Synthesis Y. Wang et al. Paper

# Easy Synthesis of Two Positional Isomeric Tetrazole Libraries

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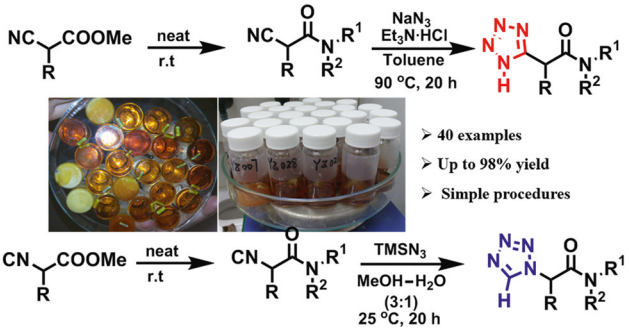



Received: 04.04.2016
Accepted after revision: 03.05.2016
Published online: 21.06.2016
DOI: 10.1055/s-0035-1562435; Art ID: ss-2016-t0232-op

**Abstract** A fast and efficient synthesis of libraries of positional isomeric 1*H*-tetrazoles and 5*H*-tetrazoles, for the purpose of testing binding hypothesis of isomeric tetrazoles in fragment-based drug discovery, is described.

**Key words** 1*H*-tetrazole, 5*H*-tetrazole, cyanoacetamide, isocyanoacetamide, [2+3] cycloaddition, Oliveri-Mandala and Alagna reaction, fragment-based drug discovery

Monosubstituted tetrazoles can exist as two isomers, the 1- and the 5-substituted form. The 1-substituted form has a mobile hydrogen and comprises a tetrazole acid with similar pKa as the carboxylic acid. The 5-substituted form, however, is charge neutral and has no mobile hydrogen. At present, there are 3 neutral and 55 negatively charged tetrazole structures in the protein data bank (PDB).[2] Both forms are expected to interact differentially with protein receptors (Figure 1).[3] To have a testable library of both isomers we decided to synthesize a small library of compounds of both isomers each based on some previously published synthetic work of us. These libraries will be useful in fragment-based drug discovery to test binding hypothesis.[4]

We have recently described two complementary straightforward ways for the diverse synthesis of libraries of cyano- and isocyanoacetamides, by simply reacting the corresponding cyano- and isocyanoacetyl methyl esters solventless with a primary or secondary amine.[7] Advantageously, the products in most cases precipitate and simple filtration affords very pure products. Here we describe their conversion into libraries of corresponding positional isomeric tetrazoles (Scheme 1).

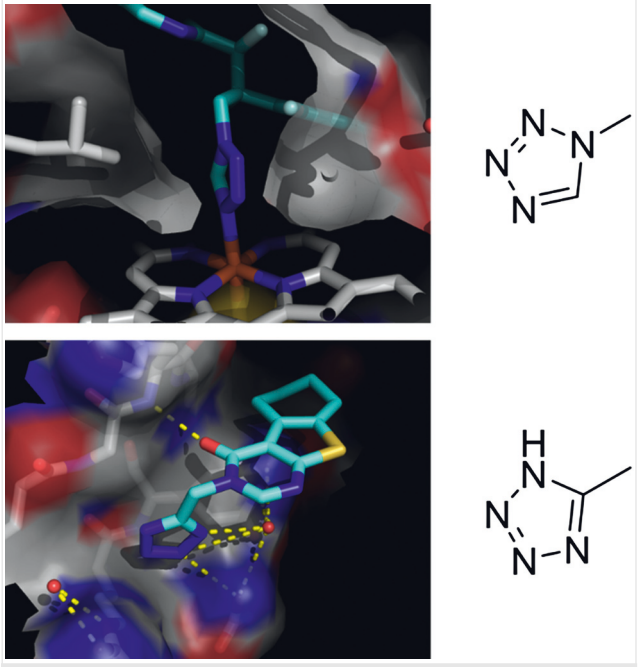
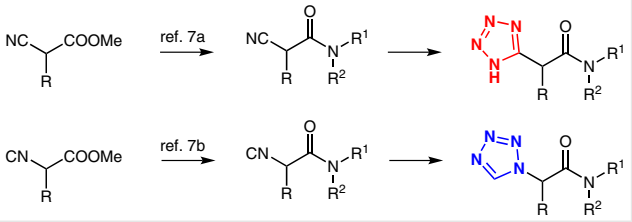


**Figure 1** Examples of characteristic receptor-tetrazole binding modes found in the PDB. Above: Sterol 14α-demethylase (CYP51) from *Trypanosoma cruzi* in complex with the 1-tetrazole derivative VT-1161 (PDB ID 5AJR) exhibiting the metal ligand character of tetrazoles;[5] Below: CTX-M-9 class A β-lactamase complexed with NH′-tetrazole (PDB ID 3G34) exhibiting a hydrogen contact to water and one hydrogen contact to Gln-188 side chain amide.[6]

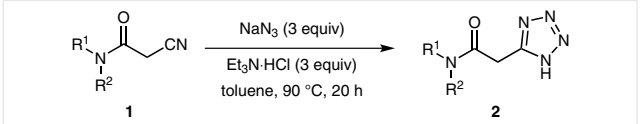
5-Substituted 1*H*-tetrazoles can be synthesized by the simple [2+3] cycloaddition of nitriles to an azide.[8] Initially, the formation of 1*H*-tetrazoles from the cyanoacetamides was tested, using various metal catalyst along with the solvents like DMF and DMSO under vigorous reaction conditions.[9] Unfortunately, multiple product formations was ob-



**Scheme 1** Synthetic strategy towards otherwise identical positional libraries of 1*H*-tetrazoles (red) and 5*H*-tetrazoles (blue)

served and it was difficult to isolate the pure product. Furthermore, under the microwave conditions[9e] we failed to obtain pure products.

The use of solvents play an important role in such type of reactions.[10] First, the synthesis of tetrazole **2a** was tested in various solvents such as toluene, DMF, DMSO, and acetonitrile at various reaction times (6 to 24 h) and temperatures from 55 to 160 °C using sodium azide (1.3 equiv) and ammonium chloride as well as trialkylamine hydrochloride salt (Scheme 2).



**Scheme 2** Optimized conditions for the synthesis of 5-substituted 1*H*-tetrazoles

We observed that using the combination of trimethylamine hydrochloride in toluene at 90 °C afforded the product with best conversion and yield. Particularly, the reaction of *N*-benzyl-2-cyanoactamide (**1a**) with sodium azide (3 equiv) and triethylamine hydrochloride salt (3 equiv) heated in toluene at 90 °C for 20 hours gave the product *N*-benzyl-2-(1*H*-tetrazol-5-yl)acetamide (**2a**) in 67% yield. In this method, the product could be isolated by simple aqueous workup followed by filtration, and tedious purifications were not required. The optimized protocol was examined for various *N*-alkyl-substituted 2-cyanoactamides to study the scope and generality of the reaction condition to obtain various 5-substituted 1*H*-tetrazoles (Table 1).

**Table 1** Synthesis of *N*-Substituted 2-(1*H*-Tetrazol-5-yl)acetamides

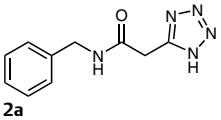
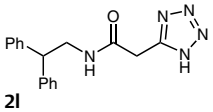
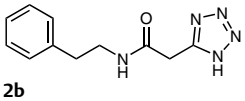
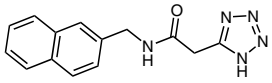
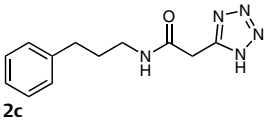
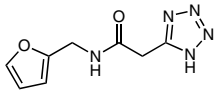
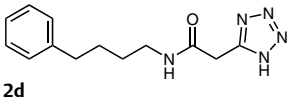
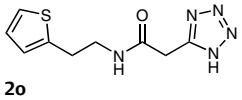
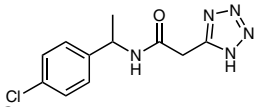
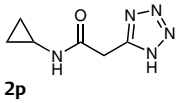
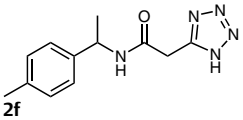
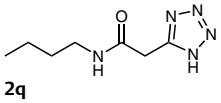
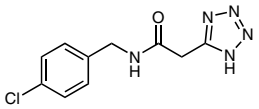
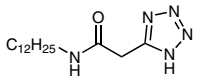
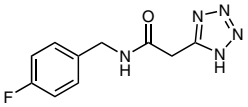
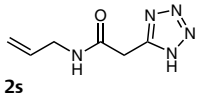
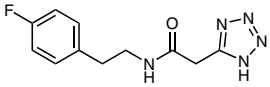
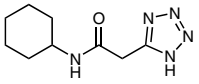
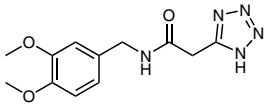
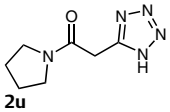
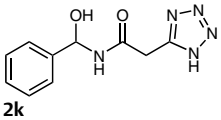
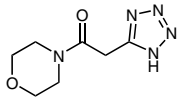
| Entry | Product **2** | Yield (%)[a] | Entry | Product **2** | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **2a** | 67 | 12 |  **2l** | 56 |
| 2 |  **2b** | 74 | 13 |  **2m** | 89 |
| 3 |  **2c** | 79 | 14 |  **2n** | 21 |
| 4 |  **2d** | 86 | 15 |  **2o** | 65 |
| 5 |  **2e** | 64 | 16 |  **2p** | 55 |
| 6 |  **2f** | 70 | 17 |  **2q** | 77 |

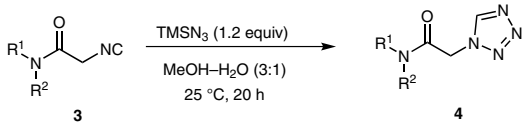
Table 1 (continued)

| Entry | Product **2** | Yield (%)[a] | Entry | Product **2** | Yield (%)[a] |
|---|---|---|---|---|---|
| 7 |  **2g** | 76 | 18 |  **2r** | 98 |
| 8 |  **2h** | 70 | 19 |  **2s** | 25 |
| 9 |  **2i** | 87 | 20 |  **2t** | 51 |
| 10 |  **2j** | 93 | 21 |  **2u** | 9 |
| 11 |  **2k** | 70 | 22 |  **2v** | 25 |

[a] Isolated yield.

Tetrazole derived from *N*-phenethyl-2-cyanoacetamide (**1b**) gave *N*-phenethyl-2-(1*H*-tetrazol-5-yl)acetamide (**2b**) in even better yield (74%) than **2a** (67%). A similar trend of increasing yields were observed as the carbon chain length of *N*-alkylphenyl in 2-cyanoacetamides increased from 3 to 4, for example, *N*-phenpropyl-2-(1*H*-tetrazol-5-yl)acetamide (**2c**) and *N*-phenbutyl-2-(1*H*-tetrazol-5-yl)acetamide (**2d**) were obtained in 79% and 86% yield, respectively. When the *N*-benzyl group of 2-cyanoacetamide was replaced with various substituted *N*-benzyl groups **1e**–**h**, the yields of products **2e**–**h** were similar. Remarkably, in the case of the highly electron rich *N*-(3,4-dimethoxypheyl)-2-cyanoacetamide (**1j**), *N*-(3,4-dimethoxyphenyl)-2-(1*H*-tetrazol-5-yl)acetamide (**2j**) was obtained in excellent yield (93%). Furthermore, simple *N*-alkyl-substituted 2-cyanoacetamides **1q**–**r** gave good yield of products **2q**–**r**. However, *N*-allyl-2-cyanoacetamide (**1s**) was found to be less reactive and gave *N*-allyl-2-(1*H*-tetrazol-5-yl)acetamide (**2s**) in only 25% yield. Unfortunately, *N*,*N*-disubstituted 2-cyanoacetamides **1u**,**v** in the same reaction conditions gave poor yields of **2u**,**v** as 9% and 25%, respectively.

Noteworthy, the herein described method does not require any expensive organometallic reagents as well as harsh reaction conditions such as very high reaction temperature or microwave irradiation.




**Scheme 3** Optimized conditions for the synthesis of 1-substituted 5*H*-tetrazoles

**Table 2** Optimization of *N*-Benzyl-2-(1*H*-tetrazol-1-yl)acetamide

| Azide | Solvent | Temp (°C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| $NaN_3$ | MeOH | 25 | 20 | 11 |
| $TMSN_3$ | $CH_2Cl_2$ | 25 | 20 | traces |
| $NaN_3$ | MeCN | 40 | 20 | traces |
| $TMSN_3$ | $CH_2Cl_2$ | 40 | 20 | traces |
| $NaN_3$ | $CH_2Cl_2$ | 25 | 20 | traces |
| $TMSN_3$ | MeOH | 25 | 20 | 27 |
| $TMSN_3$ | MeOH | 55 | 20 | 45 |
| $NaN_3$ | MeOH–$H_2O$ (3:1) | 25 | 20 | 35 |
| $TMSN_3$ | MeOH–$H_2O$ (3:1) | 25 | 20 | 97 |

[a] Isolated yield.

After successfully synthesizing the *N*-substituted-2-(1*H*-tetrazol-5-yl)acetamides, the synthesis of *N*-alkyl-2-(1*H*-tetrazol-1-yl)acetamide was examined by using the *N*-alkyl-2-isocyanoacetamides (Scheme 3).

Isocyanide to tetrazole conversion is also known as the Oliveri-Mandala and Alagna reaction.[11] The freshly prepared *N*-substituted 2-isocyanoacetamides were used as they are easily synthesized by the neat reaction of 1° or 2° alkylamines with methyl isocyanoacetate.[7b]

Initially, the formation of the tetrazole **4a** was tested by reacting the *N*-phenethyl-2-isocyanoacetamide (**3a**) with sodium azide in methanol, as in the general Oliveri-Mandala and Alagna reaction.[11] Unfortunately, poor yield (11%) was observed (Table 2). Then various solvents and azide sources were tested. By using dichloromethane as the solvent, only traces of the product formation was observed. When sodium azide was changed to trimethylsilyl azide in methanol, 27% yield was obtained at room temperature. However, the yield could be increased to 45% when the reaction was heated at 55 °C in methanol. Using 25% water in methanol as a solvent with sodium azide at room temperature gave only 35% yield of the product.

**Table 3** Synthesis of *N*-Substituted 2-(1*H*-Tetrazol-1-yl)acetamides

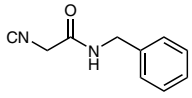
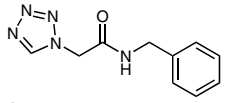
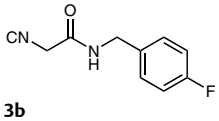
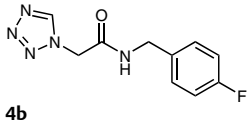
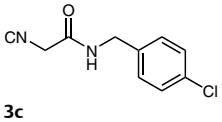
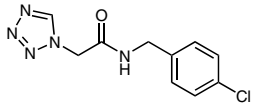
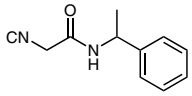
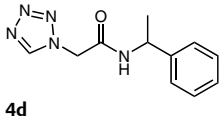
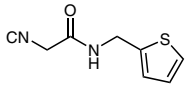
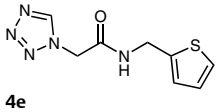
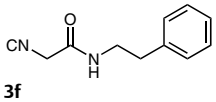
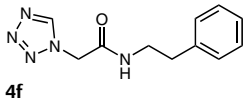
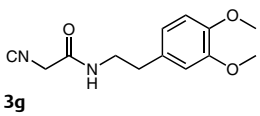
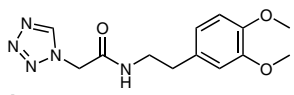
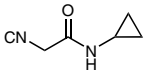
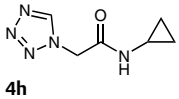
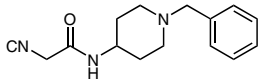
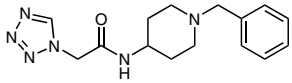
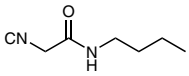
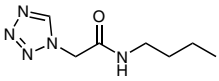
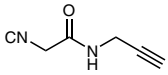
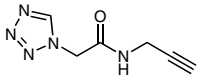
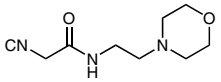
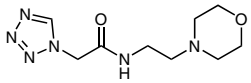
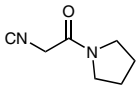
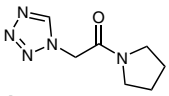
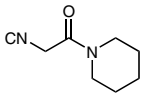
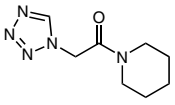
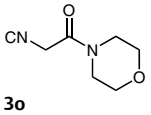
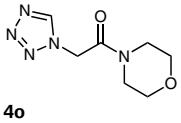
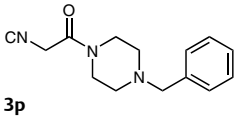
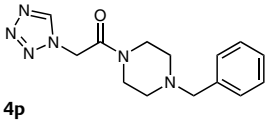
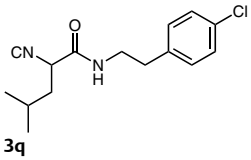
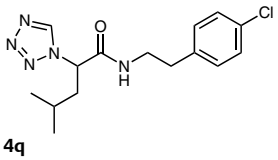
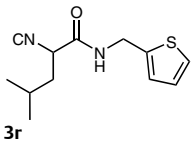
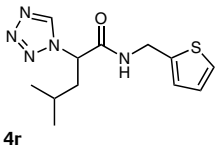
| Entry | Reactant **3** | Yield (%)[a] | Product **4** | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  **3a** | 85 |  **4a** | 97 |
| 2 |  **3b** | 87 |  **4b** | 95 |
| 3 |  **3c** | 85 |  **4c** | 98 |
| 4 |  **3d** | 83 |  **4d** | 97 |
| 5 |  **3e** | 86 |  **4e** | 98 |
| 6 |  **3f** | 89 |  **4f** | 86 |
| 7 |  **3g** | 90 |  **4g** | 95 |
| 8 |  **3h** | 86 |  **4h** | 86 |

Table 3 (continued)

| Entry | Reactant **3** | Yield (%)[a] | Product **4** | Yield (%)[a] |
|---|---|---|---|---|
| 9 |  **3i** | 75 |  **4i** | 90 |
| 10 |  **3j** | 88 |  **4j** | 92 |
| 11 |  **3k** | 92 |  **4k** | 78 |
| 12 |  **3l** | 86 |  **4l** | 74 |
| 13 |  **3m** | 89 |  **4m** | 84 |
| 14 |  **3n** | 87 |  **4n** | 87 |
| 15 |  **3o** | 81 |  **4o** | 86 |
| 16 |  **3p** | 78 |  **4p** | 72 |
| 17 |  **3q** | 83 |  **4q** | 74 |
| 18 |  **3r** | 82 |  **4r** | 69 |

[a] Isolated yield.

Surprisingly, when sodium azide was replaced by trimethylsilyl azide with 25% co-solvent water in methanol at room temperature, the yield was dramatically increased to 97% (Table 2). With this optimized conditions, substrate scope of this method was investigated for various *N*-alkyl-2-isocyanoacetamides to form *N*-alkyl-2-(1*H*-tetrazol-1-yl)acetamides (Table 3). In all cases, excellent yield of products **4a**–**n** (70–97%) were obtained. This method is very ef-

ficient, as we observed that all *N*-alkyl-2-(1*H*-tetrazol-1-yl)acetamides were precipitated during the aqueous work-up followed by simple filtration to afford the pure product. In few cases **4l** and **4o**, precipitation from water did not occur; in such cases, the products were obtained by extraction using a saturated solution of sodium chloride and dichloromethane. Noteworthy, with this method all the products **4a**–**q** were obtained in good to excellent yields. To support the fragment likeliness of our scaffolds and synthesized compounds the chemical properties MW and clogP were calculated, which are plotted in Figure 2.

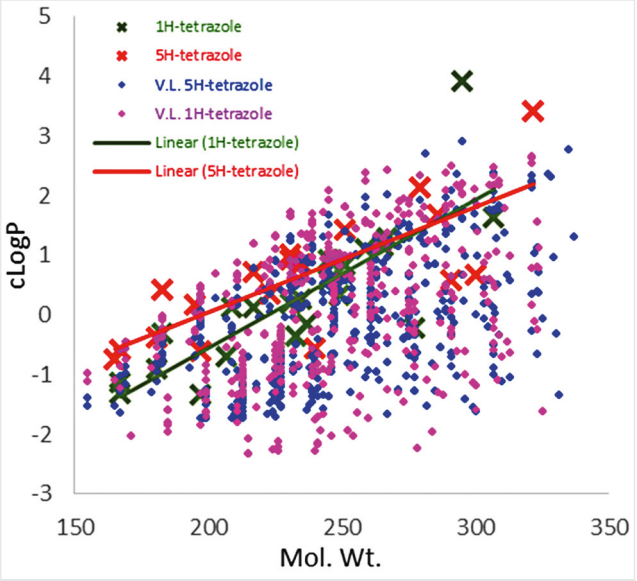



**Figure 2** cLogP vs Mol. weight of virtual libraries of 500 randomly generated molecules of 1*H*-tetrazoles (violet) and 5*H*-tetrazoles (blue) along with our synthesized library 1*H*-tetrazoles (green) and 5*H*-tetrazoles (red)

In conclusion, we have prepared two positional isomeric monosubstituted tetrazole libraries by a convenient and fast procedure. With mild reaction conditions, our new methods provide significant advantages such as easy work-up, short reaction time, and broad substrate scope. With more and more drug candidates originating from fragment-based lead discovery having been progressed into clinical trials, the efficient build-up of fragment libraries containing 'drug-like' fragments like tetrazole is of great importance. Further investigation of our herein-described positional isomeric tetrazole libraries in different protein targets is currently ongoing and will be reported in due course.

NMR spectra were recorded on a Bruker Avance 500 spectrometer [$^1$H NMR (500 MHz), $^{13}$C NMR (126 MHz)]. Chemical shifts for $^1$H NMR were reported as δ values and coupling constants were in hertz (Hz). Standard abbreviations were used for defining spin multiplicity. Chemical shifts for $^{13}$C NMR reported in ppm relative to the solvent peak. TLC was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230–400 mesh) and on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 g). Reagents were available from commercial suppliers (Sigma Aldrich, ABCR, Acros and AK Scientific) and used without any purification, unless otherwise noted. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument.

### 5-Substitubed Tetrazoles 2; General Procedure A (GP A)

To a stirred solution of *N*-alkyl-substituted 2-cyanoacetamide **1** (5 mmol) in toluene (10 mL) was added $NaN_3$ (3 equiv) and triethylamine hydrochloride salt (3 equiv). The reaction mixture was heated to 90 °C for 20 h. Ice-cold $H_2O$ (25 mL) was added to the reaction mixture and acidified with aq HCl and stirred at 0 °C for 30 min. The precipitated product was collected by filtration, washed with cold $H_2O$ (25 mL), and dried in vacuum (Table 1).

### 2-Isocyanoacetamides 3; General Procedure B (GP B)

To the appropriate amine (10 mmol) was added methyl isocyanoacetate (1 g, 10 mmol), and the mixture was stirred overnight at r.t. If the product precipitated during the reaction, it was collected by filtration, washed with cold $Et_2O$ (3 ×), and dried under vacuum overnight. If no precipitation was observable, cold $Et_2O$ was added to the reaction mixture, and the product was allowed to crystallize in the freezer at –20 °C.

### 1-Substitubed Tetrazoles 4; General Procedure C (GP C)

To the *N*-alkyl-2-isocyanoacetamide (1.0 mmol) in a mixture of solvents MeOH–$H_2O$ (3:1, 1 M) was added trimethylsilyl azide (138 mg, 1.2 mmol) and the resulting mixture was stirred overnight at r.t. The reaction, which precipitated out was filtered and washed with cold $H_2O$ (3 × 5 mL). The reactions which do not precipitate, were diluted with brine (1 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The solvents were removed under reduced pressure to afford the pure product (Table 3).

### *N*-Benzyl-2-(1*H*-tetrazol-5-yl)acetamide (2a)

The product was obtained using GP A, 8 mmol scale; yield: 1.16 g (67%); white solid; mp 166–168 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.83 (t, *J* = 5.9 Hz, 1 H), 7.40–7.19 (m, 5 H), 4.32 (d, *J* = 5.9 Hz, 2 H), 3.96 (s, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.1, 151.2, 138.9, 128.3, 127.4, 126.9, 42.5, 30.5.

SFC-MS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}N_5O$: 217.10; found $[M + H]^+$: 218.09.

### *N*-Phenethyl-2-(1*H*-tetrazol-5-yl)acetamide (2b)

The product was obtained using GP A, 8 mmol scale; yield: 1.37 g (74%); white solid; mp 170–171 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.43 (t, *J* = 5.5 Hz, 1 H), 7.38–7.11 (m, 5 H), 3.87 (s, 2 H), 3.39–3.25 (m, 2 H), 2.73 (t, *J* = 7.4 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.0, 151.2, 139.2, 128.6, 128.4, 126.2, 40.6, 35.0, 30.5.

SFC-MS (ESI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}N_5O$: 231.11; found $[M + H]^+$: 232.08.

***N*-(3-Phenylpropyl)-2-(1*H*-tetrazol-5-yl)acetamide (2c)**

The product was obtained using GP A, 8 mmol scale; yield: 1.58 g (79%); white solid; mp 104–106 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.37 (t, *J* = 5.5 Hz, 1 H), 7.27 (t, *J* = 7.5 Hz, 2 H), 7.23–7.12 (m, 3 H), 3.88 (s, 2 H), 3.10 (q, *J* = 6.6 Hz, 2 H), 2.59 (t, *J* = 7.7 Hz, 2 H), 1.72 (quint, *J* = 7.2 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.0, 151.3, 141.6, 128.3, 125.8, 38.5, 32.4, 30.7, 30.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{15}N_5O$: 245.13; found [M – H]$^+$: 244.11.

***N*-(4-Phenylbutyl)-2-(1*H*-tetrazol-5-yl)acetamide (2d)**

The product was obtained using GP A, 8 mmol scale; yield: 1.78 g (86%); white solid; mp 122–124 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.31 (t, *J* = 5.7 Hz, 1 H), 7.27 (t, *J* = 7.7 Hz, 2 H), 7.23–7.12 (m, 3 H), 3.86 (s, 2 H), 3.11 (q, *J* = 6.7 Hz, 2 H), 2.57 (t, *J* = 7.7 Hz, 2 H), 1.62–1.51 (m, 2 H), 1.48–1.38 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.9, 151.2, 142.1, 128.3, 128.2, 125.7, 38.7, 34.8, 30.5, 28.6, 28.3.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{17}N_5O$: 259.14; found [M – H]$^+$: 258.16.

***N*-[1-(4-Chlorophenyl)ethyl]-2-(1*H*-tetrazol-5-yl)acetamide (2e)**

The product was obtained using GP A, 8 mmol scale; yield: 1.37 g (64%); white solid; mp 182–184 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.84 (d, *J* = 7.8 Hz, 1 H), 7.51–7.26 (m, 4 H), 5.00–4.83 (m, 1 H), 3.95 (s, 2 H), 1.38 (d, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.3, 151.1, 143.3, 131.3, 128.3, 127.9, 47.9, 30.5, 22.3, 22.2.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{12}ClN_5O$: 265.07; found [M – H]$^+$: 263.90.

**2-(1*H*-Tetrazol-5-yl)-*N*-[1-(*p*-tolyl)ethyl]acetamide (2f)**

The product was obtained using GP A, 4 mmol scale; yield: 0.69 g (70%); white solid; mp 187–189 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.75 (d, *J* = 7.9 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 4.95–4.81 (m, 1 H), 3.92 (s, 2 H), 2.26 (s, 3 H), 1.35 (d, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.1, 151.1, 141.1, 135.9, 128.8, 125.9, 48.1, 30.5, 22.4, 20.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{15}N_5O$: 245.13; found [M – H]$^+$: 244.05.

***N*-(4-Chlorobenzyl)-2-(1*H*-tetrazol-5-yl)acetamide (2g)**

The product was obtained using GP A, 3.6 mmol scale; yield: 0.57 g (76%); white solid; mp 189–191 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 7.36 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 6.46 (t, *J* = 6.2 Hz, 1 H), 5.57 (s, 2 H), 4.08 (d, *J* = 6.2 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 158.7, 140.1, 131.0, 128.8, 128.1, 42.2, 42.1.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}ClN_5O$: 251.06; found [M + Na]$^+$: 274.17.

***N*-(4-Fluorobenzyl)-2-(1*H*-tetrazol-5-yl)acetamide (2h)**

The product was obtained using GP A, 8 mmol scale; yield: 1.32 g (70%); white solid; mp 171–173 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.85 (t, *J* = 5.9 Hz, 1 H), 7.48–7.25 (m, 2 H), 7.17 (t, *J* = 8.7 Hz, 2 H), 4.31 (d, *J* = 5.8 Hz, 2 H), 3.97 (s, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.2, 161.31 (d, *J* = 242.6 Hz), 151.2, 135.14 (d, *J* = 2.9 Hz), 129.39 (d, *J* = 8.2 Hz), 115.11 (d, *J* = 21.2 Hz), 41.8, 30.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}FN_5O$: 235.09; found [M – H]$^+$: 233.97.

***N*-(4-Fluorophenethyl)-2-(1*H*-tetrazol-5-yl)acetamide (2i)**

The product was obtained using GP A, 8 mmol scale; yield: 1.74 g (87%); white solid; mp 159–161 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.41 (s, 1 H), 7.31–7.19 (m, 2 H), 7.17–7.01 (m, 2 H), 3.85 (s, 2 H), 3.30 (q, *J* = 6.8 Hz, 2 H), 2.72 (t, *J* = 7.3 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.1, 160.90 (d, *J* = 241.5 Hz), 151.2, 135.41 (d, *J* = 3.0 Hz), 130.45 (d, *J* = 7.9 Hz), 115.01 (d, *J* = 21.0 Hz), 40.6, 34.1, 30.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{12}FN_5O$: 249.10; found [M – H]$^+$: 248.08.

***N*-(3,4-Dimethoxybenzyl)-2-(1*H*-tetrazol-5-yl)acetamide (2j)**

The product was obtained using GP A, 8 mmol scale; yield: 1.03 g (93%); white solid; mp 156–158 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.78 (s, 1 H), 6.92–6.85 (m, 2 H), 6.80 (d, *J* = 8.1 Hz, 1 H), 4.24 (d, *J* = 5.6 Hz, 2 H), 3.94 (s, 2 H), 3.73 (s, 3 H), 3.72 (s, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.1, 151.4, 148.7, 147.9, 131.3, 119.5, 111.8, 111.5, 55.6, 45.7, 42.3, 30.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{15}N_5O_3$: 277.12; found [M – H]$^+$: 276.06.

***N*-(2-Hydroxy-2-phenylethyl)-2-(1*H*-tetrazol-5-yl)acetamide (2k)**

The product was obtained using GP A, 8 mmol scale; yield: 1.39 g (70%); white solid; mp 162–164 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.47 (t, *J* = 5.7 Hz, 1 H), 7.36–7.29 (m, 4 H), 7.28–7.21 (m, 1 H), 5.53 (s, 1 H), 4.62 (dd, *J* = 8.1, 4.4 Hz, 1 H), 3.91 (s, 2 H), 3.34 (dt, *J* = 13.4, 6.2, 4.4 Hz, 1 H), 3.15 (ddd, *J* = 13.4, 8.1, 5.2 Hz, 1 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.3, 151.2, 143.5, 128.1, 127.2, 126.0, 71.2, 47.2, 30.5.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{13}N_5O_2$: 247.11; found [M – H]$^+$: 246.19.

***N*-(2,2-Diphenylethyl)-2-(1*H*-tetrazol-5-yl)acetamide (2l)**

The product was obtained using GP A, 4 mmol scale; yield: 0.69 g (56%); white solid; mp 181–183 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.42 (s, 1 H), 7.38–7.25 (m, 8 H), 7.23–7.13 (m, 2 H), 4.18 (td, *J* = 7.8, 2.2 Hz, 1 H), 3.84–3.68 (m, 4 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.2, 151.1, 142.7, 128.5, 127.9, 126.4, 50.0, 43.5, 30.4.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{17}N_5O$: 307.14; found [M – H]$^+$: 306.18.

***N*-(Naphthalen-2-ylmethyl)-2-(1*H*-tetrazol-5-yl)acetamide (2m)**

The product was obtained using GP A, 8 mmol scale; yield: 1.90 g (89%); white solid; mp 213–215 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.89 (d, *J* = 5.6 Hz, 1 H), 8.15–8.01 (m, 1 H), 8.01–7.91 (m, 1 H), 7.87 (dd, *J* = 7.0, 2.4 Hz, 1 H), 7.65–7.35 (m, 4 H), 4.79 (d, *J* = 5.6 Hz, 2 H), 3.98 (s, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.1, 151.3, 134.0, 133.4, 130.9, 128.6, 127.8, 126.4, 125.9, 125.8, 125.5, 123.5, 40.7, 30.5.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{13}N_5O$: 267.11; found [M – H]$^+$: 266.04.

***N*-(Furan-2-ylmethyl)-2-(1*H*-tetrazol-5-yl)acetamide (2n)**

The product was obtained using GP A, 8 mmol scale; yield: 0.35 g (21%); white solid; mp 166–168 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.81 (t, *J* = 5.5 Hz, 1 H), 7.59 (s, 1 H), 6.40 (d, *J* = 3.0 Hz, 1 H), 6.28 (d, *J* = 3.0 Hz, 1 H), 4.29 (d, *J* = 5.5 Hz, 2 H), 3.93 (s, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.0, 151.7, 151.1, 142.3, 110.5, 107.3, 35.8, 30.4.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_8H_9N_5O_2$: 207.08; found [M + Na]$^+$: 230.12.

**2-(1*H*-Tetrazol-5-yl)-*N*-[2-(thiophen-2-yl)ethyl]acetamide (2o)**

The product was obtained using GP A, 8 mmol scale; yield: 1.24 g (65%); white solid; mp 150–152 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.50 (t, *J* = 5.7 Hz, 1 H), 7.33 (d, *J* = 5.1 Hz, 1 H), 7.00–6.79 (m, 2 H), 3.88 (s, 2 H), 3.41–3.25 (m, 2 H), 2.95 (t, *J* = 7.1 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.2, 151.2, 141.3, 127.0, 125.3, 124.1, 40.7, 30.6, 29.1.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_9H_{11}N_5OS$: 237.07; found [M – H]$^+$: 236.05.

***N*-Cyclopropyl-2-(1*H*-tetrazol-5-yl)acetamide (2p)**

The product was obtained using GP A, 8 mmol scale; yield: 0.74 g (55%); white solid; mp 173–175 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.41 (s, 1 H), 3.81 (s, 2 H), 2.68–2.60 (m, 1 H), 0.66–0.60 (m, 2 H), 0.45–0.38 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 167.1, 151.1, 30.4, 22.5, 5.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_6H_9N_5O$: 167.08; found [M + Na]$^+$: 190.05.

***N*-Butyl-2-(1*H*-tetrazol-5-yl)acetamide (2q)**

The product was obtained using GP A, 8 mmol scale; yield: 1.14 g (77%); white solid; mp 82–84 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.28 (s, 1 H), 3.85 (s, 2 H), 3.12–3.02 (m, 2 H), 1.46–1.34 (m, 2 H), 1.33–1.22 (m, 2 H), 0.86 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 166.0, 151.2, 38.7, 31.1, 30.6, 19.6, 13.7.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_7H_{13}N_5O$: 183.11; found [M – H]$^+$: 182.11.

***N*-Dodecyl-2-(1*H*-tetrazol-5-yl)acetamide (2r)**

The product was obtained using GP A, 4 mmol scale; yield: 1.03 g (98%); white solid; mp 152–154 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.28 (d, *J* = 7.4 Hz, 1 H), 3.84 (s, 2 H), 1.45–1.15 (m, 22 H), 0.85 (t, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.8, 151.2, 38.9, 31.3, 30.5, 29.1, 28.9, 28.8, 26.4, 22.1, 13.9.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{29}N_5O$: 295.24; found [M – H]$^+$: 294.27.

***N*-Allyl-2-(1*H*-tetrazol-5-yl)acetamide (2s)**

The product was obtained using GP A, 8 mmol scale; yield: 0.34 g (25%); white solid; mp 140–142 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.49 (d, *J* = 6.0 Hz, 1 H), 5.87–5.69 (m, 1 H), 5.17 (dq, *J* = 17.2, 1.8 Hz, 1 H), 5.11–5.03 (m, 1 H), 3.91 (s, 2 H), 3.76–3.68 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.9, 151.2, 134.8, 115.5, 41.2, 30.4.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_6H_9N_5O$: 167.08; found [M – H]$^+$: 165.98.

***N*-Cyclohexyl-2-(1*H*-tetrazol-5-yl)acetamide (2t)**

The product was obtained using GP A, 8 mmol scale; yield: 0.85 g (51%); white solid; mp 215–217 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.21 (d, *J* = 7.9 Hz, 1 H), 3.84 (s, 2 H), 3.59–3.39 (m, 1 H), 1.82–1.62 (m, 4 H), 1.53 (dt, *J* = 12.3, 3.9 Hz, 1 H), 1.37–1.00 (m, 5 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.9, 151.2, 47.9, 32.3, 30.6, 25.2, 24.4.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_9H_{15}N_5O$: 209.13; found [M – H]$^+$: 208.01.

**1-(Pyrrolidin-1-yl)-2-(1*H*-tetrazol-5-yl)ethan-1-one (2u)**

The product was obtained using GP A, 8 mmol scale; yield: 0.13 g (9%); white solid; mp 137–139 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 4.10 (s, 2 H), 3.55 (t, *J* = 6.8 Hz, 2 H), 3.31 (t, *J* = 6.8 Hz, 2 H), 1.91 (quint, *J* = 6.8 Hz, 2 H), 1.80 (quint, *J* = 6.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.6, 151.1, 46.2, 45.7, 29.9, 25.5, 24.0.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_7H_{11}N_5O$: 181.10; found [M + H]$^+$: 182.11.

**1-Morpholino-2-(1*H*-tetrazol-5-yl)ethan-1-one (2v)**

The product was obtained using GP A, 8 mmol scale; yield: 0.40 g (25%); white solid; mp 196–198 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 4.21 (s, 2 H), 3.65–3.59 (m, 2 H), 3.59–3.52 (m, 4 H), 3.50–3.43 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.4, 151.3, 66.0, 66.0, 45.7, 41.9, 28.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_7H_{11}N_5O_2$: 197.09; found [M + H]$^+$: 198.12.

***N*-Benzyl-2-isocyanoacetamide (3a)**

The product was obtained using GP B, 10 mmol scale; yield: 1.48 g (85%), white solid; mp 125–127 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.66 (s, 1 H), 7.35–7.24 (m, 5 H), 4.42 (s, 2 H), 4.32 (d, *J* = 5.9 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.0, 158.2, 138.6, 128.3, 127.4, 127.0, 44.8, 42.5.

***N*-(4-Fluorobenzyl)-2-isocyanoacetamide (3b)**

The product was obtained using GP B, 10 mmol scale; yield: 1.68 g (87%); white solid; mp 135–137 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.66 (s, 1 H), 7.31 (dd, *J* = 8.5, 5.9 Hz, 2 H), 7.15 (t, *J* = 8.9 Hz, 2 H), 4.40 (s, 2 H), 4.28 (d, *J* = 5.9 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ =163.1, 162.3, 160.3, 158.2, 134.9, 134.9, 129.5, 129.4, 115.2, 115.0, 44.8, 41.8.

***N*-(4-Chlorobenzyl)-2-isocyanoacetamide (3c)**

The product was obtained using GP B, 10 mmol scale; yield: 1.79 g (85%); white solid; mp 122–124 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.69 (s, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 4.42 (s, 2 H), 4.29 (d, *J* = 5.9 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.2, 158.3, 137.8, 131.6, 129.3, 128.3, 44.8, 41.8.

**2-Isocyano-*N*-(1-phenylethyl)acetamide (3d)**

The product was obtained using GP B, 10 mmol scale; yield: 1.57 g (83%); white solid; mp 128–130 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 6.60 (s, 1 H), 5.14 (quint, *J* = 7.1 Hz, 1 H), 4.15 (d, *J* = 8.5 Hz, 2 H), 1.56 (d, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.2, 158.3, 137.8, 131.6, 129.2, 128.3, 44.8, 41.8.

**2-Isocyano-*N*-(thiophen-2-ylmethyl)acetamide (3e)**

The product was obtained using GP B, 10 mmol scale; yield: 1.55 g (86%); white solid; mp 97–99 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.27 (s, 1 H), 7.02 (d, *J* = 3.5 Hz, 1 H), 7.01 (m, 2 H), 6.80 (s, 2 H), 4.67 (d, *J* = 5.7 Hz, 2 H), 4.19 (s, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.5, 162.2, 139.3, 127.2, 126.9, 125.9, 45.3, 38.6.

**2-Isocyano-*N*-phenethylacetamide (3f)**

The product was obtained using GP B, 10 mmol scale; yield: 1.68 g (89%); white solid; mp 94–96 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.20 (s, 5 H), 6.44 (s, 1 H), 4.12 (s, 2 H), 3.59 (q, *J* = 6.9 Hz, 2 H), 2.87 (t, *J* = 7.1 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.4, 161.9, 138.1, 128.8, 128.7, 126.8, 45.2, 41.0, 35.3.

***N*-(3,4-Dimethoxyphenethyl)-2-isocyanoacetamide (3g)**

The product was obtained using GP B, 10 mmol scale; yield: 2.23 g (90%); white solid; mp 95–97 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 8.1 Hz, 1 H), 6.74 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.71 (d, *J* = 1.4 Hz, 1 H), 6.46 (s, 1 H), 4.12 (s, 2 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.56 (q, *J* = 6.8 Hz, 2 H), 2.81 (t, *J* = 7.1 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.3, 162.2, 149.2, 148.0, 130.6, 120.7, 111.8, 111.6, 56.5, 55.9, 45.3, 41.2, 35.0.

***N*-(Cyclopropylmethyl)-2-isocyanoacetamide (3h)**

The product was obtained using GP B, 10 mmol scale; yield: 1.08 g (86%); white solid; mp 89–91 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 6.52 (s, 1 H), 4.14 (s, 2 H), 2.78–2.73 (m, 1 H), 0.87–0.83 (m, 2 H), 0.62–0.59 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 163.7, 161.9, 45.2, 22.9, 8.3, 6.4.

***N*-(1-Benzylpiperidin-4-yl)-2-isocyanoacetamide (3i)**

The product was obtained using GP B, 10 mmol scale, yield: 1.94 g (75%); white solid; mp 135–137 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 5 H), 6.26 (d, *J* = 6.1 Hz, 1 H), 4.14 (s, 2 H), 3.87–3.81 (m, 1 H), 3.52 (s, 2 H), 2.84 (d, *J* = 11.6 Hz, 2 H), 2.15 (t, *J* = 11.1 Hz, 2 H), 1.92 (d, *J* = 12.6 Hz, 2 H), 1.60–1.52 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.4, 161.6, 138.2, 129.2, 128.4, 127.2, 63.0, 52.1, 47.4, 45.4, 32.0.

***N*-Butyl-2-isocyanoacetamide (3j)**

The product was obtained using GP B, 10 mmol scale; yield: 1.24 g (88%); white solid; mp 53–55 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.11 (s, 1 H), 4.30 (s, 2 H), 3.08 (q, *J* = 6.9 Hz, 2 H), 1.39 (quint, *J* = 6.9 Hz, 2 H), 1.27 (sext, *J* = 7.7 Hz, 2 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.4, 162.2, 45.4, 39.9, 31.4, 20.1, 13.8.

**2-Isocyano-*N*-(prop-2-yn-1-yl)acetamide (3k)**

The product was obtained using GP B, 10 mmol scale; yield: 1.13 g (92%); white solid; mp 108–110 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 6.66 (s, 1 H), 4.21 (s, 2 H), 4.13–4.12 (m, 2 H), 2.32–2.30 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.9, 162.2, 78.2, 72.7, 45.3, 29.8.

**2-Isocyano-*N*-(2-morpholinoethyl)acetamide (3l)**

The product was obtained using GP B, 10 mmol scale, yield: 1.70 g (86%); white solid; mp 80–81 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 8.09 (s, 1 H), 4.33 (s, 2 H), 3.56 (t, *J* = 4.5 Hz, 4 H), 3.21 (q, *J* = 6.4 Hz, 2 H), 2.34 (t, *J* = 6.8 Hz, 6 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 162.4, 162.31, 67.1, 56.3, 53.3, 45.5, 35.9.

**2-Isocyano-1-(pyrrolidin-1-yl)ethan-1-one (3m)**

The product was obtained using GP B, 10 mmol scale; yield: 1.24 g (89%); white solid; mp 71–73 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.21 (s, 2 H), 3.51 (t, *J* = 7.0 Hz, 2 H), 3.39 (t, *J* = 6.8 Hz, 2 H), 2.00 (quint, *J* = 6.8 Hz, 2 H), 1.90 (quint, *J* = 6.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 160.7, 160.1, 46.6, 46.2, 45.0, 26.1, 24.0.

**2-Isocyano-1-(piperidin-1-yl)ethan-1-one (3n)**

The product was obtained using GP B, 10 mmol scale; yield: 1.33 g (87%); white solid; mp 84–86 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.27 (s, 2 H), 3.56 (t, *J* = 5.6 Hz, 2 H), 3.31 (t, *J* = 5.5 Hz, 2 H), 1.68–1.55 (m, 6 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 160.6, 160.5, 46.5, 44.5, 43.6, 26.0, 25.2, 24.1.

**2-Isocyano-1-morpholinoethan-1-one (3o)**

The product was obtained using GP B, 10 mmol scale; yield: 1.26 g (81%); brown solid; mp 69–71 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.30 (s, 2 H), 3.70–3.66 (m, 4 H), 3.61 (t, *J* = 4.9 Hz, 2 H), 3.37 (t, *J* = 4.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 161.4, 161.2, 66.6, 66.2, 45.9, 44.4, 42.8.

**1-(4-Benzylpiperazin-1-yl)-2-isocyanoethan-1-one (3p)**

The product was obtained using GP B, 10 mmol scale; yield: 1.91 g (78%); white solid; mp 80–82 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 4.27 (s, 2 H), 3.65 (t, *J* = 4.8 Hz, 2 H), 3.53 (s, 2 H), 3.40 (t, *J* = 4.7 Hz, 2 H), 2.49–2.46 (m, 4 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 161.3, 160.8, 137.3, 129.1, 128.4, 127.4, 62.7, 52.5, 52.4, 45.7, 44.4, 42.6.

***N*-(4-Chlorobenzyl)-2-isocyano-4-methylpentanamide (3q)**

The product was obtained using GP B, 5 mmol scale; yield: 1.09 g (83%); white solid; mp 82–84 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 6.78 (s, 1 H), 4.44 (d, *J* = 5.9 Hz, 2 H), 4.27–4.22 (m, 1 H), 1.94–1.75 (m, 3 H), 1.00 (d, *J* = 6.4 Hz, 3 H), 0.97 (d, *J* = 6.4 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 166.1, 162.0, 135.8, 133.9, 129.3, 129.2, 57.3, 43.4, 41.6, 25.0, 22.9, 20.8.

**2-Isocyano-4-methyl-*N*-(thiophen-2-ylmethyl)pentanamide (3r)**

The product was obtained using GP B, 5 mmol scale; yield: 0.96 g (82%); white solid; mp 70–72 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.25 (m, 1 H), 7.01–6.99 (m, 1 H), 6.98–6.94 (m, 1 H), 6.79 (s, 1 H), 4.67–4.63 (m, 2 H), 4.25–4.21 (m, 1 H), 1.94–1.86 (m, 1 H), 1.78 (dd, *J* = 13.8, 5.1 Hz, 2 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 165.9, 162.0, 139.6, 127.2, 126.7, 125.9, 57.2, 41.5, 38.8, 25.0, 22.9, 20.9.

***N*-Benzyl-2-(1*H*-tetrazol-1-yl)acetamide (4a)**

The product was obtained using GP C, 1 mmol scale; yield: 0.211 g (97%); white solid; mp 135–137 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.39 (s, 1 H), 8.93 (t, *J* = 5.4 Hz, 1 H), 7.36–7.26 (m, 5 H), 5.32 (s, 2 H), 4.34 (t, *J* = 5.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.7, 145.2, 138.7, 128.4, 127.4, 127.1, 49.4, 42.5.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{11}N_5O$: 217.10; found [M + Na]$^+$: 240.14.

***N*-(4-Fluorobenzyl)-2-(1*H*-tetrazol-1-yl)acetamide (4b)**

The product was obtained using GP C, 1 mmol scale; yield: 0.224 g (95%); white solid; mp 164–166 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.38 (s, 1 H), 8.93 (s, 1 H), 7.33 (dd, *J* = 8.5, 5.9 Hz, 2 H), 7.17 (t, *J* = 8.9 Hz, 2 H), 5.32 (s, 2 H), 4.32 (d, *J* = 5.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.7, 162.3, 160.4, 145.2, 134.8, 134.8, 129.5, 129.4, 115.2, 115.1, 49.4, 41.8.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}FN_5O$: 235.09; found [M – H]$^+$: 234.13.

***N*-(4-Chlorobenzyl)-2-(1*H*-tetrazol-1-yl)acetamide (4c)**

The product was obtained using GP C, 1 mmol scale; yield: 0.247 g (98%); white solid; mp 160–162 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.39 (s, 1 H), 8.96 (t, *J* = 5.5 Hz, 1 H), 7.41 (dd, *J* = 45.4, 5.5 Hz, 4 H), 5.33 (s, 2 H), 4.34 (d, *J* = 5.9 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.3, 145.6, 138.2, 132.1, 129.7, 128.8, 49.9, 42.2.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}ClN_5O$: 251.06; found [M – H]$^+$: 249.94.

***N*-(1-Phenylethyl)-2-(1*H*-tetrazol-1-yl)acetamide (4d)**

The product was obtained using GP C, 1 mmol scale; yield: 0.216 g (97%); white solid; mp 143–144 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.35 (s, 1 H), 8.93 (d, *J* = 7.7 Hz, 1 H), 7.38–7.25 (m, 5 H), 5.29 (s, 2 H), 4.92 (t, *J* = 7.3 Hz, 1 H), 1.41 (d, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.7, 145.1, 143.8, 128.4, 126.9, 126.0, 49.4, 48.5, 22.4.

SFC-MS (ESI): *m*/*z* calcd for $C_{11}H_{13}N_5O$ [M]$^+$: 231.11; found [M + Na]$^+$: 254.16.

**2-(1*H*-Tetrazol-1-yl)-*N*-(thiophen-2-ylmethyl)acetamide (4e)**

The product was obtained using GP C, 1 mmol scale; yield: 0.218 g (98%); white solid; mp 153–154 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.38 (s, 1 H), 9.04 (t, *J* = 5.4 Hz, 1 H), 7.44 (dd, *J* = 5.1, 1.1 Hz, 1 H), 7.02–6.97 (m, 2 H), 5.29 (s, 2 H), 4.50 (d, *J* = 5.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.5, 145.2, 141.2, 126.8, 126.0, 125.4, 49.3, 37.4.

SFC-MS (ESI): *m*/*z* calcd for $C_8H_9N_5OS$ [M]$^+$: 223.05; found [M – H]$^+$: 222.00.

***N*-Phenethyl-2-(1*H*-tetrazol-1-yl)acetamide (4f)**

The product was obtained using GP C, 1 mmol scale; yield: 0.198 g (86%); white solid; mp 144–145 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.36 (s, 1 H), 8.56 (t, *J* = 5.2 Hz, 1 H), 7.33–7.21 (m, 5 H), 5.23 (s, 2 H), 3.37 (q, *J* = 6.9 Hz, 2 H), 2.77 (t, *J* = 7.4 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.6, 145.2, 145.1, 139.2, 128.7, 128.43, 126.3, 49.4, 40.6, 34.9.

SFC-MS (ESI): *m*/*z* calcd for $C_{11}H_{13}N_5O$ [M]$^+$: 231.11; found [M + H]$^+$: 232.20.

***N*-(3,4-Dimethoxyphenethyl)-2-(1*H*-tetrazol-1-yl)acetamide (4g)**

The product was obtained using GP C, 1 mmol scale; yield: 0.276 g (95%); white solid; mp 137–139 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.34 (s, 1 H), 8.50 (t, *J* = 5.3 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 6.82 (d, *J* = 1.9 Hz, 1 H), 6.73 (dd, *J* = 8.1, 1.9 Hz, 1 H), 5.21 (s, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.31 (t, *J* = 6.3 Hz, 2 H), 2.67 (t, *J* = 7.4 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.5, 148.6, 147.3, 145.1, 131.5, 120.4, 112.5, 111.9, 55.5, 55.4, 55.4, 49.4, 40.7, 34.5.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{17}N_5O_3$: 291.13; found [M – H]$^+$: 290.16.

**N-(Cyclopropylmethyl)-2-(1H-tetrazol-1-yl)acetamide (4h)**

The product was obtained using GP C, 1 mmol scale; yield: 0.155 g (86%); white solid; mp 149–150 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.35 (s, 1 H), 8.53 (s, 1 H), 5.17 (s, 2 H), 2.68–2.63 (m, 1 H), 0.68–0.64 (m, 2 H), 0.46–0.43 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 165.6, 145.1, 49.3, 22.4, 5.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_8H_9N_5O$: 167.08; found [M + H]$^+$: 167.93.

**N-(1-Benzylpiperidin-4-yl)-2-(1H-tetrazol-1-yl)acetamide (4i)**

The product was obtained using GP C, 1 mmol scale, yield: 0.269 g (90%); white solid; mp 126–128 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.36 (s, 1 H), 8.79 (d, *J* = 6.1 Hz, 1 H), 7.54–7.39 (m, 5 H), 5.25 (s, 2 H), 4.01 (s, 2 H), 3.74 (s, 1 H), 3.16 (d, *J* = 14.9 Hz, 2 H), 2.74 (s, 2 H), 1.90 (d, *J* = 11.4 Hz, 2 H), 1.77 (d, *J* = 11.7 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.9, 145.1, 129.6, 128.4, 127.7, 61.0, 51.0, 49.4, 45.7, 30.2.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{20}N_6O$: 300.17; found [M + H]$^+$: 301.25.

**N-Butyl-2-(1H-tetrazol-1-yl)acetamide (4j)**

The product was obtained using GP C, 1 mmol scale; yield: 0.168 g (92%); white solid; mp 132–134 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.35 (s, 1 H), 8.40 (s, 1 H), 5.22 (s, 2 H), 3.11 (q, *J* = 6.8 Hz, 2 H), 1.41 (quint, *J* = 7.4 Hz, 2 H), 1.30 (sext, *J* = 7.5 Hz, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.4, 145.1, 145.1, 49.4, 31.0, 19.5, 13.6.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_7H_{13}N_5O$: 183.11; found [M – H]$^+$: 182.11.

**N-(Prop-2-yn-1-yl)-2-(1H-tetrazol-1-yl)acetamide (4k)**

The product was obtained using GP C, 1 mmol scale; yield: 0.129 g (78%); white solid; mp 117–119 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.37 (s, 1 H), 8.92 (s, 1 H), 5.28 (s, 2 H), 3.95–3.94 (m, 2 H), 3.21 (t, *J* = 2.5 Hz, 1 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 164.5, 145.1, 80.3, 73.7, 49.2, 28.3.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_6H_7N_5O$: 165.07; found [M – H]$^+$: 163.90.

**N-(2-Morpholinoethyl)-2-(1H-tetrazol-1-yl)acetamide (4l)**

The product was obtained using GP C, 1 mmol scale; yield: 0.177 g (74%); white solid; mp 99–101 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 6.61 (s, 1 H), 5.15 (s, 2 H), 3.69 (t, *J* = 4.6 Hz, 4 H), 3.39 (q, *J* = 5.5 Hz, 2 H), 2.49 (t, *J* = 6.0 Hz, 2 H), 2.43 (t, *J* = 4.2 Hz, 4 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 163.4, 143.8, 67.0, 56.4, 53.3, 50.7, 36.1.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_9H_{16}N_6O_2$: 240.13; found [M + H]$^+$: 241.09.

**1-(Pyrrolidin-1-yl)-2-(1H-tetrazol-1-yl)ethan-1-one (4m)**

The product was obtained using GP C, 1 mmol scale; yield: 0.151 g (84%); white solid; mp 161–163 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.31(s, 1 H), 5.52 (s, 2 H), 3.54 (t, *J* = 6.8 Hz, 2 H), 3.34 (t, *J* = 6.8 Hz, 2 H), 1.99–1.91 (m, 2 H), 1.87–1.79 (m, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 162.9, 145.2, 49.2, 45.9, 45.1, 25.6, 23.7.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_7H_{11}N_5O$: 181.10; found [M + H]$^+$: 182.11.

**1-(Piperidin-1-yl)-2-(1H-tetrazol-1-yl)ethan-1-one (4n)**

The product was obtained using GP C, 1 mmol scale; yield: 0.169 g (87%); white solid; mp 189–190 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.29 (s, 1 H), 5.62 (s, 2 H), 3.45 (q, *J* = 5.5 Hz, 4 H), 1.60 (t, *J* = 7.7 Hz, 4 H), 1.47 (q, *J* = 5.5 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.0, 145.3, 48.8, 45.2, 42.6, 25.7, 25.1, 23.8.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_8H_{13}N_5O$: 195.11; found [M – H]$^+$: 194.08.

**1-Morpholino-2-(1H-tetrazol-1-yl)ethan-1-one (4o)**

The product was obtained using GP C, 1 mmol scale; yield: 0.169 g (86%); white solid; mp 133–135 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.30 (s, 1 H), 5.65 (s, 2 H), 3.66 (t, *J* = 4.6 Hz, 2 H), 3.59 (t, *J* = 4.7 Hz, 2 H), 3.52 (t, *J* = 4.9 Hz, 2 H), 3.46 (t, *J* = 5.0 Hz, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.7, 145.3, 145.3, 65.9, 65.8, 48.7, 44.7, 42.0.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_7H_{11}N_5O$: 197.09; found [M – H]$^+$: 196.31.

**1-(4-Benzylpiperazin-1-yl)-2-(1H-tetrazol-1-yl)ethan-1-one (4p)**

The product was obtained using GP C, 1 mmol scale; yield: 0.207 g (72%); white solid; mp 92–94 °C.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.30 (s, 1 H), 7.36–7.26 (m, 5 H), 5.63 (s, 2 H), 3.52 (t, *J* = 8.4 Hz, 4 H), 3.47 (s, 2 H), 2.46 (s, 2 H), 2.36 (s, 2 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 163.3, 145.3, 128.9, 128.3, 127.1, 61.8, 52.4, 51.9, 48.7, 44.2, 41.7.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{18}N_6O$: 286.15; found [M + H]$^+$: 287.16.

**N-(4-Chlorobenzyl)-4-methyl-2-(1H-tetrazol-1-yl)pentanamide (4q)**

The product was obtained using GP C, 1 mmol scale; yield: 0.228 g (74%); clear liquid.

$^1$H NMR (500 MHz, DMSO-$d_6$): δ = 9.63 (s, 1 H), 9.10 (t, *J* = 5.7 Hz, 1 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 5.58–5.54 (m, 1 H), 4.30 (s, 2 H), 2.19–2.12 (m, 1 H), 1.99–1.92 (m, 1 H), 1.25–1.15 (m, 1 H), 0.88 (d, *J* = 5.2 Hz, 3 H), 0.86 (d, *J* = 5.2 Hz, 3 H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$): δ = 167.9, 144.1, 144.1, 138.0, 132.1, 129.7, 128.8, 60.4, 55.4, 42.4, 24.9, 22.8, 21.7.

SFC-MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{18}ClN_5O$: 307.12; found [M – H]$^+$: 305.92.

**4-Methyl-2-(1*H*-tetrazol-1-yl)-*N*-(thiophen-2-ylmethyl)pentanamide (4r)**

The product was obtained using GP C, 1 mmol scale; yield: 0.193 g (69%); clear liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 7.58 (t, *J* = 5.7 Hz, 1 H), 7.21–7.15 (m, 1 H), 6.96–6.86 (m, 2 H), 5.48 (t, *J* = 7.9 Hz, 1 H), 4.68–4.51 (m, 2 H), 2.05 (t, *J* = 7.5 Hz, 2 H), 1.37–1.28 (m, 1 H), 0.89 (d, *J* = 4.2 Hz, 3 H), 0.87 (d, *J* = 4.2 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 167.2, 142.2, 139.6, 127.1, 126.5, 125.6, 61.3, 42.1, 38.8, 24.7, 22.5, 21.6.

SFC-MS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{17}N_5OS$: 279.12; found $[M - H]^+$: 278.33.

## Acknowledgment

The research leading to these results has received support from the NIH (1R01GM097082) and from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115489. These resources are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution. Y.W. acknowledges a CSC stipendship.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562435.

## References

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(2) Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. *Nucleic Acids Res.* **2000**, *28*, 235.

(3) (a) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *23*, 2699. (b) Matta, C. F.; Arabi, A. A.; Weaver, D. F. *Eur. J. Med. Chem.* **2010**, *45*, 1868.

(4) Murray, C. W.; Rees, D. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 488.

(5) Hoekstra, W. J.; Hargrove, T. Y.; Wawrzak, Z.; da Gama Jaen Batista, D.; da Silva Cristiane, F.; Nefertiti, A. S. G.; Rachakonda, G.; Schotzinger, R. J.; Villalta, F.; Soeiro, M. C.; Lepesheva, G. I. *Antimicrob. Agents Chemother.* **2016**, *60*, 1058.

(6) Chen, Y.; Shoichet, B. K. *Nat. Chem. Biol.* **2009**, *5*, 158.

(7) (a) Wang, K.; Nguyen, K.; Huang, Y.; Dömling, A. *ACS. Comb. Sci.* **2009**, *11*, 920. (b) Dömling, A.; Beck, B.; Fuchs, T.; Yazbak, A. *ACS Comb. Sci.* **2006**, *8*, 872.

(8) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908.

(9) (a) Mani, P.; Singh, A. K.; Awasthi, S. K. *Tetrahedron Lett.* **2014**, *55*, 1879. (b) Gawande, S. D.; Raihan, M. J.; Zanwar, M.; Kavala, V.; Janreddy, D.; Kuo, C. W.; Chen, M. L.; Kuo, T. S.; Yao, C. F. *Tetrahedron* **2013**, *69*, 1841. (c) Gawande, S. D.; Raihan, M. J.; Zanwar, M. R.; Kavala, V.; Janreddy, D.; Kuo, C. W.; Chen, M. L.; Kuo, T. S.; Yao, C. F. *Tetrahedron* **2013**, *69*, 1841. (d) Das, B.; Reddy, C. R.; Kumar, D. N.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, 391. (e) Yoneyama, H.; Usami, Y.; Komeda, S.; Harusawa, S. *Synthesis* **2013**, *45*, 1051. (f) Roh, J.; Artamonova, T. V.; Vávrová, K.; Koldobskii, G. I.; Hrabálek, A. *Synthesis* **2009**, 2175. (g) Vorona, S.; Artamonova, T.; Zevatskii, Y.; Myznikov, L. *Synthesis* **2014**, *46*, 781. (h) Cantillo, D.; Gutmann, B.; Kappe, C. O. *J. Am. Chem. Soc.* **2011**, *133*, 4465.

(10) Kappe, C. O.; Stadler, A.; Dallinger, D. *Microwaves in Organic and Medicinal Chemistry*, In *Methods and Principles in Medicinal Chemistry*; Vol. 52; Mannhold, R.; Kubinyi, H.; Folkers, G., Eds.; Wiley-VCH: Weinheim, **2012**, 487.

(11) Oliveri-Mandala, E.; Alagna, B. *Gazz. Chim. Ital.* **1910**, *40 (II)*, 441.