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Patil, Pravin; Zhang, Ji; Kurpiewska, Katarzyna; Kalinowska-Tłuścik, Justyna; Dömling, Alexander

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Hydrazine in the Ugi Tetrazole Reaction

Pravin Patil^{a,◇}Ji Zhang^{a,◇}Katarzyna Kurpiewska^bJustyna Kalinowska-Tłuścik^bAlexander Dömling^{*a}

^a University of Groningen, Department of Drug Design,
A. Deusinglaan 1, 9713 AV Groningen, The Netherlands
a.s.s.domling@rug.nl

^b Jagiellonian University, Faculty of Chemistry, Department of
Crystal Chemistry and Crystal Physics, Biocrystallography
Group, Ingardena 3, 30-060 Kraków, Poland

◇ The authors contributed equally to the work.

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Abstract We describe the hitherto unknown use of *N*-Boc-protected hydrazine in the Ugi tetrazole reaction to access a library of highly substituted 5-(hydrazinomethyl)-1-methyl-1*H*-tetrazoles. The reaction is very versatile and good to high yielding. A one-pot, two-step procedure is given.

Key words hydrazine, isocyanides, tetrazoles, multicomponent reaction, Ugi reaction

The Ugi multicomponent reaction (MCR) is an important reaction for the generation of molecular diversity and, together with post-condensation reactions, allows for near infinite access to compounds based on hundreds of scaffolds.¹ In the European Lead Factory project (IMI ELF) more than 100,000 small-molecular-weight compounds have been currently synthesized to complement 400,000 industry-derived compounds for a screening library.² Many of the scaffolds are based on modern MCRs.^{2b,3} While it is well-established that multiple acid components are responsible for the scaffold diversity of the Ugi MCR (e.g., azide, carboxylic acid, carbonic acid, phenol, just to name a few), the diversity of amine-like inputs has been much less elaborated. In the classical Ugi 4CR, a wide variety of primary amines can be used successfully, but ammonia already gives poor to no yield.⁴ Other amine-like components that have been reported sporadically, but with mixed or poor yields, are hydroxylamine, *N*-acylated hydrazine, *N*-sulfonated hydrazine and unprotected hydrazine.^{4a,5} Based on the poor knowledge of hydrazine in Ugi reactions, we report here our findings of the first successful use of mono-Boc-protected hydrazine in the Ugi tetrazole synthesis to yield α-(hydrazinomethyl)tetrazoles. Although hydrazine derivatives are well-

known in nature and have been associated with multiple biological activities they are, perhaps wrongly, a nonprivileged structural element in medicinal and biological chemistry.⁶ Query of the protein data bank (PDB) for the hydrazine substructure surprisingly reveals 389 structure hits (as of 25-11-2015). Analysis of the receptor hydrazine–ligand substructure interactions reveals that the major interaction patterns include hydrogen-bond donor–acceptor interactions, metal complexation, charge–charge interactions and cation–π–aromatic interactions (Figure 1).

Figure 1 Examples of characteristic receptor–hydrazine binding modes found in the PDB. A: Azasugar in complex with galactocerebrosidase (PDB ID: 4UF1) exhibiting a bifurcated charge–charge interaction with two Glu and a hydrogen bonding with a water molecule; B: a low-molecular-weight fragment bound to hepatitis C virus polymerase NS5B (PDB ID: 4IH5) exhibiting two hydrogen contacts with two water molecules, one bridging to an adjacent Tyr; C: schematic depiction of hydrazine–receptor binding modes involving metal, cation–aromatic, charge–charge and hydrogen-bonding interactions.

To promote hydrazines, we introduce here a simple, high yielding and diverse synthetic access to the large chemical space of 5-(hydrazinomethyl)-1-methyl-1*H*-tetrazoles with two points of diversity. We envisioned that substituted 5-(hydrazinomethyl)-1-methyl-1*H*-tetrazoles could be accessed from the Ugi tetrazole reaction using *tert*-butyl carbazate (Boc-hydrazine, **1**), aldehydes or ketones **2**, isocyanides **3** and trimethylsilyl azide (TMS azide, **4**), and subsequent deprotection via a two-step procedure (Scheme 1). In order to test the scope and limitations of the reaction, various aldehydes, ketones and isocyanides were used.

The *tert*-butoxycarbonyl (Boc) group is a protecting group widely used in the synthesis of proteins, peptides and natural products. Initially, it was not clear if mono-Boc-protected hydrazine would work well in the Ugi tetrazole reaction. We first performed this reaction in methanol at room temperature for 18 to 24 hours, and were pleased to find that most starting materials, in fact, can generate the expected product (see Table 2). However, we always observed and isolated various degrees of Schiff base (hydrazine) upon workup of the Ugi tetrazole reaction. This means that the conversion is not quantitative, although the yields are acceptable (see Table 2, without ZnCl₂). Mechanistically, the Schiff base is a key intermediate in all Ugi-type multicomponent reactions and is formed in the first step (Scheme 2).^{1e} Upon Schiff base activation/protonation, the carbanion of the isocyanide attacks the imine to form the intermediate nitrilium ion, then followed by the addi-

tion of azide ion; in this reaction, the last step is an irreversible sigmatropic rearrangement to afford the Ugi tetrazole product (Scheme 2).

In other words, since the bottleneck is Schiff base formation, the conversion could be improved by increasing the electrophilicity of the Schiff base. This can be accomplished by the addition of a catalytic amount of a Lewis acid. Lewis acids such as AlCl₃, InCl₃, ZnCl₂ and TiCl₄, just to name a few, are known to activate the intermediate deactivated Schiff base, thus promoting the addition of isocyanide to the Schiff base.⁷

In order to find a suitable Lewis acid to activate the Schiff base, we screened several reagents in order to promote the reaction towards example **5j** (Scheme 3, Table 1). Apart from Schiff base activation, a second issue was the protecting group stability towards the Lewis acid and the reaction conditions. The reaction of Boc-hydrazine (**1**) with isovaleraldehyde (**2j**), phenethyl isocyanide (**3j**) and TMS azide (**4**) was performed in methanol (1 M) at room temperature for 24 hours with five different Lewis acids (10 mol%) (Table 1). The results show that the addition of ZnCl₂ and Zn(OTf)₂ increases the yield, while the other three Lewis acids gave lower yields than the 39% yield of **5j** obtained without the addition of a Lewis acid (see Table 2). We speculate that the addition of these three Lewis acids may lead to side reactions (e.g., aldol-type condensations or decomposition).

Based on this reagent screening, we decided to use ZnCl₂ for all other examples as well (Table 2). As expected, the reaction yielded the products in good to very good yields in most cases. Further to our work with the 11 compounds **5a–k**, six new examples were added to the list (Table 2).

Table 1 Yield Screening of **5j** with Five Different Lewis Acids

Lewis acid (10 mol%)	Yield (%) of 5j
ZnCl ₂	63
ZrCl ₄	24
Zn(OTf) ₂	51
BF ₃ ·OEt ₂	34
TiCl ₄	23

Relative to the uncatalyzed reactions, the ZnCl₂-promoted reactions led to an average yield improvement of 20%. The highest yield achieved was 88% for **5f**.

In general, the Ugi tetrazole reaction works well with aromatic and aliphatic aldehydes and ketones.^{1a} The results summarized in Table 2 show that various ketones and aldehydes generated the corresponding products in good yield. However, we also found that benzaldehyde did not give a result. This is presumably due to the higher stability of the Schiff base produced from Boc-hydrazine and benzaldehyde. Cyclohexanone gave a very positive result, even without the ZnCl₂ catalyst: the reaction yielded the Ugi intermediate **5a** in slightly higher yield than upon addition of ZnCl₂.

In the case of isovaleraldehyde, the use of ZnCl₂ also did not increase the yield; rather, there was a slight drop in the yield of product **5d**. By comparing entries **5o**, **5p** and **5q**, derived from the same isocyanide, it appears that reaction with a more electron-rich aldehyde or ketone is higher yielding. All of the employed isocyanides worked well, even the bulky isocyanides such as cyclohexyl isocyanide and *tert*-butyl isocyanide, despite the potential steric hindrance due to the bulkiness of the three components, oxo, Boc-hydrazine and isocyanide. Cyclohexyl isocyanide gave a better yield than benzyl isocyanide, with and without ZnCl₂, for the examples **5e** and **5f**. Deprotection of the Ugi tetrazole intermediates **5** to give products **6** was performed under acidic conditions (methanolic HCl, r.t., 24 to 48 h) giving good to very good yields. After reaction completion (disappearance of **5** on TLC), the products were obtained as their HCl salts upon evaporation of the solvent. As the purity of the products was excellent in all cases, as confirmed by NMR spectroscopy and SFC-MS, we concluded that there is no need for further purification. Next, we grew crystals of **5a**, **5k** and **5n** to investigate the structure of representative compounds in the solid state (Figure 2 and Supporting Information).⁸

Table 2 Structures and Yields of *N*-Boc-Protected Intermediates **5** and *N*-Deprotected Final Products **6**

2	3	Yield (%) of 5	Yield (%) of 6			
			Without ZnCl ₂	With ZnCl ₂
5a	70	69	6a	80
5b	55	64	6b	86
5c	46	71	6c	71
5d	35	34	6d	65
5e	44	68	6e	77
5f	46	88	6f	91
5g	42	54	6g	80

Table 2 (continued)

2	3	Yield (%) of 5	Yield (%) of 6			
			Without ZnCl ₂	With ZnCl ₂
5h	37	71	6h	82
5i	29	77	6i	87
5j	39	63	6j	66
5k	38	45	6k	82
5l	–	51	6l	82
5m	–	40	6m	99
5n	–	74	7	86
5o	–	66	6o	79
5p	–	42	6p	83
5q	–	37	6q	85

Figure 2 Compound **5n** in the solid state rendered as a stereo picture. The crystal contacts are dominated by hydrophobic and hydrogen bondings (yellow dotted lines). Hydrazine-N1 forms a hydrogen bond with N4 of an adjacent tetrazole moiety (2.3 Å); hydrazine-N2 forms an intramolecular hydrogen bond contact (2.3 Å) with the carbonyl-O of the Leu methyl ester of the former isocyanide.

Last, but not least, as a potential scaffold extension, we cyclized **5n** to access the interesting tetrazolotriazepine ring system **7**, as shown in Scheme 4.

Scheme 4 Deprotection of **5n** and subsequent intramolecular cyclization

In conclusion, we have prepared 5-(hydrazinomethyl)-1-methyl-1*H*-tetrazoles via two steps involving an Ugi tetrazole reaction and Boc deprotection. The reaction conditions are mild, and we have demonstrated the application of Boc-hydrazine in the Ugi tetrazole synthesis. Currently we are investigating the biological activity of the new hydrazine compounds and their use in the further synthesis of complex heterocycles, results of which will be reported in due course.

NMR spectra were recorded on a Bruker Avance 500 spectrometer [¹H NMR (500 MHz), ¹³C NMR (126 MHz)]. Chemical shifts for ¹H NMR are reported as δ values and coupling constants are given in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, m = multiplet. Chemical shifts for ¹³C NMR are reported in ppm relative to the solvent peak. TLC was performed on Fluka precoated silica gel plates (0.20-mm thick, particle size 25 μ m). Flash chromatography was performed on a Teledyne ISCO CombiFlash Rf system using RediSep Rf normal-phase silica flash columns (silica gel 60 Å, 230–400 mesh) and on a Reveleris® X2 flash chromatography system 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.

Compounds 5 by the Zinc Chloride Promoted Ugi Tetrazole Reaction; General Procedure A

To a stirred solution of oxo compound **2** (1 mmol) in MeOH (1 M) were added successively *tert*-butyl carbazate (**1**, 1 mmol), trimethylsilyl azide (**4**, 1 mmol), isocyanide **3** (1 mmol) and ZnCl₂ (10 mol%). The resulting mixture was stirred at r.t. for 18 to 24 h. The solvent was removed under reduced pressure and the residue was purified using flash chromatography to obtain the Ugi product.

Compounds 6, 7 by the Deprotection of Compounds 5; General Procedure B

A solution of Ugi tetrazole product **5** (1 mmol) in 2 M methanolic hydrochloric acid (5 mL) was stirred at r.t. for 24 to 48 h. The solvent was evaporated to obtain the crude, which was then washed with Et₂O (10 mL) to afford the pure product.

tert-Butyl 2-(1-(1-Phenethyl-1*H*-tetrazol-5-yl)cyclohexyl)hydrazine-1-carboxylate (**5a**)

Obtained using procedure A on a 1-mmol scale; yield: 0.265 g (69%); white solid; mp 119–121 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.28–7.25 (m, 2 H), 7.23–7.20 (m, 1 H), 7.15 (d, J = 7.4 Hz, 2 H), 4.95 (br s, 1 H), 4.89 (t, J = 7.1 Hz, 2 H), 4.09 (br s, 1 H), 3.38 (t, J = 7.1 Hz, 2 H), 2.10–2.05 (m, 2 H), 1.70–1.64 (m, 4 H), 1.51–1.39 (m, 4 H), 1.36 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.9, 156.6, 137.1, 129.0, 128.8, 127.3, 81.7, 59.4, 50.5, 35.7, 33.3, 28.2, 25.2, 21.9.

MS (ESI): m/z calcd for C₂₀H₃₀N₆O₂ [M]⁺: 386.24; found [M – H]⁺: 385.19; found [M + Na]⁺: 409.24.

tert-Butyl 2-(Cyclohexyl(1-phenethyl-1*H*-tetrazol-5-yl)methyl)hydrazine-1-carboxylate (**5b**)

Obtained using procedure A on a 1-mmol scale; yield: 0.258 g (64%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.30–7.23 (m, 3 H), 7.12 (d, J = 7.1 Hz, 2 H), 5.27 (s, 1 H), 4.78–4.72 (m, 1 H), 4.57–4.52 (m, 1 H), 4.35–4.12 (m, 2 H), 3.42–3.36 (m, 1 H), 3.25–3.20 (m, 1 H), 1.97 (d, J = 7.4 Hz, 1 H), 1.76 (d, J = 13.5 Hz, 1 H), 1.72–1.66 (m, 1 H), 1.62–1.60 (m, 2 H), 1.38 (s, 9 H), 1.21–1.16 (m, 1 H), 1.11–1.05 (m, 4 H), 0.87–0.82 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.5, 154.6, 136.7, 128.9, 127.3, 81.0, 61.0, 49.0, 40.0, 35.8, 29.8, 29.3, 28.2, 25.9, 25.6.

MS (ESI): m/z calcd for C₂₁H₃₂N₆O₂ [M]⁺: 400.26; found [M – H]⁺: 399.08; found [M + Na]⁺: 423.27.

tert-Butyl 2-(1-(1-Benzyl-1*H*-tetrazol-5-yl)-2-methylpropyl)hydrazine-1-carboxylate (**5c**)

Obtained using procedure A on a 1-mmol scale; yield: 0.245 g (71%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.37–7.31 (m, 3 H), 7.25–7.24 (m, 2 H), 6.20 (s, 1 H), 5.78 (d, J = 15.4 Hz, 1 H), 5.56 (d, J = 15.4 Hz, 1 H), 4.42 (br s, 1 H), 4.22 (br s, 1 H), 2.07–2.00 (m, 1 H), 1.40 (s, 9 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.58 (d, J = 6.7 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.7, 154.9, 133.9, 129.1, 128.8, 127.6, 81.0, 61.4, 51.1, 30.6, 28.2, 19.2, 19.1.

MS (ESI): m/z calcd for C₁₇H₂₆N₆O₂ [M]⁺: 346.21; found [M – H]⁺: 345.27; found [M + Na]⁺: 369.28.

tert-Butyl 2-(1-(1-Benzyl-1*H*-tetrazol-5-yl)-3-methylbutyl)hydrazine-1-carboxylate (**5d**)

Obtained using procedure A on a 1-mmol scale; yield: 0.122 g (34%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.34 (m, 3 H), 7.24–7.22 (m, 2 H), 5.87 (s, 1 H), 5.81 (d, J = 15.4 Hz, 1 H), 5.60 (d, J = 15.4 Hz, 1 H), 4.54 (br s, 1 H), 4.20 (br s, 1 H), 1.61–1.54 (m, 1 H), 1.52–1.45 (m, 1 H), 1.41 (s, 9 H), 1.38–1.29 (m, 1 H), 0.74 (d, J = 6.7 Hz, 3 H), 0.72 (d, J = 6.7 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.6, 155.2, 134.0, 129.2, 128.8, 127.5, 81.2, 53.9, 51.2, 40.7, 28.2, 24.7, 22.3, 22.2.

MS (ESI): m/z calcd for C₁₈H₂₈N₆O₂ [M]⁺: 360.23; found [M – H]⁺: 359.12; found [M + Na]⁺: 383.18.

tert-Butyl 2-((1-Benzyl-1*H*-tetrazol-5-yl)(cyclohexyl)methyl)hydrazine-1-carboxylate (**5e**)

Obtained using procedure A on a 1-mmol scale; yield: 0.264 g (68%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.33 (m, 3 H), 7.24–7.23 (m, 2 H), 5.77 (d, J = 15.3 Hz, 1 H), 5.76 (br s, 1 H), 5.59 (d, J = 15.3 Hz, 1 H), 4.38 (br s, 1 H), 4.28 (d, J = 7.3 Hz, 1 H), 1.91 (d, J = 9.8 Hz, 1 H), 1.71–1.63 (m, 2 H), 1.57–1.48 (m, 2 H), 1.40 (s, 9 H), 1.12–1.00 (m, 4 H), 0.92–0.85 (m, 1 H), 0.78–0.70 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.5, 154.7, 134.1, 129.1, 128.8, 127.6, 81.2, 61.1, 51.2, 39.8, 29.6, 29.4, 28.2, 25.9, 25.6, 25.5.

MS (ESI): m/z calcd for C₂₀H₃₀N₆O₂ [M]⁺: 386.24; found [M – H]⁺: 385.01; found [M + Na]⁺: 409.20.

tert-Butyl 2-(Cyclohexyl(1-cyclohexyl-1H-tetrazol-5-yl)methyl)hydrazinecarboxylate (5f)

Obtained using procedure A on a 1-mmol scale; yield: 0.334 g (88%); white solid; mp 124–126 °C.

¹H NMR (500 MHz, CDCl₃): δ = 5.89 (br s, 1 H), 4.46 (br s, 1 H), 4.35–4.28 (m, 2 H), 2.14–2.06 (m, 2 H), 2.02–1.88 (m, 6 H), 1.82–1.76 (m, 3 H), 1.66 (d, *J* = 9.4 Hz, 3 H), 1.41 (s, 9 H), 1.39–1.13 (m, 6 H), 1.01–0.94 (m, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.5, 153.9, 81.1, 60.4, 57.9, 40.5, 33.4, 33.0, 29.9, 29.4, 28.3, 26.0, 25.7, 25.4, 24.8.

MS (ESI): *m/z* calcd for C₁₉H₃₄N₆O₂ [M]⁺: 378.27; found [M – H]⁺: 377.05; found [M + Na]⁺: 401.28.

tert-Butyl 2-(1-(1-tert-Butyl-1H-tetrazol-5-yl)-3-phenylpropyl)hydrazine-1-carboxylate (5g)

Obtained using procedure A on a 1-mmol scale; yield: 0.203 g (54%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.30–7.27 (m, 2 H), 7.24–7.18 (m, 3 H), 6.29 (s, 1 H), 4.66 (br s, 1 H), 4.46 (br s, 1 H), 2.89–2.77 (m, 2 H), 2.31–2.23 (m, 1 H), 2.07–2.01 (m, 1 H), 1.58 (s, 9 H), 1.41 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.3, 155.9, 140.6, 128.7, 128.6, 126.3, 80.8, 61.3, 55.1, 35.3, 31.9, 30.0, 28.2.

MS (ESI): *m/z* calcd for C₁₉H₃₀N₆O₂ [M]⁺: 374.24; found [M – H]⁺: 373.10; found [M + Na]⁺: 397.29.

tert-Butyl 2-(1-(1-Benzyl-1H-tetrazol-5-yl)-3-phenylpropyl)hydrazine-1-carboxylate (5h)

Obtained using procedure A on a 1-mmol scale; yield: 0.289 g (71%); white solid; mp 72–73 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.34–7.33 (m, 3 H), 7.24–7.21 (m, 2 H), 7.18–7.15 (m, 3 H), 6.97 (d, *J* = 7.3 Hz, 2 H), 5.97 (br s, 1 H), 5.63 (d, *J* = 15.3 Hz, 1 H), 5.54 (d, *J* = 15.3 Hz, 1 H), 4.43 (s, 1 H), 4.25 (br s, 1 H), 2.46–2.43 (m, 2 H), 2.10–1.95 (m, 2 H), 1.41 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.6, 154.8, 140.3, 133.8, 129.2, 128.8, 128.5, 128.3, 127.6, 126.2, 81.2, 54.9, 51.1, 33.4, 31.6, 28.2.

MS (ESI): *m/z* calcd for C₂₂H₂₈N₆O₂ [M]⁺: 408.23; found [M – H]⁺: 407.43; found [M + Na]⁺: 431.22.

tert-Butyl 2-(2-Methyl-1-(1-phenethyl-1H-tetrazol-5-yl)propyl)hydrazine-1-carboxylate (5i)

Obtained using procedure A on a 1-mmol scale; yield: 0.279 g (77%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.30–7.24 (m, 3 H), 7.12 (d, *J* = 7.1 Hz, 2 H), 5.33 (s, 1 H), 4.78–4.72 (m, 1 H), 4.58–4.53 (m, 1 H), 4.23 (br s, 1 H), 4.11 (br s, 1 H), 3.42–3.36 (m, 1 H), 3.26–3.21 (m, 1 H), 2.01–1.97 (m, 1 H), 1.38 (s, 9 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 0.69 (d, *J* = 6.7 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.5, 154.6, 136.7, 128.9, 127.4, 81.0, 61.7, 49.1, 35.8, 30.8, 28.2, 19.3, 19.2.

MS (ESI): *m/z* calcd for C₁₈H₂₈N₆O₂ [M]⁺: 360.23; found [M + Na]⁺: 383.31.

tert-Butyl 2-(3-Methyl-1-(1-phenethyl-1H-tetrazol-5-yl)butyl)hydrazine-1-carboxylate (5j)

Obtained using procedure A on a 2-mmol scale; yield: 0.47 g (63%); white solid; mp 85–86 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.29–7.23 (m, 3 H), 7.07 (d, *J* = 7.0 Hz, 2 H), 5.38 (d, *J* = 2.9 Hz, 1 H), 4.77–4.71 (m, 1 H), 4.60–4.57 (m, 1 H), 4.37 (br s, 1 H), 4.03 (br s, 1 H), 3.41–3.35 (m, 1 H), 3.28–3.22 (m, 1 H), 1.60–1.58 (m, 1 H), 1.53–1.48 (m, 1 H), 1.39 (m, 9 H), 1.37–1.34 (m, 1 H), 0.88 (d, *J* = 2.7 Hz, 3 H), 0.86 (d, *J* = 2.7 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 158.0, 155.4, 136.7, 129.0, 128.9, 127.4, 81.0, 53.7, 49.0, 40.7, 35.9, 28.2, 24.8, 22.7, 22.2.

MS (ESI): *m/z* calcd for C₁₉H₃₀N₆O₂ [M]⁺: 374.24; found [M – H]⁺: 373.47; found [M + Na]⁺: 397.22.

tert-Butyl 2-(1-(1-Benzyl-1H-tetrazol-5-yl)-2-phenylethyl)hydrazine-1-carboxylate (5k)

Obtained using procedure A on a 1-mmol scale; yield: 0.177 g (45%); yellow solid; mp 126–128 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.30–7.28 (m, 3 H), 7.22–7.20 (m, 3 H), 7.03–7.02 (m, 2 H), 6.96–6.95 (m, 2 H), 5.87 (br s, 1 H), 5.29 (d, *J* = 15.4 Hz, 1 H), 5.18 (d, *J* = 15.2 Hz, 1 H), 4.68 (br s, 1 H), 4.32 (br s, 1 H), 3.15–3.11 (m, 1 H), 3.05–3.01 (m, 1 H), 1.38 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.5, 154.8, 135.6, 133.6, 129.2, 129.1, 128.8, 128.7, 127.4, 127.2, 81.1, 56.6, 50.6, 38.8, 28.2.

MS (ESI): *m/z* calcd for C₂₁H₂₆N₆O₂ [M]⁺: 394.21; found [M – H]⁺: 393.46; found [M + Na]⁺: 417.24.

Benzyl 4-(2-(tert-Butoxycarbonyl)hydrazino)-4-(1-(2-(1H-indol-3-yl)ethyl)-1H-tetrazol-5-yl)piperidine-1-carboxylate (5l)

Obtained using procedure A on a 2-mmol scale; yield: 0.57 g (51%); colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 8.06 (br s, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.36 (dd, *J* = 8.2, 2.1 Hz, 2 H), 7.34–7.28 (m, 4 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 6.81 (d, *J* = 2.1 Hz, 1 H), 5.08 (d, *J* = 4.2 Hz, 2 H), 5.00 (br s, 1 H), 4.89–4.75 (m, 2 H), 3.93 (d, *J* = 3.9 Hz, 1 H), 3.68–3.59 (m, 2 H), 3.56 (d, *J* = 5.9 Hz, 2 H), 3.30–2.90 (m, 2 H), 2.05–1.75 (m, 2 H), 1.60–1.54 (m, 2 H), 1.34 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.7, 156.1, 155.0, 136.6, 136.0, 128.5, 128.1, 127.9, 126.5, 123.0, 122.6, 120.1, 118.0, 111.6, 110.7, 81.0, 67.2, 58.3, 49.7, 40.1, 32.7, 28.1, 25.4.

MS (ESI): *m/z* calcd for C₂₉H₃₆N₈O₄ [M]⁺: 560.29; found [M + Na]⁺: 583.42.

tert-Butyl 2-(1-Benzyl-4-(1-(4-chlorobenzyl)-1H-tetrazol-5-yl)piperidin-4-yl)hydrazine-1-carboxylate (5m)

Obtained using procedure A on a 1-mmol scale; yield: 0.199 g (40%); white solid; mp 181–183 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.32–7.22 (m, 7 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 5.94 (s, 2 H), 5.70 (s, 1 H), 4.16 (s, 1 H), 3.45 (s, 2 H), 2.59 (dd, *J* = 9.5, 5.8 Hz, 2 H), 2.36 (s, 2 H), 2.24 (dd, *J* = 11.5, 5.5 Hz, 2 H), 1.92–1.88 (m, 2 H), 1.35 (s, 9 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.4, 138.3, 134.5, 133.2, 129.2, 129.0, 128.6, 128.3, 127.1, 81.1, 62.7, 58.0, 51.6, 49.3, 33.0, 28.1.

MS (ESI): *m/z* calcd for C₂₅H₃₂ClN₇O₂ [M]⁺: 497.23; found [M + H]⁺: 498.38.

tert-Butyl 2-(2-(1-(1-Methoxy-4-methyl-1-oxopent-2-yl)-1H-tetrazol-5-yl)propan-2-yl)hydrazine-1-carboxylate (5n)

Obtained using procedure A on a 1-mmol scale; yield: 0.274 g (74%); white solid; mp 115–117 °C.

^1H NMR (500 MHz, CDCl_3): δ = 6.0 (br s, 1 H), 5.90 (dd, J = 9.9, 5.2 Hz, 1 H), 4.21 (br s, 1 H), 3.79 (s, 3 H), 2.45 (ddd, J = 14.6, 10.0, 5.3 Hz, 1 H), 2.22 (ddd, J = 14.6, 8.5, 5.3 Hz, 1 H), 1.71 (s, 3 H), 1.57–1.55 (m, 1 H), 1.54 (s, 3 H), 1.43 (s, 9 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 171.6, 170.2, 158.4, 81.0, 60.2, 57.7, 53.3, 40.0, 28.2, 25.6, 24.9, 24.3, 22.7, 21.8.

MS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{30}\text{N}_6\text{O}_4$ $[\text{M}]^+$: 370.23; found $[\text{M} + \text{Na}]^+$: 393.32.

tert-Butyl 2-(2-(1-(4-Chlorobenzyl)-1H-tetrazol-5-yl)butan-2-yl)hydrazine-1-carboxylate (5o)

Obtained using procedure A on a 1-mmol scale; yield: 0.25 g (66%); colorless oil.

^1H NMR (500 MHz, CDCl_3): δ = 7.34 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H), 6.01 (d, J = 15.5 Hz, 1 H), 5.89 (d, J = 15.5 Hz, 1 H), 5.56 (br s, 1 H), 4.09 (d, J = 2.3 Hz, 1 H), 1.85–1.79 (m, 1 H), 1.77–1.69 (m, 1 H), 1.58 (s, 3 H), 1.39 (s, 9 H), 0.69 (t, J = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 156.8, 156.7, 134.5, 133.2, 129.1, 128.9, 81.0, 60.8, 51.6, 30.7, 28.2, 21.4, 8.1.

MS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{25}\text{ClN}_6\text{O}_2$ $[\text{M}]^+$: 380.17; found $[\text{M} - \text{H}]^+$: 379.08; found $[\text{M} + \text{Na}]^+$: 403.20.

tert-Butyl 2-(1-Chloro-2-(1-(4-chlorobenzyl)-1H-tetrazol-5-yl)propan-2-yl)hydrazine-1-carboxylate (5p)

Obtained using procedure A on a 2-mmol scale; yield: 0.335 g (42%); white solid; mp 120–121 °C.

^1H NMR (500 MHz, CDCl_3): δ = 7.34 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H), 6.35 (d, J = 15.7 Hz, 1 H), 5.96 (d, J = 15.7 Hz, 1 H), 5.79 (d, J = 1.7 Hz, 1 H), 4.33 (d, J = 2.2 Hz, 1 H), 4.30 (d, J = 12.1 Hz, 1 H), 4.05 (d, J = 12.1 Hz, 1 H), 1.39 (s, 9 H), 1.35 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 156.0, 154.8, 134.5, 133.3, 129.2, 129.0, 81.3, 59.5, 51.8, 48.4, 28.1, 21.4.

MS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{Cl}_2\text{N}_6\text{O}_2$ $[\text{M}]^+$: 400.12; found $[\text{M} + \text{Na}]^+$: 423.06.

tert-Butyl 2-(2-Chloro-1-(1-(4-chlorobenzyl)-1H-tetrazol-5-yl)ethyl)hydrazine-1-carboxylate (5q)

Obtained using procedure A on a 2-mmol scale; yield: 0.283 g (37%); yellow oil.

^1H NMR (500 MHz, CDCl_3): δ = 7.35 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H), 6.03 (br s, 1 H), 5.83–5.72 (m, 2 H), 4.56–4.55 (m, 1 H), 4.53–4.49 (m, 1 H), 3.95–3.87 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 156.6, 152.3, 135.1, 131.9, 129.4, 129.2, 81.8, 56.4, 50.7, 42.9, 28.2.

MS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{N}_6\text{O}_2$ $[\text{M}]^+$: 386.10; found $[\text{M} - \text{H}]^+$: 385.23; found $[\text{M} + \text{Na}]^+$: 409.18.

5-(1-Hydrazinocyclohexyl)-1-phenethyl-1H-tetrazole (6a)

Obtained using procedure B on a 1-mmol scale; yield: 0.257 g (80%); white solid; mp 152–153 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 9.29 (br s, 2 H), 7.33–7.30 (m, 2 H), 7.27–7.24 (m, 3 H), 6.22 (br s, 1 H), 4.80–4.74 (m, 2 H), 3.27–3.22 (m, 2 H), 2.04–2.00 (m, 2 H), 1.76–1.73 (m, 2 H), 1.63–1.59 (m, 2 H), 1.44–1.30 (m, 4 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 154.2, 135.5, 127.1, 127.0, 125.3, 55.8, 49.0, 33.9, 31.2, 22.9, 19.5.

MS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{22}\text{N}_6$ $[\text{M}]^+$: 286.19; found $[\text{M} + \text{Na}]^+$: 309.26.

5-(Cyclohexyl(hydrazino)methyl)-1-phenethyl-1H-tetrazole (6b)

Obtained using procedure B on a 1-mmol scale; yield: 0.291 g (86%); white semi-solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 9.38 (br s, 2 H), 7.34–7.24 (m, 5 H), 5.97 (br s, 1 H), 4.75–4.62 (m, 2 H), 4.42 (d, J = 6.4 Hz, 1 H), 3.41–3.19 (m, 2 H), 1.88 (d, J = 12.6 Hz, 1 H), 1.67–1.55 (m, 4 H), 1.13–1.02 (m, 4 H), 0.91–0.79 (m, 2 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 154.9, 138.4, 130.1, 129.9, 128.3, 59.0, 50.4, 41.1, 36.4, 30.3, 29.7, 26.9, 26.8, 26.6.

MS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}_6$ $[\text{M}]^+$: 300.21; found $[\text{M} + \text{Na}]^+$: 323.27.

1-Benzyl-5-(1-hydrazino-2-methylpropyl)-1H-tetrazole (6c)

Obtained using procedure B on a 1-mmol scale; yield: 0.201 g (71%); yellow semi-solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 9.51 (br s, 2 H), 7.45–7.36 (m, 5 H), 5.92 (d, J = 15.3 Hz, 1 H), 5.82 (d, J = 15.3 Hz, 1 H), 4.57 (d, J = 7.4 Hz, 1 H), 1.94–1.90 (m, 1 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.46 (d, J = 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.2, 132.4, 127.3, 127.1, 126.4, 56.7, 49.3, 29.2, 16.4, 15.5.

MS (ESI): m/z calcd for $\text{C}_{12}\text{H}_{18}\text{N}_6$ $[\text{M}]^+$: 246.16; found $[\text{M} + \text{Na}]^+$: 269.24.

1-Benzyl-5-(1-hydrazino-3-methylbutyl)-1H-tetrazole (6d)

Obtained using procedure B on a 0.69-mmol scale; yield: 0.135 g (65%); yellow solid; mp 153–155 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.42–7.37 (m, 3 H), 7.32 (d, J = 7.6 Hz, 2 H), 5.88 (d, J = 15.7 Hz, 1 H), 5.80 (d, J = 15.7 Hz, 1 H), 4.69 (t, J = 7.4 Hz, 1 H), 1.63–1.60 (m, 1 H), 1.38–1.30 (m, 2 H), 0.75 (d, J = 6.4 Hz, 3 H), 0.66 (d, J = 6.4 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.5, 132.6, 127.3, 127.0, 126.0, 50.2, 49.3, 38.5, 22.8, 19.5, 19.4.

MS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{20}\text{N}_6$ $[\text{M}]^+$: 260.17; found $[\text{M} + \text{Na}]^+$: 283.25.

1-Benzyl-5-(cyclohexyl(hydrazino)methyl)-1H-tetrazole (6e)

Obtained using procedure B on a 0.92-mmol scale; yield: 0.23 g (77%); white solid; mp 125–128 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 9.45 (br s, 2 H), 7.41–7.36 (m, 5 H), 5.89 (d, J = 15.4 Hz, 1 H), 5.82 (d, J = 15.4 Hz, 1 H), 4.59 (d, J = 7.6 Hz, 1 H), 1.77 (d, J = 11.9 Hz, 1 H), 1.59–1.38 (m, 4 H), 1.00–0.78 (m, 5 H), 0.61–0.54 (m, 1 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.1, 132.6, 127.3, 127.1, 126.3, 56.4, 49.4, 38.3, 27.6, 26.6, 23.9, 23.8.

MS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{22}\text{N}_6$ $[\text{M}]^+$: 286.19; found $[\text{M} + \text{Na}]^+$: 309.23.

1-Cyclohexyl-5-(cyclohexyl(hydrazino)methyl)-1H-tetrazole (6f)

Obtained using procedure B on a 0.92-mmol scale; yield: 0.264 g (91%); yellow solid; mp 130–132 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 9.40 (br s, 2 H), 4.70–4.66 (m, 1 H), 4.58 (d, J = 8.1 Hz, 1 H), 2.13–2.09 (m, 1 H), 2.03–1.97 (m, 1 H), 1.88–1.77 (m, 6 H), 1.72–1.67 (m, 2 H), 1.59–1.45 (m, 4 H), 1.29–1.19 (m, 2 H), 1.14–1.08 (m, 3 H), 1.02–0.93 (m, 2 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 151.1, 56.3, 56.1, 38.8, 31.6, 31.4, 27.5, 24.1, 23.9, 23.8, 23.2, 23.1.

MS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{26}\text{N}_6$ $[\text{M}]^+$: 278.22; found $[\text{M} + \text{Na}]^+$: 301.30.

1-tert-Butyl-5-(1-hydrazino-3-phenylpropyl)-1H-tetrazole (6g)

Obtained using procedure B on a 0.33-mmol scale; yield: 83 mg (80%); yellow semi-solid.

^1H NMR (500 MHz, CD_3OD): δ = 7.33–7.29 (m, 2 H), 7.26–7.20 (m, 3 H), 5.13–4.91 (m, 1 H), 4.72–4.69 (m, 1 H), 2.91–2.85 (m, 1 H), 2.82–2.76 (m, 1 H), 2.26–2.18 (m, 2 H), 1.61 (d, J = 1.5 Hz, 9 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.7, 138.6, 126.8, 124.6, 60.7, 51.3, 33.2, 29.7, 27.2.

MS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{22}\text{N}_6$ $[\text{M}]^+$: 274.19; found $[\text{M} + \text{Na}]^+$: 297.26.

1-Benzyl-5-(1-hydrazino-3-phenylpropyl)-1H-tetrazole (6h)

Obtained using procedure B on a 0.29-mmol scale; yield: 83 mg (82%); yellow solid; mp 168–170 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 9.68 (br s, 2 H), 7.41–7.35 (m, 5 H), 7.22 (t, J = 7.4 Hz, 2 H), 7.15 (t, J = 7.2 Hz, 1 H), 6.98 (d, J = 7.3 Hz, 2 H), 5.89 (d, J = 15.4 Hz, 1 H), 5.83 (d, J = 15.4 Hz, 1 H), 4.83 (dd, J = 7.6, 5.4 Hz, 1 H), 2.32–2.26 (m, 1 H), 2.18–2.09 (m, 2 H), 1.87–1.78 (m, 1 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.3, 138.4, 132.4, 127.4, 127.1, 126.7, 126.5, 126.1, 124.5, 51.0, 49.2, 31.7, 29.5.

MS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{20}\text{N}_6$ $[\text{M}]^+$: 308.17; found $[\text{M} + \text{Na}]^+$: 331.23.

5-(1-Hydrazino-2-methylpropyl)-1-phenethyl-1H-tetrazole (6i)

Obtained using procedure B on a 0.58-mmol scale; yield: 0.151 g (87%); white solid; mp 183–186 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.29 (t, J = 7.3 Hz, 2 H), 7.25–7.19 (m, 3 H), 4.71 (m, 1 H), 4.67–4.60 (m, 1 H), 4.18 (d, J = 7.0 Hz, 1 H), 3.35 (td, J = 7.0, 2.6 Hz, 2 H), 1.88–1.74 (m, 1 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.72 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.4, 135.7, 127.4, 127.3, 125.6, 56.9, 47.7, 33.8, 29.4, 16.8, 15.6.

MS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{20}\text{N}_6$ $[\text{M}]^+$: 260.17; found $[\text{M} + \text{Na}]^+$: 283.29.

5-(1-Hydrazino-3-methylbutyl)-1-phenethyl-1H-tetrazole (6j)

Obtained using procedure B on a 0.53-mmol scale; yield: 0.11 g (66%); white semi-solid.

^1H NMR (500 MHz, CD_3OD): δ = 7.31–7.22 (m, 3 H), 7.13 (d, J = 7.6 Hz, 2 H), 4.75 (dt, J = 13.0, 6.3 Hz, 1 H), 4.66–4.58 (m, 1 H), 4.40 (t, J = 7.2 Hz, 1 H), 3.34 (d, J = 7.2 Hz, 2 H), 1.64–1.56 (m, 1 H), 1.49 (td, J = 13.0, 6.3 Hz, 1 H), 1.14 (dt, J = 14.0, 7.2 Hz, 1 H), 0.87–0.84 (m, 6 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.7, 135.5, 127.1, 125.4, 49.7, 47.6, 38.4, 33.6, 22.7, 19.9, 19.2.

MS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{22}\text{N}_6$ $[\text{M}]^+$: 274.19; found $[\text{M} + \text{Na}]^+$: 297.30.

1-Benzyl-5-(1-hydrazino-2-phenylethyl)-1H-tetrazole (6k)

Obtained using procedure B on a 0.76-mmol scale; yield: 0.207 g (82%); white solid; mp 113–115 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.33–7.32 (m, 3 H), 7.19–7.18 (m, 3 H), 7.11–7.10 (m, 2 H), 6.96–6.94 (m, 2 H), 5.43 (s, 2 H), 4.86–4.83 (m, 1 H), 3.26–3.23 (dd, J = 13.3, 6.0 Hz, 1 H), 3.06–3.02 (dd, J = 13.3, 9.2 Hz, 1 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 154.8, 136.2, 134.9, 130.4, 130.2, 129.8, 129.0, 128.5, 56.1, 51.9, 39.4.

MS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{18}\text{N}_6$ $[\text{M}]^+$: 294.16; found $[\text{M} + \text{Na}]^+$: 317.26.

Benzyl 4-Hydrazino-4-(1-(2-(1H-indol-3-yl)ethyl)-1H-tetrazol-5-yl)piperidine-1-carboxylate (6l)

Obtained using procedure B on a 0.9-mmol scale; yield: 0.367 g (82%); white semi-solid.

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 10.97 (s, 1 H), 9.43 (s, 2 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.42–7.38 (m, 2 H), 7.35–7.32 (m, 4 H), 7.12 (d, J = 2.2 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 6.98 (t, J = 7.4 Hz, 1 H), 6.36 (s, 1 H), 5.05 (s, 2 H), 4.80–4.75 (m, 2 H), 3.54 (d, J = 13.7 Hz, 2 H), 3.40 (t, J = 7.1 Hz, 1 H), 2.84 (t, J = 10.4 Hz, 2 H), 1.98–1.82 (m, 2 H), 1.76–1.69 (m, 2 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 155.1, 154.6, 136.3, 136.0, 128.5, 128.2, 127.9, 126.7, 123.3, 122.1, 119.6, 117.8, 111.6, 110.0, 67.4, 56.2, 50.5, 39.2, 32.3, 25.6.

MS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{28}\text{N}_8\text{O}_2$ $[\text{M}]^+$: 460.23; found $[\text{M} - \text{H}]^+$: 459.14; found $[\text{M} + \text{Na}]^+$: 483.33.

1-Benzyl-4-(1-(4-chlorobenzyl)-1H-tetrazol-5-yl)-4-hydrazino-piperidine (6m)

Obtained using procedure B on a 0.34-mmol scale; yield: 0.146 g (99%); white solid; mp 170–172 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.62 (br s, 1 H), 7.55–7.45 (m, 4 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.39 (d, J = 7.8 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 2 H), 6.00 (s, 1 H), 5.89 (s, 1 H), 4.43 (s, 1 H), 4.29 (s, 1 H), 3.54–3.44 (m, 3 H), 3.16–3.10 (m, 1 H), 2.69–2.61 (m, 2 H), 2.42–2.36 (m, 1 H), 2.27 (d, J = 15.4 Hz, 1 H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$): δ = 155.9, 134.1, 133.3, 131.9, 130.2, 130.0, 129.9, 129.2, 129.1, 58.8, 54.6, 51.2, 46.0, 28.5.

MS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{24}\text{ClN}_7$ $[\text{M}]^+$: 397.18; found $[\text{M} + \text{H}]^+$: 398.26.

1-(4-Chlorobenzyl)-5-(2-hydrazinobutan-2-yl)-1H-tetrazole (6o)

Obtained using procedure B on a 0.48-mmol scale; yield: 0.12 g (79%); white solid; mp 128–129 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.39 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 5.88 (s, 2 H), 1.86–1.77 (m, 2 H), 1.67 (s, 3 H), 0.63 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 154.2, 132.7, 131.7, 127.7, 127.2, 57.2, 49.8, 28.8, 18.7, 5.2.

MS (ESI): m/z calcd for $\text{C}_{12}\text{H}_{17}\text{ClN}_6$ $[\text{M}]^+$: 280.12; found $[\text{M} - \text{H}]^+$: 279.42; found $[\text{M} + \text{Na}]^+$: 303.18.

1-(4-Chlorobenzyl)-5-(1-chloro-2-hydrazinopropan-2-yl)-1H-tetrazole (6p)

Obtained using procedure B on a 0.2-mmol scale; yield: 56 mg (83%); white solid; mp 96–98 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.42 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 5.92 (s, 2 H), 4.15 (d, J = 12.4 Hz, 1 H), 4.12 (d, J = 12.4 Hz, 1 H), 1.65 (s, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 152.5, 132.8, 131.4, 127.7, 127.3, 57.1, 49.9, 45.5, 18.9.

MS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{N}_6$ $[\text{M}]^+$: 300.07; found $[\text{M} + \text{Na}]^+$: 323.10.

1-(4-Chlorobenzyl)-5-(2-chloro-1-hydrazinoethyl)-1H-tetrazole (6q)

Obtained using procedure B on a 0.73-mmol scale; yield: 0.201 g (85%); brown solid; mp 149–151 °C.

^1H NMR (500 MHz, CD_3OD): δ = 7.43 (d, J = 7.5 Hz, 2 H), 7.38 (d, J = 7.5 Hz, 2 H), 5.81 (d, J = 15.6 Hz, 1 H), 5.76 (d, J = 15.6 Hz, 1 H), 4.99–4.96 (m, 1 H), 4.06–4.02 (m, 1 H), 4.00–3.96 (m, 1 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 150.2, 133.0, 130.9, 128.0, 127.3, 52.2, 48.6, 40.3.

MS (ESI): m/z calcd for $\text{C}_{10}\text{H}_{12}\text{Cl}_2\text{N}_6$ $[\text{M}]^+$: 286.05; found $[\text{M} + \text{Na}]^+$: 309.13.

5-Isobutyl-9,9-dimethyl-8,9-dihydro-5H-tetrazolo[5,1-d][1,2,5]triazepin-6(7H)-one (7)

Obtained using procedure B on a 0.74-mmol scale; yield: 0.174 g (86%); white semi-solid.

^1H NMR (500 MHz, CD_3OD): δ = 5.39 (t, J = 6.6 Hz, 1 H), 2.19–2.14 (m, 1 H), 2.07–2.02 (m, 1 H), 1.90–1.86 (m, 1 H), 1.82 (s, 3 H), 1.77 (s, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 162.7, 153.3, 56.5, 56.3, 40.6, 24.8, 23.7, 22.8, 20.4, 19.2.

MS (ESI): m/z calcd for $\text{C}_{10}\text{H}_{18}\text{N}_6\text{O}$ $[\text{M}]^+$: 238.15; found $[\text{M} + \text{H}]^+$: 239.27.

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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1561353x>.

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