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Multicomponent reactions: development, scope, and applications

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Chapter 9

2-Nitrobenzyl Isocyanide as a Universal Convertible Isocyanide

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A. L. Chandgude
J. Li
A. Dömling
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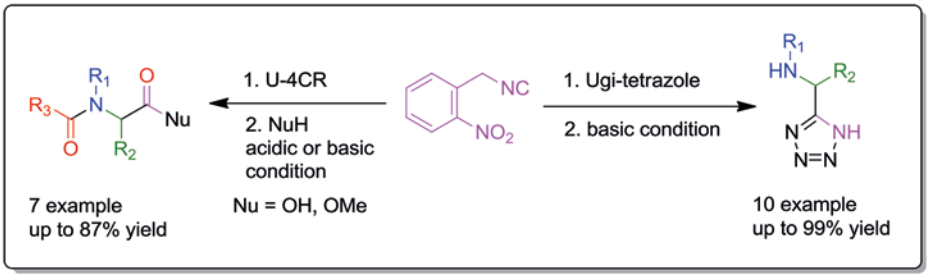


Abstract

2-Nitrobenzyl isocyanide is reported as a universal convertible isocyanide with extensive applicability in both Ugi-4CR and Ugi-tetrazole reactions. The cleavage of this isocyanide from 17 examples in both acidic and basic conditions is presented. Additionally, this isocyanide has various handling and synthetic advantages, such as easy to prepare, odorless, stable and easy to handle as a solid.

Introduction

Multicomponent reactions are considered as ideal reactions due to a wide range of advantages, such as simplicity, high efficiency, green nature, and time efficacy.[1] Isocyanide-based multicomponent reaction (IMCR) is a promising synthetic methodology for the synthesis of peptidomimetics and peptides which find broad applications in pharmaceutical and organic industries.[2] The Ugi reaction is the most extensively studied and widely used IMCR which directly accesses bis-amides or more complex structures by means of substrate modification and post-condensations.[3,4]

However, IMCR has several drawbacks, for instance, the commercial availability of a rather few number of isocyanides and their notorious stench which makes handling unpleasant. Moreover, isocyanide stability and synthesis are always key concerns. One of the solutions to these problems is the use of so-called convertible isocyanides which can be easily transformed to other functional groups such as acids, esters or amides. This consequently circumvents the use of specific isocyanides to gain similar molecular diversity and complexity. Earlier in 1963, Ugi and Rosendahl reported the first convertible isocyanide, cyclohexenyl isocyanide, which later on was also called Armstrong isocyanide.[5] Subsequently, a plenty of convertible isocyanides have been reported in Ugi-4CR[6] or Ugi-T4CR,[7] which are cleavable under acidic condition, basic condition or in some case require multistep methods. The use of these convertible isocyanides became a considerable step in the synthesis of peptidomimetics and natural products.

Despite the increasing popularity of using convertible isocyanides for further molecular modification, these isocyanides suffer from major disadvantages, such as lengthy synthesis procedures, instability, incompatibility with more delicate substrates, laborious workup and multistep cleavage. Furthermore, these isocyanides are only applicable in one type of reactions either Ugi-4CR or Ugi-tetrazole reactions (Ugi-T-4-CR). Thus, the development of a "truly universal convertible isocyanide" which could be applicable in both Ugi-4CR and Ugi-T-4-CR and also cleavable under more than one conditions remains a significant challenge.

Herein, we are reporting the 2-nitrobenzyl isocyanide as a truly universal convertible isocyanide which is applicable not only in Ugi-4CR but also in Ugi-tetrazole reactions, and also cleavable under both acidic and basic conditions.

The 2-nitro benzyl group is prevalent in a variety of synthetic transformations mainly due to its photocleavable nature.[8] It is also used in the preparation of polymers[9] and natural products.[1c,10] Nonetheless, the use of 2-nitrobenzyl isocyanide as a convertible isocyanide has not been sufficiently explored with the exception of only one example as photocleavable isocyanide (sunlight for 5 days) in polymers.[11]

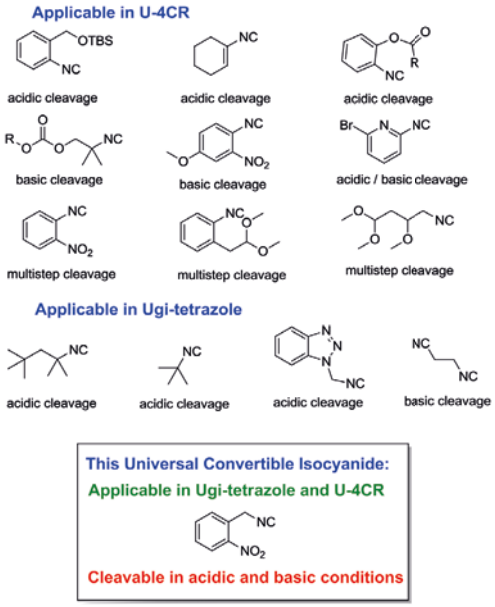
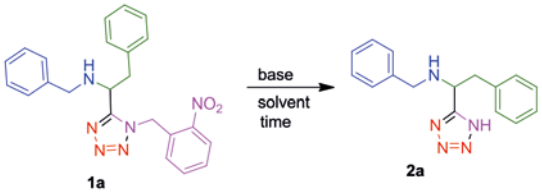


Figure 1. Convertible isocyanides

Results and Discussion

We envisioned the use of this isocyanide as an extensively practical convertible isocyanide in both acidic and basic conditions.[12] At first, the Ugi-tetrazole reaction product was chosen as the model substrate to verify this hypothesis. Recently, our group reported a basic condition (LiOH in THF:H_2O) for the cleavage of β-cyanoethyl isocyanide.[7a] Therefore, we start our optimization by using similar condition and attempted to cleave the 2-nitro benzyl group from the Ugi-tetrazole product (Table 1). Unfortunately, the reaction did not show any product formation under this condition (Table 1, entry **1**). The farther increase in the temperature even to reflux for overnight did not show any effect on reaction and the starting material still remained intact. Meanwhile, change in the solvent to acetonitrile was also ineffective which indicated that LiOH is not applicable for this isocyanide cleavage (Table 1, entry **4**). Next, we screened different bases and different conditions. The reaction with NaOH in toluene did not form any product, but trace product formation occurred in acetonitrile while starting material remained intact in the acetonitrile-water system.

Table 1. Optimization of reaction conditions.



Entry	Base	Equiv	Solvent	Temp	Time (°C)	Yield (%)[a]
1	LiOH	2	THF : H_2O	rt	12	—
2	LiOH	2	THF : H_2O	60	12	—
3	LiOH	2	THF : H_2O	reflux	12	—
4	LiOH	2	CH_3CN	rt	48	—
5	NaOH	2	Toluene	rt	12	—
6	NaOH	2	CH_3CN	rt	12	trace
7	NaOH	2	CH_3CN : H_2O	rt	12	—
8	NaOH	2	THF	rt	12	nd
9[b]	NaOH	>10	CH_3CN	rt	12	32
10[b]	NaOH	8	MeOH	reflux	12	69
11[b]	NaOH	>10	MeOH : H_2O	reflux	6	90
12	KO*t*Bu	1	CH_3CN	rt	12	nd
13	KO*t*Bu	2	CH_3CN	rt	48	nd
14	KO*t*Bu	4	CH_3CN	rt	12	63
15	KO*t*Bu	4	THF	rt	12	84

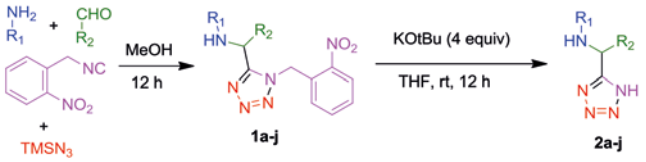
[a]Yield of isolated product **2a**. [b]20% NaOH used. n.d. = not deter-mined.

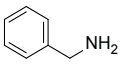
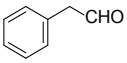
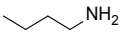
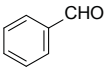
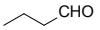
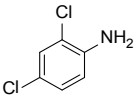
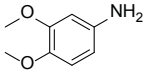
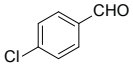
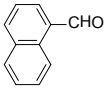
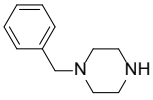
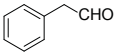
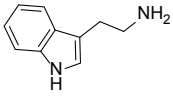
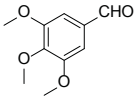
Remarkably, the increase of NaOH equivalence to 20% efficiently promoted the reaction with a promising reaction conversion. From the further evaluation, we found that the 20% aqueous NaOH in refluxing MeOH:water solution gave an excellent yield of 90% (Table 1, entry **11**). Aiming for milder conditions instead of refluxing, we next screened KOtBu in different solvents. To our delight, superior conditions were found in acetonitrile. With only 4 equivalent of KOtBu at room temperature, we obtained a 63% yield (Table 1, entry **14**). The reaction worked best in THF with an 84% yield (Table 1, entry **15**).

With these optimized conditions in hand, we next examined the scope of this convertible isocyanide in various Ugi-tetrazole products (Table 2). This isocyanide performed moderate to good in the Ugi-tetrazole reactions and was compatible with diverse substrates under optimized condition. The aliphatic butyl amine substrate gave a moderate deprotection yield, 45% (Table 2, entry **1b**). Aromatic amines with electron withdrawing and electron donating functionalities provided excellent yields (Table 2, entries **1c**–**1e**). Secondary amines and cyclic heterocycles gave moderate to good yield ranging from 62% to 69% (Table 2, entries **1f**–**1h**). Heterocycles, such as 2-amino pyridine and indole, also worked well (Table 2, entries **1i**–**1j**).

Different aldehydes were also compatible with this protocol. Aliphatic aldehydes, such as phenylacetaldehyde, butyraldehyde, and isobutyraldehyde, worked well with 84%, 91%, and 99% yields respectively. Aromatic aldehyde with electron withdrawing and electron donating functionalities resulted in moderate to good yields (Table 2, entries **1b**, **1f**, **1g**, and **1j**). Ketones, for example, cyclohexanone and acetone afforded 55% and 99% yields respectively (Table 1, entries **1e** and **1i**).

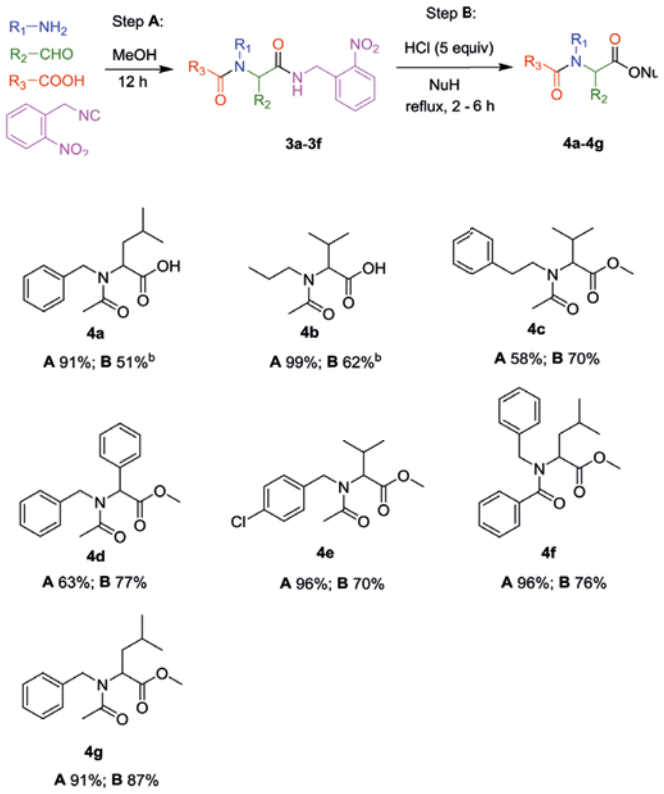
Table 2. Yields of the Ugi Products (1) and Deprotected 5-Substituted 1*H*-Tetrazoles.[a]



Entry	Amine	Aldehyde / ketone	1	2 yield[b]
a			53	84
b			86	45
c[c]			30	91
d			41	99
e			40	99
f			30	69
g			81	62
h			58	63
i			55	55
j			60	84

[a]The reaction was carried out using aldehyde (1.0 mmol), amine (1.0 mmol), isocyanide (1.0 mmol) and TMS-azide (1 mmol) in 1 mL MeOH. [b]Yield of isolated product **1** and **2**. [c]The Ugi-tetrazole reaction require 24 h.

We next sought to cleave this 2-nitorbenzyl group from Ugi-4CR products. When the Ugi-4CR product was treated with the optimized condition, no cleavage was detected. Nevertheless, the use of NaOH in place of KOtBu to cleave the 2-nitrobenzyl group was successful. A 38% yield (**4a**) was obtained with 5 equivalent of NaOH at 60 °C. However, the yield did not improve even when the reaction was refluxed in 20% NaOH.



Scheme 1. Substrate Scope of Deprotection from a Ugi-4CR Products.[a]

[a]Deprotection carried out in 4 N HCl in dioxane and methanol as solvent. [b]Deprotection with 1 N HCl and H_2O:methanol (3 : 1) as a solvent.

Afterward, we attempted to achieve one step transformation of this convertible isocyanide to acid or ester from Ugi-4CR products under acidic conditions. After different temperature conditions screening, we observed that cleavage in acid worked best with 1 N HCl under reflux condition and provided free acids in 51% and 62% yields (Scheme 1, entries **4a** and **4b**). Here aliphatic and aromatic substituents on Ugi-4CR products displayed comparable results. Furthermore, with the purpose of one step acidic esterification, 4 N HCl in dioxane was used and the desired product was obtained in good yields (Scheme 1, entries **4c**–**4g**). Under acidic esterification conditions, we observed that aromatic substitution on the a-carbon afford the ester product in a good yield of 70% (Scheme 1,

entry **4c**). Aromatic amines enclosing Ugi-4CR products also performed well with 70% and 87% yields. Benzoic acid in Ugi-4CR product is also valid with 76% yield (Scheme 1, entry **4f**).

Conclusion

In conclusion, the current findings add to a growing body of literature on the developments of convertible isocyanides. This isocyanide could be called as a true universal convertible isocyanide owing to its application in more than one reaction types and methods. Many advantages appeared in this isocyanide such as easy synthesis, odorless, good yields during Ugi-reactions and also in deprotection steps. We believe that this isocyanide will provide a good choice in multicomponent reactions as a convertible isocyanide.

Experimental Procedures and Spectral Data

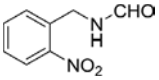
General procedure for the synthesis of 2-nitrobenzyl isocyanide (gm scale):

2-Nitrobenzaldehyde (199 mmol, 30 g), formamide (240 mmol, 95 mL) and formic acid (160 mmol, 60 mL) were transferred into 500 mL round bottle flask. The round bottle flask was placed in an oil bath and the reaction mixture was heated at 180 °C for 5 hours. After cooling down, extractions with DCM (3x200 ml) followed. The organic layer was separated, washed with water, dried with $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with hexane-EtOAc (1 : 2) afforded the corresponding formamide as a brown solid (18.86 g, 105 mmol, 53%).

To a solution of N-(2-nitrobenzyl)formamide (18.1 g, 100 mmol) in DCM (200 mL) was added Et_3N (400 mmol, 4.0 equiv, 55.7 mL). The mixture was cooled to -5 °C at which $POCl_3$ (100 mmol, 1.0 equiv, 9.3 mL) was added dropwise over 60 minutes maintaining the temperature below 0 °C. After the addition, the reaction was stirred at room temperature for 4 hours. A saturated solution of Na_2CO_3 was added carefully. The organic layer was separated. The water layer was extracted with DCM. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by filtration over silica (DCM) and after evaporation of the solvent obtained as a pale yellow solid (14.07 g, 87 mmol, 87 %).

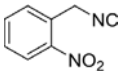
Spectral Data

N-(2-nitrobenzyl)formamide[1]



Obtained from 199 mmol reaction as brown solid, yield: 18.86 g (53%); mixture of rotamers is observed, major rotamer is given. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.24 (s, 1H), 8.07 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.51 – 7.46 (m, 1H), 6.70 (s, 1H), 4.72 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 148.3, 134.3, 133.1, 132.3, 129.0, 125.2, 39.8.

1-(isocyanomethyl)-2-nitrobenzene[2]

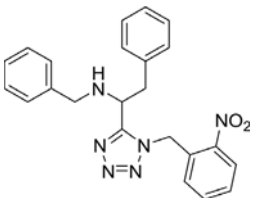


Obtained from 100 mmol reaction as pale yellow solid, yield: 14.07 g (87%); mixture of rotamers is observed, major rotamer is given. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.21 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.78 (td, *J* = 7.7, 1.3 Hz, 1H), 7.62 – 7.54 (m, 1H), 5.15 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 146.5, 134.8, 129.5, 128.7, 125.6, 44.2.

General procedure for the synthesis of Ugi-Tetrazole products:

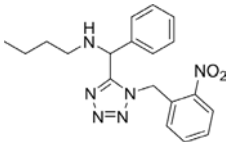
A solution of aldehyde or ketone (1.0 equiv) and amine (1.0 equiv) in MeOH was stirred at room temperature for 30 minutes. Subsequently, isocyanide (1.0 equiv) and TMS azide (1.0 equiv) were added and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent.

N-benzyl-1-(1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)-2-phenylethan-1-amine (**1a**)



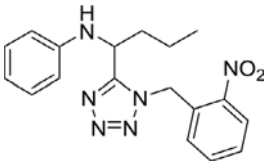
Obtained from 5 mmol reaction as yellow oil, yield: 1100 mg (53%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.14 – 8.07 (m, 1H), 7.49 – 7.44 (m, 2H), 7.25 – 7.18 (m, 6H), 7.06 – 7.00 (m, 2H), 7.00 – 6.95 (m, 2H), 6.64 – 6.55 (m, 1H), 5.65 (d, *J* = 16.9 Hz, 1H), 5.49 (d, *J* = 16.8 Hz, 1H), 4.29 (t, *J* = 7.5 Hz, 1H), 3.61 (d, *J* = 13.4 Hz, 1H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.11 – 3.05 (m, 2H), 1.97 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 147.3, 138.4, 136.1, 134.2, 129.8, 129.4, 129.2, 129.0, 129.0, 128.5, 127.9, 127.4, 127.4, 125.4, 54.4, 51.3, 47.6, 41.0. MS (ESI) m/z calculated $[M+H]^+$: 415.48; found $[M+H]^+$: 415.12.

N-((1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)butan-1-amine (**1b**)



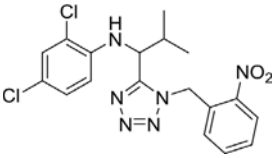
Obtained from 2 mmol reaction as yellow oil, yield: 632 mg (86%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.09 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.43 (td, *J* = 7.8, 1.4 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.27 – 7.19 (m, 2H), 7.18 – 7.12 (m, 3H), 6.34 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.06 (d, *J* = 17.2 Hz, 1H), 5.95 (d, *J* = 17.2 Hz, 1H), 5.33 (s, 1H), 2.60 – 2.51 (m, 1H), 2.46 – 2.39 (m, 1H), 1.94 (brs, 1H), 1.46 – 1.35 (m, 2H), 1.32 – 1.21 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 147.0, 137.2, 134.0, 129.9, 129.029, 128.9, 128.4, 128.3, 126.9, 125.3, 57.8, 48.2, 47.7, 31.8, 20.3, 13.9. MS (ESI) m/z calculated $[M+H]^+$: 367.43; found $[M+H]^+$: 367.23.

N-(1-(1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)butyl)aniline (**1c**)



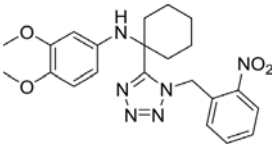
Obtained from 2 mmol reaction as yellow oil, yield: 210 mg (30%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.05 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.37 (td, *J* = 7.8, 1.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.98 (t, *J* = 7.9 Hz, 2H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.50 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 2H), 6.06 (d, *J* = 6.9 Hz, 2H), 4.97 – 4.88 (m, 1H), 4.29 (d, *J* = 5.6 Hz, 1H), 2.01 – 1.84 (m, 2H), 1.53 – 1.42 (m, 1H), 1.41 – 1.28 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1, 147.0, 145.9, 134.1, 129.9, 129.3, 129.2, 128.8, 125.2, 119.0, 113.2, 49.7, 48.6, 36.3, 19.2, 13.6. MS (ESI) m/z calculated $[M+H]^+$: 353.41; found $[M+H]^+$: 353.18.

2,4-dichloro-*N*-(2-methyl-1-(1-(2-nitrobenzyl)-*1*H-tetrazol-5-yl)propyl)aniline (**1d**)



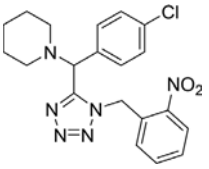
Obtained from 2 mmol reaction as yellow solid, yield: 337 mg (41%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.48 – 7.41 (m, 1H), 7.33 – 7.28 (m, 1H), 7.25 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.29 (d, *J* = 8.7 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.1 Hz, 1H), 3.56 (t, *J* = 4.6 Hz, 1H), 2.40 – 2.27 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 148.1, 141.7, 133.9, 133.2, 132.3, 128.9, 128.8, 127.8, 125.1, 123.1, 120.3, 112. 9, 65.0, 41.2, 31.2, 19.6, 17.8. MS (ESI) m/z calculated $[M+H]^+$: 421.09; found $[M+H]^+$: 421.10.

3,4-dimethoxy-*N*-(1-(1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)cyclohexyl)aniline (**1e**)



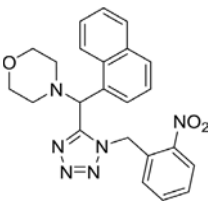
Obtained from 2 mmol reaction as a yellow oil, yield: 352 mg (40%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.99 – 7.93 (m, 1H), 7.43 – 7.35 (m, 2H), 6.87 – 6.82 (m, 1H), 6.46 (d, *J* = 8.6 Hz, 1H), 6.17 (s, 2H), 5.79 (d, *J* = 2.7 Hz, 1H), 5.60 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.93 (s, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 2.17 – 2.05 (m, 4H), 1.70 – 1.60 (m, 3H), 1.56 – 1.44 (m, 2H), 1.43 – 1.30 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 149.5, 147.7, 142.5, 137.8, 133.6, 130.0, 129.3, 128.9, 124.9, 112.4, 106.1, 100.6, 56.3, 55.5, 54.4, 48.6, 34.0, 24.8, 21.0. MS (ESI) m/z calculated $[M+Na]^+$: 461.48; found $[M+Na]^+$: 461.17.

1-((4-chlorophenyl)(1-(2-nitrobenzyl)-1H-tetrazol-5-yl)methyl)piperidine (**1f**)



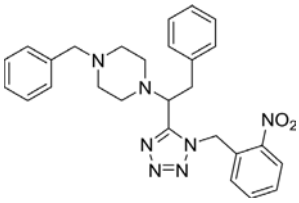
Obtained from 2 mmol reaction as yellow oil, yield: 251 mg (30%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.18 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.42 (td, *J* = 7.7, 1.3 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.43 (d, *J* = 7.8 Hz, 1H), 6.20 (d, *J* = 17.3 Hz, 1H), 6.15 (d, *J* = 17.2 Hz, 1H), 4.96 (s, 1H), 2.48 – 2.35 (m, 2H), 2.26 – 2.16 (m, 2H), 1.53 – 1.41 (m, 4H), 1.41 – 1.31 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 147.0, 134.3, 134.2, 132.1, 130.3, 129.9, 129.2, 128.6, 128.3, 125.4, 64.8, 52.0, 48.3, 25.8, 23.9. MS (ESI) m/z calculated $[M+H]^+$: 413.89; found $[M+H]^+$: 413.10.

4-(naphthalen-1-yl(1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)methyl)morpholine (**1g**)



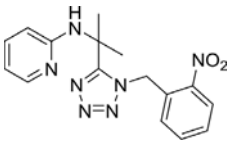
Obtained from 2 mmol reaction as yellow solid, yield: 694 mg (81%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.34 (d, *J* = 8.5 Hz, 1H), 7.97 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.68 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.51 – 7.45 (m, 1H), 7.45 – 7.40 (m, 1H), 7.27 – 7.21 (m, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.91 (td, *J* = 7.6, 1.3 Hz, 1H), 6.01 (d, *J* = 17.3 Hz, 1H), 5.85 (d, *J* = 17.3 Hz, 1H), 5.77 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.71 (s, 1H), 3.77 – 3.65 (m, 4H), 2.74 – 2.64 (m, 2H), 2.52 – 2.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 146.3, 133.8, 133.6, 131.2, 129.5, 129.4, 129.1, 128.8, 128.7, 127.4, 127.0, 126.7, 126.1, 125.1, 124.6, 123.0, 77.4, 66.8, 52.2, 48.5. MS (ESI) m/z calculated $[M+H]^+$: 431.47; found $[M+H]^+$: 431.12.

1-benzyl-4-(1-(1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)-2-phenylethyl)piperazine (**1h**)



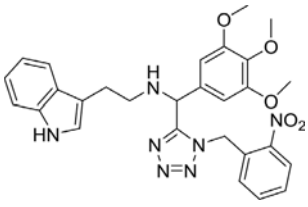
Obtained from 2 mmol reaction as yellow solid, yield: 560 mg (58%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.11 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.43 (td, *J* = 7.8, 1.3 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.26 – 7.25 (m, 2H), 7.24 (brs, 1H), 7.18 – 7.13 (m, 3H), 7.10 (dd, *J* = 7.5, 2.0 Hz, 2H), 6.34 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.82 (d, *J* = 17.3 Hz, 1H), 5.75 (d, *J* = 17.2 Hz, 1H), 3.97 (dd, *J* = 10.6, 3.4 Hz, 1H), 3.48 (dd, *J* = 13.3, 10.5 Hz, 1H), 3.41 (s, 2H), 3.23 (dd, *J* = 13.2, 3.4 Hz, 1H), 2.63 (d, *J* = 8.4 Hz, 2H), 2.56 (p, *J* = 4.6, 4.1 Hz, 2H), 2.26 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 147.1, 137.8, 134.3, 129.9, 129.4, 129.2, 129.1, 128.6, 128.3, 128.3, 127.2, 126.6, 125.3, 62.9, 61.8, 52.8, 47.4, 32.7. MS (ESI) m/z calculated $[M+H]^+$: 484.58; found $[M+H]^+$: 484.17.

N-(2-(1-(2-nitrobenzyl)-1*H*-tetrazol-5-yl)propan-2-yl)pyridin-2-amine (**1i**)



Obtained from 2 mmol reaction as yellow solid, yield: 372 mg (55%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 – 7.95 (m, 1H), 7.73 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.36 – 7.33 (m, 2H), 7.23 – 7.15 (m, 1H), 6.74 – 6.67 (m, 1H), 6.47 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.33 (d, *J* = 8.3 Hz, 1H), 6.10 (s, 2H), 5.44 (s, 1H), 1.83 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 156.3, 147.3, 137.1, 133.6, 130.0, 129.4, 128.8, 124.9, 114.2, 109.5, 51.42, 48.7, 27.9. MS (ESI) m/z calculated $[M+H]^+$: 340.37; found $[M+H]^+$: 340.20.

2-(1H-indol-3-yl)-N-((1-(2-nitrobenzyl)-1H-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methyl)ethan-1-amine (**1j**)

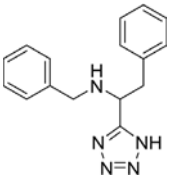


Obtained from 2 mmol reaction as yellow oil, yield: 648 mg (60%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.63 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.06 – 7.01 (m, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 6.27 (s, 2H), 6.20 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.01 (d, *J* = 17.4 Hz, 1H), 5.83 (d, *J* = 17.5 Hz, 1H), 5.20 (s, 1H), 3.68 (s, 3H), 3.55 (s, 6H), 2.95 – 2.71 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 153.4, 146.7, 137.4, 136.4, 133.8, 132.5, 129.9, 129.0, 127.8, 127.3, 125.1, 122.5, 122.0, 119.3, 118.5, 112.8, 111.4, 103.6, 77.5, 60.7, 57.6, 55.9, 48.1, 47. 9, 25.4. MS (ESI) m/z calculated $[M+H]^+$: 544.58; found $[M+H]^+$: 544.21.

General procedure for the synthesis of 1H-Tetrazoles:

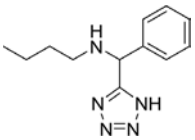
To a solution of protected tetrazole (around 100 mg) in THF (2mL) was added KOtBu (4.0 equiv). The resulting suspension was stirred at room temperature for overnight. The solvent was removed under reduced pressure and water (2 mL) was added. The solution was cooled to 0 °C and acidified to pH 4–5 with HCl (1 N). Additional EtOAc (5 mL) was added and the organic layer was separated. The water layer was extracted with EtOAc (5 mL × 5). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using MeOH–DCM as eluent.

N-benzyl-2-phenyl-1-(1*H*-tetrazol-5-yl)ethan-1-amine (**2a**)



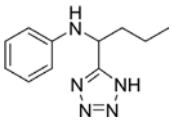
Obtained from 0.27 mmol reaction as yellow solid, yield: 63 mg (84%); ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.35 – 7.31 (m, 3H), 7.30 – 7.26 (m, 2H), 7.09 – 7.04 (m, 3H), 6.90 (d, *J* = 7.0 Hz, 2H), 4.70 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.99 (d, *J* = 13.0 Hz, 1H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.42 – 3.30 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 157.8, 137.4, 129.6, 129.4, 128.8, 128.6, 128.2, 126.9, 57.3, 54.7, 49.8. MS (ESI) m/z calculated $[M+H]^+$: 280.35; found $[M+H]^+$: 280.22.

N-(phenyl(1*H*-tetrazol-5-yl)methyl)butan-1-amine (**2b**)



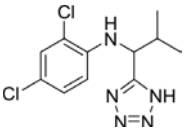
Obtained from 0.33 mmol reaction as brown oil, yield: 34 mg (45%); ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.64 – 7.58 (m, 2H), 7.52 – 7.44 (m, 3H), 5.78 (s, 1H), 3.04 – 2.88 (m, 2H), 1.77 – 1.64 (m, 2H), 1.40 – 1.34 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 156.6, 132.5, 127.9, 127.3, 127.0, 57.0, 44.6, 26.0, 17.9, 10.9. MS (ESI) m/z calculated $[M+H]^+$: 232.30; found $[M+H]^+$: 232.14.

N-(1-(1*H*-tetrazol-5-yl)butyl)aniline (**2c**)



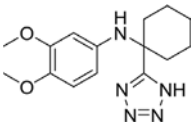
Obtained from 0.31 mmol reaction as brown oil, yield: 61 mg (91%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.02 (t, *J* = 7.7 Hz, 2H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 2H), 5.01 (t, *J* = 7.0 Hz, 1H), 1.99 – 1.85 (m, 2H), 1.45 – 1.32 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 146.0, 129.4, 118.7, 113.3, 49.2, 37.6, 19.0, 13.6. MS (ESI) m/z calculated $[M+H]^+$: 218.28; found $[M+H]^+$: 218.22.

2,4-dichloro-*N*-(2-methyl-1-(1*H*-tetrazol-5-yl)propyl)aniline (**2d**)



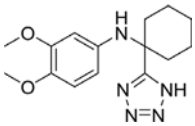
Obtained from 0.25 mmol reaction as brown oil, yield: 71 mg (99%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.15 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 1H), 5.03 (s, 1H), 4.78 (d, *J* = 6.6 Hz, 1H), 2.48 – 2.37 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 140.9, 129.0, 127.9, 122.9, 120.0, 112.3, 55.5, 33.4, 18.9, 18.8. MS (ESI) m/z calculated $[M+H]^+$: 286.05; found $[M+H]^+$: 286.08.

N-(1-(1*H*-tetrazol-5-yl)cyclohexyl)-3,4-dimethoxyaniline (**2e**)



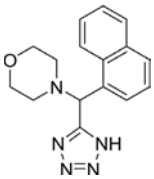
Obtained from 0.26 mmol reaction as a a brown oil, yield: 78 mg (99%); ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.76 (s, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 5.91 (d, *J* = 2.6 Hz, 1H), 5.79 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.55 (s, 3H), 3.48 (s, 3H), 2.13 (t, *J* = 10.6 Hz, 2H), 2.05 – 1.93 (m, 2H), 1.60 (dd, *J* = 9.2, 4.5 Hz, 2H), 1.42 (d, *J* = 7.8 Hz, 1H), 1.39 – 1.28 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 160.4, 148.0, 142.0, 135.0, 111.2, 107.9, 101.7, 54.2, 54.1, 53.2, 53.1, 32.9, 23.2, 19.6. MS (ESI) m/z calculated $[M+H]^+$: 304.37; found $[M+H]^+$: 304.22.

1-((4-chlorophenyl)(1*H*-tetrazol-5-yl)methyl)piperidine (**2f**)



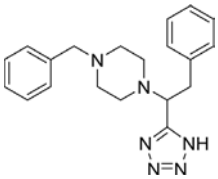
Obtained from 0.24 mmol reaction as yellow solid, yield: 46 mg (69%); ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 5.69 (s, 1H), 3.11 (brs, 2H), 3.00 (brs, 2H), 1.84 – 1.73 (m, 4H), 1.58 (brs, 2H). ^{13}C NMR (126 MHz, MeOD) δ 155.6, 134.1, 129.9, 129.8, 127.4, 64.2, 50.5, 21.3, 20.0. MS (ESI) m/z calculated $[M+H]^+$: 278.76; found $[M+H]^+$: 278.14.

4-(naphthalen-1-yl(1*H*-tetrazol-5-yl)methyl)morpholine (**2g**)



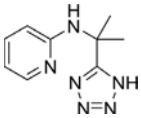
Obtained from 0.25 mmol reaction as brown oil, yield: 46 mg (62%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.43 (d, *J* = 7.1 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 6.26 (s, 1H), 5.86 (s, 1H), 3.69 – 3.57 (m, 4H), 2.74 – 2.60 (m, 2H), 2.53 – 2.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 134.0, 131.7, 131.3, 129.4, 129.0, 126.9, 126.9, 126.1, 125.4, 123.2, 66.5, 62.5, 52.0, 50.8, 29.7. MS (ESI) m/z calculated $[M+H]^+$: 296.35; found $[M+H]^+$: 296.22.

1-benzyl-4-(2-phenyl-1-(1*H*-tetrazol-5-yl)ethyl)piperazine (**2h**)



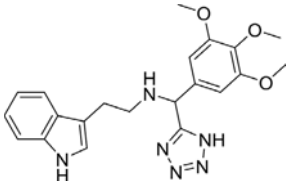
Obtained from 0.22 mmol reaction as brown oil, yield: 48 mg (63%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.32 – 7.27 (m, 5H), 7.16 – 7.11 (m, 2H), 7.09 (d, *J* = 6.8 Hz, 3H), 4.42 (t, *J* = 7.6 Hz, 1H), 3.98 – 3.82 (m, 2H), 3.39 (dd, *J* = 13.7, 8.4 Hz, 1H), 3.26 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.87 (brs, 6H), 2.70 – 2.48 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 138.7, 130.6, 129.2, 129.1, 128.9, 128.1, 126.1, 61.6, 61.3, 52.3, 37.5. MS (ESI) m/z calculated $[M+H]^+$: 349.45; found $[M+H]^+$: 349.27.

N-(2-(1*H*-tetrazol-5-yl)propan-2-yl)pyridin-2-amine (**2i**)



Obtained from 0.44 mmol reaction as brown oil, yield: 49 mg (55%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.06 – 7.96 (m, 1H), 7.50 – 7.41 (m, 1H), 7.06 (s, 1H), 6.72 – 6.64 (m, 1H), 6.48 (d, *J* = 8.6 Hz, 1H), 1.87 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 155.5, 143.7, 139.6, 113.8, 111.6, 51.6, 50.7, 27.9. MS (ESI) m/z calculated $[M+H]^+$: 205.24; found $[M+H]^+$: 205.17.

N-((1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methyl)-2-(1*H*-indol-3-yl)ethan-1-amine (**2j**)

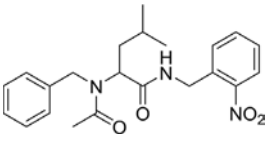


Obtained from 0.44 mmol reaction as brown solid, yield: 58 mg (84%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.83 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.01 (s, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 5.74 (s, 1H), 3.85 (s, 1H), 3.75 (s, 6H), 3.64 (s, 3H), 3.15 – 3.04 (m, 2H), 3.04 – 2.91 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 153.3, 152.8, 138.0, 136.7, 131.7, 127.1, 123.6, 121.6, 118.9, 118.4, 112.0, 110.0, 108.5, 106.6, 60.5, 58.3, 56.4, 46.6, 22.2. MS (ESI) m/z calculated $[M+H]^+$: 409.46; found $[M+H]^+$: 409.13.

General procedure for the synthesis of Ugi-4CR products:

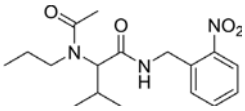
A solution of aldehyde (1.0 equiv) and amine (1.0 equiv) in MeOH was stirred at room temperature for 30 minutes. Subsequently, isocyanide (1.0 equiv) and acid (1.0 equiv) were added and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent.

2-(*N*-benzylacetamido)-4-methyl-*N*-(2-nitrobenzyl)pentanamide (**3a**)



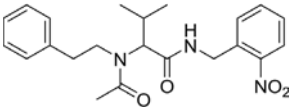
Obtained from 1 mmol reaction as colorless oil, yield: 360 mg (91%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.02 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.58 (td, *J* = 7.5, 1.3 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.36 (t, *J* = 6.4 Hz, 1H), 7.32 – 7.21 (m, 3H), 7.19 – 7.13 (m, 2H), 5.11 – 5.02 (m, 1H), 4.62 (d, *J* = 6.2 Hz, 2H), 4.57 (s, 2H), 2.06 (s, 3H), 1.87 – 1.80 (m, 1H), 1.51 – 1.40 (m, 2H), 0.89 – 0.79 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 171.2, 148.3, 137.3, 133.7, 131.4, 128.7, 128.5, 127.3, 126.1, 125.0, 56.0, 49.3, 41.1, 37.2, 25.2, 22.8, 22.4. MS (ESI) m/z calculated $[M+H]^+$: 398.23; found $[M+H]^+$: 398.48.

3-methyl-*N*-(2-nitrosobenzyl)-2-(*N*-propylacetamido)butanamide (**3b**)



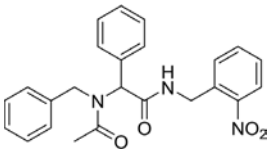
Obtained from 5 mmol reaction as colorless oil, yield: 1577 mg (99%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.03 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.46 – 7.42 (m, 1H), 4.68 (d, *J* = 6.2 Hz, 2H), 4.17 (s, 1H), 3.25 – 3.12 (m, 2H), 2.55 – 2.43 (m, 1H), 2.13 (s, 3H), 1.47 – 1.37 (m, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87 – 0.76 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.5, 148.3, 133.5, 131.3, 128.4, 125.0, 41.0, 26.3, 22.5, 21.9, 19.8, 19.1, 11.3. MS (ESI) m/z calculated $[M+H]^+$: 336.40; found $[M+H]^+$: 336.17.

3-methyl-*N*-(2-nitrobenzyl)-2-(*N*-phenethylacetamido)butanamide (**3c**)



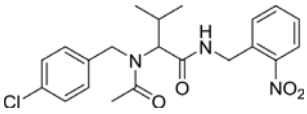
Obtained from 5 mmol reaction as colorless oil, yield: 1158 mg (58%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.99 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.72 (s, 1H), 7.60 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.30 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 7.14 – 7.09 (m, 2H), 4.73 (d, *J* = 6.2 Hz, 2H), 4.41 (brs, 1H), 3.49 – 3.43 (m, 2H), 2.69 – 2.59 (m, 2H), 2.53 – 2.43 (m, 1H), 2.11 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 171.3, 148.3, 138.1, 133.6, 133.6, 131.4, 128.7, 128.5, 126.7, 125.0, 41.1, 35.5, 26.4, 21.8, 19.8, 18.8. MS (ESI) m/z calculated $[M+H]^+$: 398.48; found $[M+H]^+$: 398.23.

2-(*N*-benzylacetamido)-*N*-(2-nitrobenzyl)-2-phenylacetamide (**3d**)



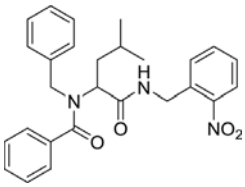
Obtained from 1 mmol reaction as colorless oil, yield: 262 mg (63%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.31 – 7.27 (m, 2H), 7.25 – 7.20 (m, 3H), 7.20 – 7.12 (m, 3H), 7.00 (d, *J* = 6.5 Hz, 2H), 6.47 (t, *J* = 6.4 Hz, 1H), 5.83 (s, 1H), 4.76 – 4.65 (m, 3H), 4.49 (d, *J* = 17.6 Hz, 1H), 2.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.0, 148.1, 137.2, 134.6, 134.1, 133.5, 131.7, 129.8, 128.9, 128.8, 128.54, 128.4, 128.4, 127.1, 126.1, 125.1, 63.3, 50.9, 41.5, 22.4. MS (ESI) m/z calculated $[M+H]^+$: 418.47; found $[M+H]^+$: 418.20.

2-(*N*-(4-chlorobenzyl)acetamido)-3-methyl-*N*-(2-nitrobenzyl)butanamide (**3e**)



Obtained from 1 mmol reaction as colorless oil, yield: 400 mg (96%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.03 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.60 (s, 1H), 7.55 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.74 (d, *J* = 17.3 Hz, 1H), 4.62 (d, *J* = 6.3 Hz, 1H), 4.59 (dd, *J* = 6.2, 3.7 Hz, 2H), 4.50 (d, *J* = 17.4 Hz, 1H), 2.43 – 2.29 (m, 1H), 1.97 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 170.3, 148.4, 135.9, 133.7, 133.4, 132.8, 131.9, 128.7, 128.6, 127.4, 125.0, 40.9, 27.4, 22.4, 19.6, 19.0. MS (ESI) m/z calculated $[M+H]^+$: 418.89; found $[M+H]^+$: 418.14.

N-benzyl-*N*-(4-methyl-1-((2-nitrobenzyl)amino)-1-oxopentan-2-yl)benzamide (**3f**)

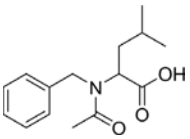


Obtained from 1 mmol reaction as colorless oil, yield: 440 mg (96%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.78 (brs, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.40 – 7.33 (m, 5H), 7.14 (brs, 3H), 7.00 (brs, 1H), 4.84 (s, 1H), 4.65 – 4.48 (m, 3H), 4.45 (dd, *J* = 15.3, 6.1 Hz, 1H), 1.90 (brs, 2H), 1.65 (brs, 1H), 0.93 (brs, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 171.2, 148.4, 136.1, 133.8, 131.4, 130.0, 128.6, 128.4, 127.6, 126.9, 125.0, 57.9, 51.9, 41.0, 37.3, 25.2, 22.8, 22.3. MS (ESI) m/z calculated $[M+H]^+$: 460.55; found $[M+H]^+$: 460.23.

General procedure for the synthesis of Hydrolysis of Ugi-4CR product under basic condition:

To a solution of compound **3a** (114 mg) in MeOH (3mL) was added 1N NaOH (5.0 equiv, 1.4 mL). The resulting suspension was stirred at reflux for 6h. The reaction was concentrated to dryness and water (2 mL) was added. The water layer was cooled to 0 °C and acidified to pH 1 with HCl (1 N). Additional EtOAc (5 mL) was added and the organic layer was separated. The water layer was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using MeOH–DCM as eluent.

N-acetyl-N-benzylleucine (**4a**)

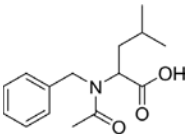


Obtained from 0.3 mmol reaction as colorless oil, yield: 30 mg (38%); Two rotamers were present on NMR timescale (R1 : R2 = 1: 0.2). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 0.8H), 7.27 (d, *J* = 5.9 Hz, 3H), 7.22 – 7.18 (m, 0.2H), 4.99 (d, *J* = 15.4 Hz, 0.2H), 4.67 (d, *J* = 17.0 Hz, 1H), 4.50 (d, *J* = 17.0 Hz, 2H), 4.42 (s, 0.2H), 4.21 (d, *J* = 15.5 Hz, 0.2H), 2.27 (s, 0.6H), 2.18 (s, 3H), 2.03 – 1.91 (m, 1H), 1.77 – 1.67 (m, 0.2H), 1.63 – 1.47 (m, 2H), 1.40 – 1.31 (m, 0.4H), 0.90 – 0.84 (m, 3.6H), 0.75 (d, J = 6.2 Hz, 3H), 0.60 (d, J = 6.6 Hz, 0.6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 173.6, 136.2, 129.0, 128.3, 127.9, 126.8, 58.8, 52.6, 38.2, 29.7, 25.2, 22.4, 22.2. MS (ESI) m/z calculated $[M+H]^+$: 264.34; found $[M+H]^+$: 264.15.

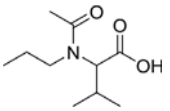
General procedure for the synthesis of Hydrolysis of Ugi-4CR products under acidic condition:

To a solution of protected Ugi-4CR product (around 100 mg) in MeOH was added 1N HCl (5.0 equiv). The resulting suspension was stirred at reflux for 6h. The reaction was concentrated to dryness and 1N NaOH (2 mL) was added. The water layer was extracted with DCM (5 mL). The water layer was cooled to 0 ℃ and acidified to pH 1 with HCl (1 N). Additional EtOAc (5 mL) was added and the organic layer was separated. The water layer was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure to get our product.

N-acetyl-*N*-benzylleucine (**4a**) THIS IS THE SAME AS ABOVE



Obtained from 0.40 mmol reaction as colorless oil, yield: 54 mg (51%); Two rotamers were present on NMR timescale (R1 : R2 = 1: 0.2). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 0.8H), 7.27 (d, *J* = 5.9 Hz, 3H), 7.22 – 7.18 (m, 0.2H), 4.99 (d, *J* = 15.4 Hz, 0.2H), 4.67 (d, *J* = 17.0 Hz, 1H), 4.50 (d, *J* = 17.0 Hz, 2H), 4.42 (s, 0.2H), 4.21 (d, *J* = 15.5 Hz, 0.2H), 2.27 (s, 0.6H), 2.18 (s, 3H), 2.03 – 1.91 (m, 1H), 1.77 – 1.67 (m, 0.2H), 1.63 – 1.47 (m, 2H), 1.40 – 1.31 (m, 0.4H), 0.90 – 0.84 (m, 3.6H), 0.75 (d, *J* = 6.2 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 0.6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 173.6, 136.2, 129.0, 128.3, 127.9, 126.8, 58.8, 52.6, 38.2, 29.7, 25.2, 22.4, 22.2. MS (ESI) m/z calculated $[M+H]^+$: 264.34; found $[M+H]^+$: 264.15.



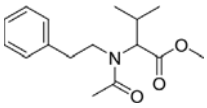
N-acetyl-N-propylvaline (**4b**)

Obtained from 0.47 mmol reaction as colorless oil, yield: 59 mg (62%); ^{1}H NMR (500 MHz, Chloroform-d) δ 10.42 (s, 1H), 3.56 (d, *J* = 10.8 Hz, 1H), 3.48 – 3.38 (m, 1H), 3.20 – 3.07 (m, 1H), 2.77 – 2.64 (m, 1H), 2.21 (s, 3H), 1.76 – 1.60 (m, 2H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.96 – 0.89 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 171.6, 74.0, 55.2, 26.6, 22.4, 22.0, 19.6, 19.5, 11.0. MS (ESI) m/z calculated $[M+H]^+$: 202.27; found $[M+H]^+$: 202.15.

General procedure for the esterification under acidic condition:

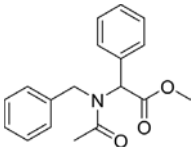
To a solution of Ugi-4CR product (around 100 mg) in DCM (2mL) was added 4N HCl in dioxane (5.0 equiv. around 0.25 mL) and 1mL MeOH . The resulting suspension was stirred at reflux for 2–6h. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent.

methyl *N*-acetyl-*N*-phenethylvalinate (**4c**)



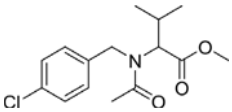
Obtained from 0.36 mmol reaction as colorless oil, yield: 70 mg (70%); Two rotamers were present on NMR timescale (R1 : R2 = 1: 1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.31 (m, 3H), 7.30 – 7.27 (m, 5H), 7.25 – 7.22 (m, 2H), 4.71 (d, *J* = 10.5 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.75 – 3.64 (m, 1H), 3.58 – 3.46 (m, 2H), 3.33 – 3.21 (m, 1H), 3.00 (td, *J* = 12.1, 5.2 Hz, 1H), 2.93 – 2.75 (m, 2H), 2.60 (td, *J* = 12.0, 4.7 Hz, 1H), 2.45 – 2.30 (m, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.1, 139.5, 138.2, 128.9, 128.8, 128.6, 128.4, 126.8, 126.3, 66.9, 62.1, 52.2, 51.9, 48.5, 45.0, 36.0, 34.0, 29.7, 27.8, 27.7, 22.5, 21.5, 20.2, 19.7, 18.8, 18.8. MS (ESI) m/z calculated $[M+H]^+$: 278.36; found $[M+H]^+$: 278.20.

methyl 2-(*N*-benzylacetamido)-2-phenylacetate (**4d**)



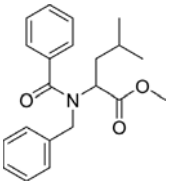
Obtained from 0.22 mmol reaction as colorless oil, yield: 50 mg (77%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.23 (brs, 5H), 7.21 – 7.12 (m, 3H), 6.97 (d, *J* = 7.0 Hz, 2H), 6.00 (s, 1H), 4.64 (d, *J* = 17.7 Hz, 1H), 4.43 (d, *J* = 17.7 Hz, 1H), 3.73 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 171.1, 137.3, 134.0, 129.8, 128.7, 128.6, 128.4, 127.0, 126.0, 62.1, 52.4, 50.1, 22.3. MS (ESI) m/z calculated $[M+H]^+$: 298.35; found $[M+H]^+$: 298.17.

methyl *N*-acetyl-*N*-(4-chlorobenzyl)valinate (**4e**)



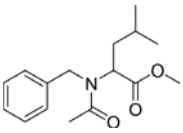
Obtained from 0.24 mmol reaction as colorless oil, yield: 50 mg (70%); Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.94 (d, *J* = 10.4 Hz, 1H), 4.88 (d, *J* = 15.4 Hz, 1H), 4.62 (d, *J* = 17.7 Hz, 1H), 4.57 (d, *J* = 17.7 Hz, 1H), 4.23 (d, *J* = 15.4 Hz, 1H), 3.94 (d, *J* = 10.9 Hz, 1H), 3.47 (s, 3H), 3.39 (s, 3H), 2.39 – 2.31 (m, 1H), 2.29 (s, 3H), 2.28 – 2.24 (m, 1H), 2.06 (s, 3H), 0.98 (d, *J* = 2.8 Hz, 3H), 0.96 (d, *J* = 2.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.8, 171.0, 170.1, 136.4, 135.7, 133.1, 132.6, 129.2, 128.9, 128.2, 127.2, 67.0, 61.6, 51.9, 51.7, 48.4, 44.9, 27.9, 27.5, 22.4, 22.0, 19.9, 19.7, 18.7, 18.7. MS (ESI) m/z calculated $[M+H]^+$: 298.78; found $[M+H]^+$: 298.11.

methyl N-benzoyl-N-benzylleucinate (**4f**)



Obtained from 0.22 mmol reaction as colorless oil, yield: 57 mg (76%); Two rotamers were present on NMR timescale (R^1: R^2=1: 0.7). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.48 (brs, 3.4H), 7.40 (brs, 6.8H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.28 – 7.19 (m, 2.8H), 4.91 – 4.33 (m, 5.1H), 3.64 (brs, 2.1H), 3.52 (brs, 3H), 2.11 (brs, 0.7H), 1.66 (brs, 3H), 1.35 (brs, 1.4H), 0.84 (d, *J* = 48.5 Hz, 4.2H), 0.56 (d, *J* = 22.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 171.6, 138.1, 136.2, 129.7, 128.6, 128.4, 128.0, 127.8, 127.1, 126.7, 60.1, 56.7, 53.1, 52.2, 46.5, 38.5, 25.4, 24.3, 22.4, 21.8. MS (ESI) m/z calculated $[M+H]^+$: 340.44; found $[M+H]^+$: 340.20.

methyl *N*-acetyl-*N*-benzylleucinate (**4g**)



Obtained from 0.23 mmol reaction as a colorless liquid, yield: 56 mg (87%);Two rotamers were present on NMRtimescale (R^1: R^2=1: 0.33). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 (t, J = 7.5 Hz, 2H), 7.32 – 7.24 (m, 3H), 4.98 – 4.92 (m, 1H), 4.69 – 4.62 (m, 1.33H), 4.51 (d, *J* = 17.6 Hz, 1H), 4.43 – 4.38 (m, 0.33H), 3.60 (s, 3H), 3.49 (s, 1H), 2.27 (s, 1H), 2.12 (s, 3H), 1.87 – 1.79 (m, 1H), 1.79 – 1.74 (m, 0.33H), 1.69 – 1.61 (m, 0.33H), 1.59 – 1.49 (m, 2H), 1.45 – 1.38 (m, 0.33H), 0.89 (dd, *J* = 6.5, 3.0 Hz, 4H), 0.78 (d, *J* = 6.3 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 171.4, 138.1, 137.1, 128.7, 128.2, 128.0, 127.5, 127.0, 126.5, 58.9, 55.8, 52.2, 52.0, 50.6, 46.4, 38.4, 25.2, 24.5, 22.5, 22.5, 22.3, 22.2, 22.2, 22.0. MS (ESI) m/z calculated $[M+H]^+$: 278.38; found $[M+H]^+$: 278.20.

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