 42–48 °C; R_f = 0.18 (cyclohexane/EtOAc, 1:1).

IR (neat): 3305 (m), 2956 (s), 2931 (s), 2871 (s), 2360 (m), 1651 (s), 1546 (s), 1421 (s), 1365 (s), 1284 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.22 (t, *J* = 5.0 Hz, 1 H), 4.40 (s, 1 H), 3.76–3.68 (m, 1 H), 3.66–3.58 (m, 1 H), 3.21–3.12 (m, 1 H), 3.00–2.91 (m, 1 H), 2.31–2.14 (m, 2 H), 1.86 (quint, *J* = 7.6 Hz, 2 H), 1.37 (quint, *J* = 7.3 Hz, 2 H), 1.24–1.12 (m, 4 H), 0.94 (s, 9 H), 0.76 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (C), 168.7 (C), 62.4 (CH), 47.4 (CH_2), 39.0 (CH_2), 34.7 (C), 30.9 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.6 (CH_3), 22.2 (CH_2), 19.0 (CH_2), 13.9 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}N_2NaO_2$: 291.2043; found: 291.2031.

N-(2,6-Dimethylphenyl)-3,3-dimethyl-2-(2-oxopyrrolidin-1-yl)butanamide (4j)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), pivalaldehyde (86 mg, 1.0 mmol, 1 equiv) and 2,6-dimethylphenyl isocyanide (131 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 2:1; R_f = 0.17).

Yield: 139 mg (0.46 mmol, 46%); white solid; mp 147–155 °C.

IR (neat): 3169 (w), 2957 (w), 1655 (s), 1533 (m), 1161 (m), 770 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.10–6.97 (s, 3 H), 4.73 (s, 1 H), 3.86–3.65 (m, 2 H), 2.46–2.23 (m, 2 H), 2.18 (s, 6 H), 2.04–1.85 (m, 2 H), 1.16 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3 (C), 167.6 (C), 135.2 (C), 134.0 (C), 128.2 (CH), 127.1 (CH), 62.6 (CH), 47.3 (C), 35.2 (CH_2), 30.9 (CH_2), 27.8 (CH_3), 19.3 (CH_2), 18.7 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}N_2NaO_2$: 325.1886; found: 325.1879.

3,3-Dimethyl-2-(2-oxopyrrolidin-1-yl)-*N*-(tosylmethyl)butanamide (4k)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), pivalaldehyde (86 mg, 1.0 mmol, 1 equiv) and tosylmethyl isocyanide (195 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:2; R_f = 0.36).

Yield: 238 mg (0.65 mmol, 65%); white solid; mp 182–192 °C.

IR (neat): 3200 (w), 2959 (w), 1655 (s), 1547 (w), 1315 (m), 1140 (s), 567 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 4.94 (dd, *J* = 14.0, 7.0 Hz, 1 H), 4.70 (s, 1 H), 4.43 (dd, *J* = 14.0, 7.0 Hz, 1 H), 3.53–3.47 (m, 1 H), 3.11–3.05 (m, 1 H), 2.56–2.47 (m, 1 H), 2.44–2.35 (m, 1 H), 2.40 (s, 3 H), 1.95–1.86 (m, 1 H), 1.86–1.77 (m, 1 H), 0.93 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7 (C), 168.6 (C), 145.0 (C), 134.2 (C), 129.9 (CH), 129.2 (CH), 61.9 (CH), 59.9 (CH_2), 47.3 (CH_2), 35.7 (C), 30.8 (CH_2), 27.5 (CH_3), 21.8 (CH_3), 18.8 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}N_2O_4S$: 367.1686; found: 367.1683.

2-(2-Oxopyrrolidin-1-yl)-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (4n)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to General Procedure A (reflux, 3 h reaction time). The product was purified by column chromatography on silica gel (100% EtOAc to EtOAc/MeOH, 19:1).

Yield: 148 mg (0.582 mmol, 58%); colorless oil; R_f = 0.52 (EtOAc/MeOH, 19:1).

IR (neat): 3310 (w), 2951 (w), 1659 (s), 1551 (m), 920 (w), 731 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.14 (s, 1 H), 3.72 (s, 2 H), 3.41 (t, *J* = 7.0 Hz, 2 H), 2.31 (t, *J* = 8.0 Hz, 2 H), 1.96 (quint, *J* = 7.0 Hz, 2 H), 1.62 (s, 2 H), 1.72 (s, 6 H), 0.87 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (C), 166.9 (C), 55.1 (C), 51.2 (CH_2), 48.4 (CH_2), 48.0 (CH_2), 31.5 (C), 31.3 (CH_3), 30.4 (CH_2), 29.1 (CH_3), 17.9 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}N_2NaO_2$: 277.1886; found: 277.1893.

N-(6-Bromopyridin-2-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (4o)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 2-bromo-6-isocyanopyridine (183 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:1 to 1:3, R_f = 0.13).

Yield: 143 mg (0.48 mmol, 48%); green solid; mp 168–170 °C.

IR (neat): 3034 (w), 2945 (w), 1672 (s), 1571 (s), 1427 (s), 1288 (s), 1126 (s), 791 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 7.5 Hz, 1 H), 4.16 (s, 2 H), 3.56 (t, *J* = 7.0 Hz, 2 H), 2.52 (t, *J* = 8.0 Hz, 2 H), 2.14 (quint, *J* = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.8 (C), 167.1 (C), 151.1 (C), 140.7 (CH), 139.5 (C), 124.0 (CH), 112.6 (CH), 48.6 (CH_2), 47.7 (CH_2), 30.4 (CH_2), 18.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}BrN_3NaO_2$: 320.0005; found: 320.0004.

N-Isopropyl-2-(2-oxopyrrolidin-1-yl)-2-phenylacetamide (4q)

Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), benzaldehyde (106 mg, 1.0 mmol, 1 equiv) and isopropyl isocyanide (69 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1 to 100% EtOAc).

Yield: 109 mg (0.417 mmol, 42%); white solid; mp 148–151 °C; R_f = 0.36 (EtOAc).

IR (neat): 3265 (s), 2970 (s), 2360 (m), 1666 (s), 1643 (s), 1556 (s), 1431 (s), 1417 (s), 1365 (s), 1284 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 6.50 (d, *J* = 7.3 Hz, 1 H), 5.86 (s, 1 H), 4.08–3.97 (m, 1 H), 3.83–3.74 (m, 1 H), 2.99–2.91 (m, 1 H), 2.40–2.22 (m, 2 H), 2.02–1.91 (m, 1 H), 1.84–1.73 (m, 1 H), 1.07 (d, *J* = 6.3 Hz, 3 H), 1.05 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.3 (C), 168.3 (C), 135.2 (C), 128.8 (CH), 128.7 (CH), 128.3 (CH), 58.4 (CH), 45.0 (CH_2), 41.6 (CH), 31.1 (CH_2), 22.4 (CH_3), 18.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}N_2NaO_2$: 283.1417; found: 283.1411.

N-Cyclohexyl-2-(4-methoxyphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide (4r)

Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), *p*-methoxybenzaldehyde (136 mg, 1.0 mmol, 1 equiv) and cyclohexyl isocyanide (109 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 10:1 to 100% EtOAc).

Yield: 111 mg (0.336 mmol, 34%); white solid; mp 139–143 °C; R_f = 0.12 (cyclohexane/EtOAc, 1:1).

IR (neat): 3255 (s), 2931 (s), 2852 (s), 2358 (m), 1651 (s), 1608 (s), 1546 (s), 1512 (s), 1438 (s), 1365 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.22 (d, *J* = 7.9 Hz, 1 H), 5.77 (s, 1 H), 3.75 (s, 3 H), 3.79–3.66 (m, 2 H), 2.97 (td, *J* = 8.8, 5.7 Hz, 1 H), 2.42–2.33 (m, 1 H), 2.32–2.23 (m, 1 H), 2.03–1.92 (m, 1 H), 1.87–1.74 (m, 3 H), 1.67–1.57 (m, 2 H), 1.53 (dt, *J* = 12.6, 3.5 Hz, 1 H), 1.34–1.21 (m, 2 H), 1.12–0.96 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.3 (C), 168.5 (C), 159.5 (C), 130.2 (CH), 127.1 (C), 114.1 (CH), 57.9 (CH), 55.3 (CH_3), 48.5 (CH), 44.9 (CH_2), 32.7 (CH_2), 31.2 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 18.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{26}N_2NaO_3$: 353.1836; found: 353.1820.

2-(2-Oxopyrrolidin-1-yl)-*N*-pentyl-2-[4-(trifluoromethyl)phenyl]acetamide (4s)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), *p*-trifluoromethylbenzaldehyde (174 mg, 1.0 mmol, 1 equiv) and 1-pentyl isocyanide (97 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 15:1 to 100% EtOAc).

Yield: 145 mg (0.406 mmol, 41%); white solid; mp 84–88 °C; R_f = 0.47 (cyclohexane/EtOAc, 1:1).

IR (neat): 3253 (m), 2927 (s), 2360 (m), 1679 (s), 1672 (s), 1649 (s), 1552 (s), 1421 (s), 1325 (s), 1286 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.08 (t, *J* = 5.0 Hz, 1 H), 6.00 (s, 1 H), 3.86–3.77 (m, 1 H), 3.29–3.20 (m, 1 H), 3.19–3.11 (m, 1 H), 3.08–3.01 (m, 1 H), 2.44–2.27 (m, 2 H), 2.08–1.97 (m, 1 H), 1.93–1.82 (m, 1 H), 1.44 (quint, *J* = 7.3 Hz, 2 H), 1.31–1.16 (m, 4 H), 0.83 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (C), 168.5 (C), 139.2 (C), 130.5 (q, J_{C-F} = 33 Hz, C), 129.1 (CH), 125.8 (q, J_{C-F} = 4, CH), 124.0 (q, J_{C-F} = 270, C), 58.0 (CH), 45.1 (CH_2), 39.7 (CH_2), 31.0 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 22.3 (CH_2), 18.2 (CH_2), 14.0 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}F_3N_2NaO_2$: 379.1604; found: 379.1588.

***N*-Cyclohexyl-2-(2-oxopyrrolidin-1-yl)-2-[2-(trifluoromethyl)phenyl]acetamide (4t)**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), 2-trifluoromethylbenzaldehyde (174 mg, 1.0 mmol, 1 equiv) and cyclohexyl isocyanide (109 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:1 to 1:2).

Yield: 169 mg (0.46 mmol, 46%); white solid; mp 160–165 °C; R_f = 0.26 (cyclohexane/EtOAc, 1:1).

IR (neat): 3254 (w), 2932 (w), 1664 (s), 1439 (m), 1313 (m), 1124 (s), 1040 (m), 779 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (t, *J* = 8.0 Hz, 2 H), 7.55 (t, *J* = 7.0 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 5.97 (s, 1 H), 5.74 (d, *J* = 6.5 Hz, 1 H), 3.80–3.68 (m, 1 H), 3.68–3.57 (m, 1 H), 2.91–2.78 (m, 1 H), 2.48–2.29 (m, 2 H), 2.08–1.94 (m, 1 H), 1.92–1.76 (m, 3 H), 1.71–1.45 (m, 3 H), 1.36–0.87 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1 (C), 168.1 (C), 133.1 (C), 132.1 (CH), 131.2 (CH), 129.8 (q, J_{C-F} = 30 Hz, C), 129.0 (CH), 126.8 (q, J_{C-F} = 6 Hz, CH), 124.0 (q, J_{C-F} = 275 Hz, C), 55.5 (CH), 48.9 (C), 45.7 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 31.0 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 18.3 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}F_3N_2O_2$: 369.1784; found: 369.1785.

Methyl [2-(2-oxopyrrolidin-1-yl)-2-(pyridin-3-yl)acetyl]glycinate (4u)

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), nicotinaldehyde (107 mg, 1.0 mmol, 1 equiv) and methyl isocyanoacetate (99 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (EtOAc/MeOH, 9:1; R_f = 0.23).

Yield: 118 mg (0.404 mmol, 40%); gummy yellow solid.

IR (neat): 3294 (w), 2955 (w), 1749 (m), 1659 (s), 1416 (m), 1204 (s), 714 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56–8.48 (m, 2 H), 7.77 (d, *J* = 7.5 Hz, 1 H), 7.38 (br, 1 H), 7.30 (t, *J* = 5.0 Hz, 1 H), 6.0 (s, 1 H), 4.10–3.96 (m, 2 H), 3.80–3.64 (m, 4 H), 3.10–3.00 (m, 1 H), 2.50–2.29 (m, 2 H), 2.14–2.00 (m, 1 H), 2.00–1.84 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.0 (C), 170.1 (C), 168.8 (C), 150.4 (CH), 149.8 (CH), 136.9 (CH), 130.5 (C), 123.7 (CH), 56.3 (CH), 52.5 (CH_3), 44.9 (CH_2), 41.3 (CH_2), 30.9 (CH_2), 18.2 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}N_3NaO_4$: 314.1108; found: 314.1104.

2-(2-Oxopyrrolidin-1-yl)-2-(pyridin-4-yl)-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (4v)

Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), 4-pyridinecarboxaldehyde (107 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:2, to EtOAc/MeOH, 9:1).

Yield: 165 mg (0.499 mmol, 50%); white solid; mp 165–173 °C; R_f = 0.45 (EtOAc/MeOH, 9:1).

IR (neat): 3276 (s), 2964 (s), 2362 (m), 1654 (s), 1598 (s), 1556 (s), 1436 (s), 1382 (s), 1359 (s), 1259 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 6.0 Hz, 2 H), 7.18 (d, *J* = 6.0 Hz, 2 H), 6.73 (br, 1 H), 5.83 (s, 1 H), 3.79–3.71 (m, 1 H), 3.09–3.02 (m, 1 H), 2.41–2.26 (m, 2 H), 2.05–1.95 (m, 1 H), 1.92–1.83 (m, 1 H), 1.81 (d, *J* = 14.8 Hz, 1 H), 1.53 (d, *J* = 14.8 Hz, 1 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 0.87 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (C), 166.7 (C), 150.2 (CH), 144.2 (C), 123.4 (CH), 57.9 (CH), 55.8 (C), 51.4 (CH_2), 45.1 (CH_2), 31.6 (CH_2), 31.3 (CH_3), 30.8 (C), 29.2 (CH_3), 28.7 (CH_3), 18.3 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{29}N_3NaO_2$: 354.2152; found: 354.2137.

***N*-Isopropyl-1-(2-oxopyrrolidin-1-yl)cyclohexane-1-carboxamide (4x)**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), cyclohexanone (98 mg, 1.0 mmol, 1 equiv) and isopropyl isocyanide (69 mg, 1.0 mmol, 1 equiv) according to General Procedure A. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:4; R_f = 0.23).

Yield: 97 mg (0.385 mmol, 38%); colorless oil.

IR (neat): 3300 (w), 2930 (m), 1668 (s), 1639 (s), 1535 (m), 1256 (m), 642 (w) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.65 (d, *J* = 8.0 Hz, 1 H), 3.97 (sept, *J* = 7.5 Hz, 1 H), 3.41 (t, *J* = 7.0 Hz, 2 H), 2.35 (t, *J* = 8.0 Hz, 2 H), 2.30–2.17 (m, 2 H), 2.03–1.85 (m, 4 H), 1.62–1.50 (m, 2 H), 1.49–1.30 (m, 4 H), 1.08 (d, *J* = 6.5 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7 (C), 172.2 (C), 63.6 (C), 46.3 (CH_2), 41.4 (CH), 33.1 (CH_2), 32.4 (CH_2), 25.3 (CH_2), 22.7 (CH_3), 22.6 (CH_2), 18.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{24}N_2NaO_2$: 275.1730; found: 275.1724.

Racetam Derivative 5a

Prepared from N_α-Boc-L-2,4-diaminobutyric acid (218 mg, 1.0 mmol, 1 equiv), isobutyraldehyde (72 mg, 1.0 mmol, 1 equiv) and cyclohexyl isocyanide (109 mg, 1.0 mmol, 1 equiv) according to General Procedure A. Diastereoisomers formed in ca. 1:1 ratio. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 2:1 to 1:1). Diastereoisomers were not resolved.

Yield: 174 mg (0.46 mmol, 46%); white solid; R_f = 0.29 and 0.14 for the two diastereoisomers (cyclohexane/EtOAc, 2:1).

IR (neat): 3327 (w), 3274 (w), 2927 (m), 1670 (s), 1533 (s), 1435 (m), 1283 (m), 1160 (s), 1047 (w), 707 (w) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.50 (br, 1 H, D1), 6.28 (d, *J* = 7.0 Hz, 1 H, D2), 5.25 (d, *J* = 5.0 Hz, 1 H, D1), 5.18 (br, 1 H, D2), 4.23–4.07 (m, 1 H, D1, 1 H, D2), 4.00 (d, *J* = 10.4 Hz, 1 H, D2), 3.93 (d, *J* = 11.3 Hz, 1 H, D1), 3.71–3.59 (m, 2 H, D1, 1 H, D2), 3.42–3.21 (m, 1 H, D1, 2 H, D2), 2.64–2.37 (m, 2 H, D1, 2 H, D2), 2.34–2.19 (m, 1 H, D1, 1 H, D2), 1.90–1.50 (m, 5 H, D1, 5 H, D2), 1.40 (s, 9 H, D1, 9 H, D2), 1.35–1.03 (m, 4 H, D1, H, D2), 0.93 (d, *J* = 7.0 Hz, 3 H, D2), 0.91 (d, *J* = 7.0 Hz, 3 H, D2), 0.80 (d, *J* = 7.0 Hz, 3 H, D1), 0.78 (d, *J* = 7.0 Hz, 3 H, D1).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.2 (C, D2), 173.0 (C, D1), 168.2 (C, D1), 167.8 (C, D2), 155.7 (C, D1 and D2), 79.9 (C, D1 and D2), 62.8 (CH, D1), 62.1 (CH, D2), 52.9 (CH, D2), 52.3 (CH, D1), 48.3 (CH, D1 and D2), 41.6 (CH_2, D2), 41.4 (CH_2, D1), 32.8 (CH_2, D1), 32.7 (CH_2, D2), 29.7 (CH_2, D2), 29.7 (CH_2, D1), 28.3 (CH_3, D1 and D2), 27.1 (CH, D1), 26.1 (CH, D2), 25.5 (CH_2, D1), 25.5 (CH_2, D2), 24.9 (CH_2, D1), 24.8 (CH_2, D2), 19.5 (CH_3, D2), 19.3 (CH_3, D1), 19.1 (CH_3, D1), 18.7 (CH_3, D2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{35}N_3NaO_4$: 404.2520; found: 404.2503.

2-(2-Oxopyrrolidin-1-yl)acetamide (4aa)[28]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to General Procedure B. The product was purified by column chromatography on silica gel (EtOAc to EtOAc/MeOH, 9:1).

Yield: 82 mg (0.58 mmol, 58%); off-white solid; mp 136–141 °C; R_f = 0.21 (EtOAc/MeOH, 9:1).

IR (neat): 3333 (m), 3160 (m), 2958 (w), 1688 (s), 1651 (s), 1406 (s), 1306 (s), 1290 (s), 1163 (m), 1032 (w), 613 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$/DMSO-d_6): δ = 6.72 (br, 1 H), 6.22 (br, 1 H), 3.27 (s, 2 H), 2.86 (t, *J* = 7.0 Hz, 2 H), 1.75 (t, *J* = 8.0 Hz, 2 H), 1.45 (quint, *J* = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$/DMSO-d_6): δ = 174.0 (C), 169.1 (C), 46.6 (CH_2), 44.2 (CH_2), 29.2 (CH_2), 16.4 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_6H_{10}N_2NaO_2$: 165.0634; found: 165.0627.

2-(2-Oxopyrrolidin-1-yl)butanamide (4bb)[29]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), propionaldehyde (58 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to General Procedure **A**. The product was purified by column chromatography on silica gel (EtOAc/MeOH, 9:1; R_f = 0.31).

Yield: 90 mg (0.53 mmol, 53%); brown crystals; mp 63–90 °C.

IR (neat): 3379 (w), 2966 (w), 1650 (s), 1421 (m), 1269 (m), 1204 (m), 1130 (m), 611 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.55 (s, 1 H), 5.88 (s, 1 H), 4.45 (q, *J* = 6.0 Hz, 1 H), 3.50–3.31 (m, 2 H), 2.49–2.32 (m, 2 H), 2.10–2.00 (m, 2 H), 2.00–1.86 (m, 1 H), 1.73–1.59 (m, 1 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3 (C), 172.7 (C), 56.2 (CH), 44.0 (CH_2), 31.2 (CH_2), 21.2 (CH_2), 18.3 (CH_2), 10.7 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{14}N_2NaO_2$: 193.0954; found: 193.0954.

2-(2-Oxopyrrolidin-1-yl)-*N*-[(*S*)-1-phenylethyl]butanamide (4cc)[26]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), propionaldehyde (58 mg, 1.0 mmol, 1 equiv) and (*S*)-α-methylbenzyl isocyanide (131 mg, 1.0 mmol, 1 equiv) according to General Procedure A. Diastereoisomers formed in ca. 1:1 ratio. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 1:2 to 1:4). Diastereoisomers were not resolved.

Yield: 55 mg (0.20 mmol, 20%); pale-yellow oil; R_f = 0.22 and 0.15 for the two diastereoisomers (cyclohexane/EtOAc, 1:2).

IR (neat): 3299 (w), 2969 (w), 1651 (s), 1533 (m), 1449 (m), 1287 (m), 1213 (w), 700 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 5 H, D1, 5 H, D2), 6.67 (br, 1 H, D2), 6.64 (br, 1 H, D1), 5.05 (quint, *J* = 7.0 Hz, 1 H, D1, 1 H, D2), 4.43 (t, *J* = 7.0 Hz, 1 H, D1), 4.40 (t, *J* = 7.0 Hz, 1 H, D2), 3.56–3.48 (m, 1 H, D2), 3.45–3.39 (m, 1 H, D2), 3.34–3.27 (m, 1 H, D1), 3.20–3.13 (m, 1 H, D1), 2.48–2.36 (m, 1 H, D1, 2 H, D2), 2.27 (ddd, *J* = 16.0, 10.0, 6.5 Hz, 1 H, D1), 2.10–1.80 (m, 3 H, D1, 3 H, D2), 1.74–1.60 (m, 1 H, D1, 1 H, D2), 1.46 (d, *J* = 7.0 Hz, 3 H, D1), 1.44 (d, *J* = 7.0 Hz, 3 H, D2), 0.90 (t, *J* = 7.3 Hz, 3 H, D1), 0.85 (t, *J* = 7.3 Hz, 3 H, D2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (C, D2), 176.1 (C, D1), 169.3 (C, D2), 169.0 (C, D1), 143.7 (C, D1), 143.2 (C, D2), 128.8 (CH, D2), 128.7 (CH, D1), 127.4 (CH, D2), 127.3 (CH, D1), 126.1 (CH, D2), 126.0 (CH, D1), 56.9 (CH, D2), 56.6 (CH, D1), 49.0 (CH, D2), 49.0 (CH, D1), 44.1 (CH_2, D2), 43.8 (CH_2, D1), 31.3 (CH_2, D2), 31.2 (CH_2, D1), 22.2 (CH_3, D1), 22.2 (CH_3, D2), 21.4 (CH_2, D2), 20.9 (CH_2, D1), 18.4 (CH_2, D2), 18.2 (CH_2, D1), 10.7 (CH_3, D2), 10.6 (CH_3, D1).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{22}N_2NaO_2$: 297.1573; found: 297.1570.

***N*-(2,6-Dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide (4dd)**[30]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 2,6-dimethylphenyl isocyanide (131 mg, 1.0 mmol, 1 equiv) according to General Procedure A (reflux, 6 h reaction time). The product was purified by column chromatography on silica gel (EtOAc to EtOAc/MeOH, 19:1).

Yield: 97 mg (0.392 mmol, 39%); white solid; mp 139–142 °C; R_f = 0.14 (EtOAc).

IR (neat): 3258 (s), 2920 (m), 2365 (m), 1697 (s), 1663 (s), 1530 (s), 1468 (s), 1439 (s), 1425 (s), 1406 (s) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (br, 1 H), 7.10–6.97 (m, 3 H), 4.02 (s, 2 H), 3.51 (t, *J* = 6.9 Hz, 2 H), 2.34 (t, *J* = 8.2 Hz, 2 H), 2.14 (s, 6 H), 2.03 (quint, *J* = 7.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2 (C), 167.0 (C), 135.2 (C), 133.5 (C), 128.1 (CH), 127.3 (CH), 48.5 (CH_2), 47.2 (CH_2), 30.4 (CH_2), 18.4 (CH_3), 18.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}N_2NaO_2$: 269.1260; found: 269.1256.

N-[2-(Diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide (4ee)[31]

To Ugi product **4o** (20 mg, 0.065 mmol, 1 equiv) was added *N*1,*N*1-diisopropylethane-1,2-diamine (0.1 mL) and the mixture was stirred at 110 °C for 11 h (under N_2 atmosphere). Crude NMR analysis indicated the complete conversion of **4o** into **4ee** and 2-amino-6-bromopyridine. The product **4ee** was not isolated.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 2 H), 3.47 (t, *J* = 7.0 Hz, 2 H), 3.28 (q, *J* = 5.5 Hz, 2 H), 3.08 (sept, *J* = 7.0 Hz, 2 H), 2.65 (t, *J* = 5.5 Hz, 2 H), 2.43 (t, *J* = 8.0 Hz, 2 H), 2.08 (quint, *J* = 7.5 Hz, 2 H), 1.05 (d, *J* = 7.5 Hz, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.9 (C), 168.2 (C), 48.4 (CH_2), 48.1 (CH), 47.1 (CH_2), 37.8 (CH_2), 36.5 (CH_2), 30.4 (CH_2), 20.9 (CH_3), 18.1 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{28}N_3O_2$: 270.2176; found: 270.2171.

Ethyl 2-(2-Oxopyrrolidin-1-yl)acetate (6)[31]

To a solution of **4o** (34 mg, 0.11 mmol, 1 equiv) in EtOH (0.3 mL) was added acetyl chloride (44 mg, 0.56 mmol, 5 equiv) and the mixture was stirred at r.t. for 22 h. EtOH was then removed in vacuo and the crude mixture was redissolved in diethyl ether. A solution of HCl in cyclopentylmethyl ether (3 M, 0.2 mL) was then added, precipitating the hydrochloride salt of 2-amino-6-bromopyridine. This byproduct was filtered off and concentration of the filtrate afforded the product.

Yield: 14 mg (0.08 mmol, 70%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.17 (q, *J* = 7.0 Hz, 2 H), 4.03 (s, 2 H), 3.47 (t, *J* = 7.0 Hz, 2 H), 2.41 (t, *J* = 8.0 Hz, 2 H), 2.06 (quint, *J* = 7.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (C), 168.8 (C), 61.4 (CH_2), 47.8 (CH_2), 44.2 (CH_2), 30.4 (CH_2), 18.0 (CH_2), 14.2 (CH_3).

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Supporting Information

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