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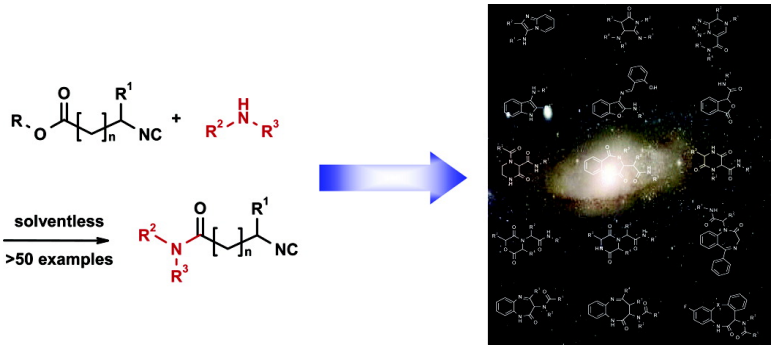

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Parallel Synthesis of Arrays of Amino-Acid-Derived Isocyanoamides Useful As Starting Materials in IMCR

Alexander Dömling,*,† Barbara Beck,‡ Thilo Fuchs,‡ and Ahmad Yazbak§

ABC-Pharma, Franckensteinstrasse 9a, 81243 München, Germany, Morphochem AG, Gmunderstrasse 37, 81379 München, Germany, and Synthatex Ltd., Shefa-Amr, Industrial Park, P.O. Box 437, 20200 Israel

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Arrays of amino-acid-derived isocyanoamides are conveniently produced on a multigram scale in one step by the solventless aminolysis of the corresponding methyl esters with primary or secondary aliphatic amines. Most of the corresponding isocyanides precipitate during the reaction and can be filtered to yield highly pure, colorless, and odorless solids. They are potentially useful in the combinatorial chemistry of multicomponent reactions.

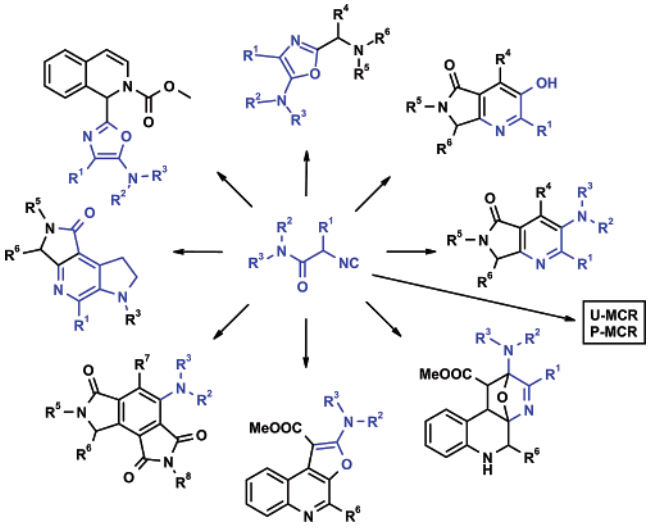
Introduction

Isocyanides constitute a special group of starting materials useful for producing small-molecule libraries in isocyanide-based multicomponent reactions (IMCRs)[1] due to their unique reactivity involving the formation of α-adducts with nucleophiles and electrophiles. This reactivity as well as the α-acidic character and the propensity for metal organic and radical reactions make isocyanides uniquely suited for the formation of many different scaffolds and libraries. However, in most publications, the combinatorial chemistry of isocyanides is described for just a handful of those more commonly used; for example, *tert*-butyl-, benzyl-, cyclohexyl-, morpholinoethyl-, and tosmic. Despite this, isocyanides are easily accessible by a plethora of methods; the most useful are based on procedures starting with primary amines.[2−8] Moreover, several hundred isocyanides of different classes are currently commercially available. Although isocyanides are highly useful in library synthesis, they unfortunately are often difficult to handle due to their inherent toxicity and their very bad smell.

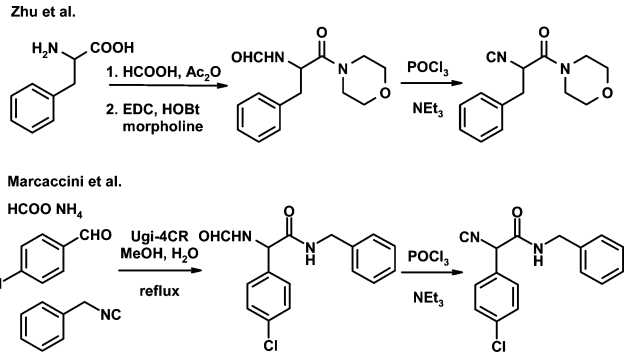
Recently, different groups have launched a new chemistry relying on α-amino-acid-derived α-isocyanoamides. It is based on an initial Ugi 3-CR, followed by a 5-amino oxazole cyclocondensation and subsequently the exploitation of the cycloaddition capability of this electron-rich azadiene (Scheme 1).[9] The herein reported methodology to access large arrays of such isocyanides possesses the potential to greatly expand the usefulness of these and other IMCRs as well as classical reactions of this starting material.

The required α-isocyanoamides in the past have been synthesized primarily in a stepwise sequential process starting with the amino acid via the amide and the formamide.[10] Alternatively, Marccacini et al. introduced a MCR approach toward α-isocyanoamides (Scheme 2).[11] Moreover, the method of aminolysis of isocyanomethyl carboxylic acid methyl ester has been described in the past in a few examples.[12] However the study reported herein provides data from variations of several α-, β-, and γ-amino-acid-derived isocyano esters with primary and secondary amines. It also

Scheme 1. α-Isocyanoamides Are the Starting Materials for a Plethora of Combinatorial Scaffolds



Scheme 2. Currently Used Synthetic Schemes Leading to α-Isocyanoamides



* To whom correspondence should be addressed. E-mail: Alex.doemling@abc-pharma.de.
† ABC-Pharma.
‡ Morphochem AG.
§ Synthatex Ltd.

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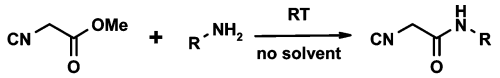
Table 1. Reaction of Primary Amines with Isocyano Acetic Acid Methyl Ester



1 85%	**2** 84%
3 91%	**4** 96%
5 78%	**6** 85%
7 70%	**8** 43%

takes into account the functional group tolerability of this reaction. Thus, we systematically investigated a highly convenient access to a special and important subclass of isocyanides derived from amino acids. This class of isocyanides has the advantages of being very easy to prepare from their commercial ester precursors and being straightforward to handle. The products are mostly odorless solids.

Initially, we observed that simple solventless mixing of equivalent amounts of primary amine and isocyanoacetic acid methyl ester at room temperature led to precipitation of the isocyanoamide products (Table 1). Simple filtration and washing with cold ether typically yielded NMR pure isocyanoamides, which could be used without further purification. When the product did not precipitate, cooling of the reaction mixture to −20 °C and trituration with ether can yield a precipitate. If the amine educt was insoluble, the mixture was carefully titrated with methanol to yield a partial solution. The amine had to react as the free base; therefore, amine salts have to be liberated in advance.

The quality and yields of this simple procedure were outstanding. We then decided to evaluate the usefulness and limitations of this synthetic approach toward these isocyanides. Several examples of isocyanoacetic acid amides derived from primary amines are shown in Table 1. A large variety of aliphatic amines showed a clean reaction, including those containing additional functional groups, such as (substituted) aromates (**1**, **3**, **4**), heteroaromates (**2**, **5**−**8**), or phenol (**3**). However, we noted that anilines did not react.[13] Interestingly, almost all of the isocyanoamides are stable and colorless solids devoid of the typical isocyanide odor.

We also investigated the corresponding reaction of the lower priced isocyanoacetic acid ethyl ester with primary amines. However, the reaction turned out to be slower, and in many cases, the product did not precipitate as consistently as with the methyl ester.

Encouraged by the efficient reaction of primary amines, we next investigated the corresponding reaction with secondary amines. Table 2 contains representative synthesized structures. Again, we found that the procedure was easy and the yields of this reaction were excellent. Apart from aromatic secondary amines, all the other classes of secondary amines were good substrates in this reaction. Many functional groups, such as free hydroxyl groups (**13**, **15**, **17**, **18**, **25**, **26**−**31**); basic groups, such as tertiary amines (**10**, **12**, **33**, **37**−**40**, **44**); primary amides (**20**, **35**, **36**); bulky groups (**42**); and even labile propargylic systems (**11**) were very well tolerated. Methyl (**21**), ethyl (**22**), and *tert*-butyl ester (**19**) and carbamate functionalities (**41**) were also well tolerated with no overamination or deprotection noted.

The reaction starting from substituted α-amino acids (other than Gly), such as Phe, Val, Leu, or Ala, was next examined. It was found that α-amino-acid-derived isocyanides also react easily. Presumably, the electron-withdrawing property of the isocyano functionality in α-position to the ester increases the reactivity toward amine nucleophiles.

Finally, we investigated the aminolysis of higher amino-acid-derived isocyano esters, such a β-alanine and γ-aminobutyric acid (Table 4). We observed a decrease in reactivity (reaction time and yields) of higher homologues of glycine-derived isocyanides; for example, β-alanine, and γ-aminobutyric acid.

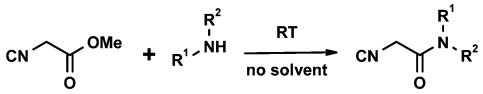
As part of our interest in GPCR ligands, the synthesis of GPCR-like motif building blocks was of interest. Thus, we synthesized compounds consisting of tetrahydroisoquinoline and spiro piperidine moieties (**24**). These compounds contain privileged structures, which frequently reoccur as hits in GPCR screens.[14] Moreover, we introduced mimics of relevant amino acids of bioactive ligand peptides; for example, Asn, Asp, Gln, Glu, Tyr, Phe, and Trp (**1**, **3**, **5**−**9**, **15**, **20**−**22**, **35**−**36**, **45**, **47**, **49**−**51**; see Table 3). Used in appropriate IMCR scaffolds as building blocks, they should substantially enhance the hit rate of corresponding libraries.

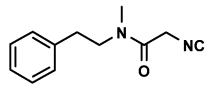
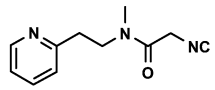
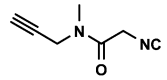
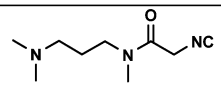
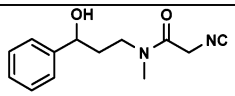
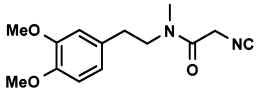
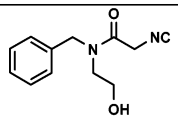
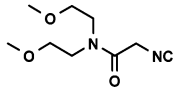
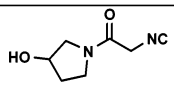
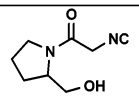
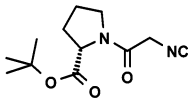
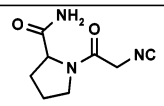
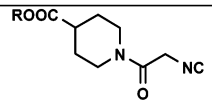
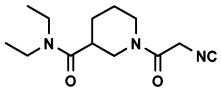
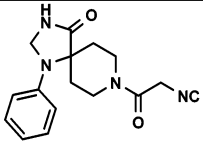
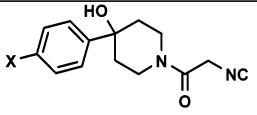
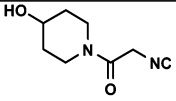
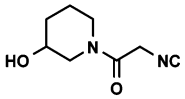
Due to the wide availability of primary and secondary aliphatic amines, hundreds of isocyanoamides were conveniently accessible. Thus, we were able to produce over 200 isocyanoamides from 2 l of the readily available isocyanoacetic acid methyl esters, each in multigram quantities, by one labworker performing this reaction in a 2-week time period, including the requisite analytics. The reaction was easily scalable, and we prepared several kilograms of a specific isocyanoamide.[15] Additional synthesized products are described in the Supporting Information.

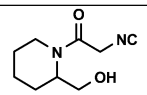
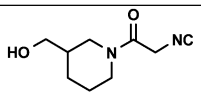
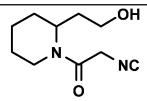
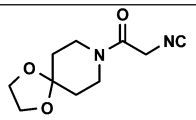
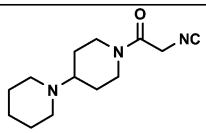
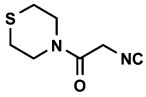
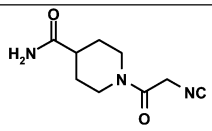
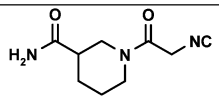
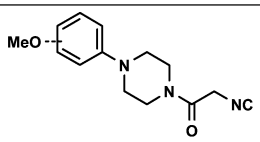
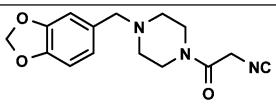
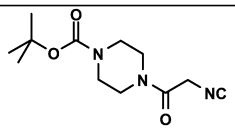
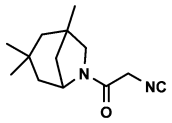
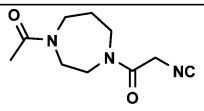
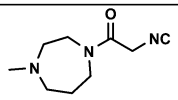
Although the kinetics of this reactants were at times slower in Ugi- and Passerini-type reactions, the expected products were consistently formed.[1]

In summary, we are presenting an experimentally simple and general approach for synthesizing a library of structurally diverse and valuable isocyanoamides. The starting compounds are commercially available amines and easily ac-

Table 2. Reaction of Secondary Amines with Isocyanoacetic Acid Methyl Ester

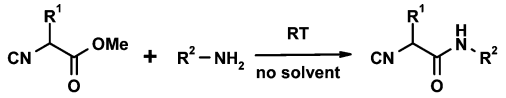


 **9**	65%	 **10**	98%
 **11**	56%	 **12**	76%
 **13**	98%	 **14**	75%
 **15**	82%	 **16**	76%*
 **17**	97%	 **18**	73%
 **19**	49%	 **20**	96%
 **21** R = Me	69%	 **23**	75%
22 R = Et	84%		
 **24**	86%	 **25** X = H	87%
		26 X = Br	83%
 **27**	96%	 **28**	66%

 **29**	89%	 **30**	90%
 **31**	66%	 **32**	81%
 **33**	22%	 **34**	62%
 **35**	96%	 **36**	87%
 **37** R = o-MeO	76%	 **40**	88%
38 R = m-MeO	85%		
39 R = p-MeO	68%		
 **41**	44%	 **42**	31%
 **43**	72%*	 **44**	96%
*orange oil;			

cessible isocyanocarboxylic acid esters. The diversity and limitations of this reaction were studied, and more than 50 examples are presented. Advantages of the current class of isocyanides include their dominant solid and odorless character while maintaining the isocyanide reactivity in IMCR chemistries.[16] Including the current approach, now four complementary synthetic pathways are available to access this important starting material class.[10,11,17] Current evaluation of this isocyanide class for use in new IMCR is ongoing in our laboratory. We are also investigating the broad use of the described compound class in the synthesis of 1-alkyl-4-carboxamidoimidazoles,[18] 2,3,4-trisubstituted

Table 3. Reaction of Primary Amines with Substituted Isocyanoacetic Acid Methyl Ester



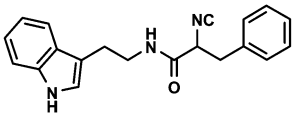
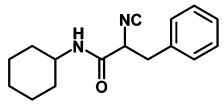
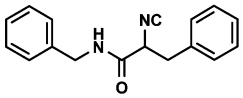
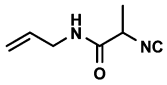
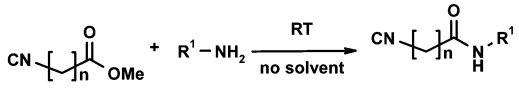
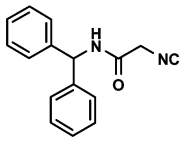
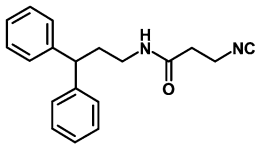
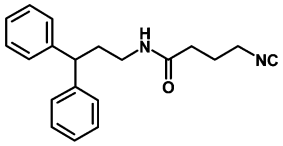
 **45** 61%	 **46** 82%
 **47** 83%	 **48** 83%

Table 4. Reaction of Primary Amines with Isocyano Butyric and Propionic Acid Methyl Ester



 **49** 81%	 **50** 50%
 **51** 25%	

pyrroles,[19] isoxazolinopyrroles,[20] macrocycles,[21] lennoxamine-type natural products,[22] silver catalyzed imidazolidines and oxazoles,[23] oxazolines,[24] spiroimidazolones,[10b,25] peptides,[26] 1*H*-imidazole-2-thiones,[27] 2,4-bis(arylthio)-5-[*N*-alkyl-*N*-phenylamino]oxazoles,[9b] α-keto esters,[28] mesoionic 3-alkyl-2-(arylthio)-1,3-diazolium-4-olates,[29] 2-aminoimidazoles,[30] optically active threo-*β*-hydroxyamino acids,[31] 2-imidazolin-5-ones,[32] 5-amino oxazoles,[9a] or 1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid derivatives.[33] This class of isocyanides will provide the foundation of focused and general libraries for use in the discovery of biologically active compounds.

Experimental Section

General. Proton and carbon NMR spectra were obtained in DMSO, $CDCl_3$, or CD_3OD and determined with a Mercury 400 spectrometer. Chemical shifts are expressed in parts per million (δ) with respect to TMS as an internal standard. Electrospray ionization mass spectra (ESI) were obtained using a MSD (Hewlett-Packard HPLC 1100 driven electrospray MS instrument). Products were purified by crystallization out of cold diethyl ether or preparative chromatography with silica gel and ethyl acetate as eluent. The purity was determined utilizing a Hewlett-Packard LC 1100 system using a YMC column, 2 mm × 50 mm, 2 μm ODSA; detection wave length at 220 and 254 nm; flow, 0.6 mL/min with a 6-min gradient from 90% H_2O to 10% H_2O (0.5% CH_3COOH) vs CH_3CN. Due to the existence of rotamers around the amide bonds in the described isocyanoamides, signals assignment in the NMR spectra is not completely resolved, and some signals are doubled; in this case, the major peak is listed.

General Procedure. To 30 mmol of amine 30 mmol of isocyanoacetic acid methyl ester was added, and the mixture was stirred overnight at room temperature. If the product precipitated during the reaction, it was filtered off, washed three times with cold diethyl ether, and dried under vacuum overnight. If no precipitation was observable, cold diethyl ether was added to the reaction mixture, and the product was allowed to crystallize in the freezer at −20 °C. In the rare cases the product was formed as an oil or no crystallization occurred, the product was purified by preparative chromatography with silica gel and ethyl acetate as eluent. Crystallization could also be enhanced in several cases by using ultrasound.

Analytical Data of Described Compounds. 2-Isocyano-*N*-phenethylacetamide (1). 85% yield; $C_{11}H_{12}N_2O$ MW 188.23 g/mol. HPLC/MS (ESI-TOF): t_R = 2.94 min; m/z = 189 $[M + H]^+$, 211 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.77 (tr, J = 6.9 Hz, 2H), 3.47 (dd, J = 6.1 Hz, J = 12.9 Hz, 2H), 3.99 (s, 2H), 6.55 (br, 1H), 7.11−7.26 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.6, 41.3, 45.5, 127.1, 128.9, 129.0, 138.4, 162.7.

2-Isocyano-*N*-(2-pyridin-2-yl-ethyl)-acetamide (2). 84% yield; $C_{10}H_{11}N_3O$ MW 189.22 g/mol. HPLC/MS (ESI-TOF): t_R = 0.45 min; m/z = 190 $[M + H]^+$, 212 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.00 (tr, J = 6.2 Hz, 2H), 3.71 (dd, J = 5.5 Hz, J = 11.9, 2H), 4.12 (s, 2H), 7.14−7.17 (m, 2H), 7.60−7.64 (m, 1H), 8.36 (br, 1H), 8.53−8.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.5, 38.7, 45.3, 121.7, 123.3, 136.8, 149.1, 159.2, 161.8, 162.2.

***N*-[2-(4-Hydroxyphenyl)-ethyl]-2-isocyanoacetamide (3).** 91% yield; $C_{11}H_{12}N_2O_2$ MW 204.23 g/mol. HPLC/MS (ESI-TOF): t_R = 2.18 min; m/z = 205 $[M + H]^+$, 227 $[M + Na]^+$. ^1H NMR (CD_3OD, 400 MHz): δ = 2.70 (tr, J = 7.3 Hz, 2H), 3.39 (tr, J = 7.2 Hz, 2H), 4.93 (s, 2H), 6.72 (d, J = 8,2 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz): δ = 35.4, 42.6, 116.3, 130.7, 157.0, 165.4.

***N*-(3,4-Dimethoxybenzyl)-2-isocyanoacetamide (4).** 96% yield; $C_{12}H_{14}N_2O_3$ 234.26. HPLC/MS (ESI-TOF): t_R = 2.97; m/z = 257 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.54 (tr, J = 6.8 Hz, 2H), 3.67 (tr, J = 6.8 Hz, 2 H), 3.62 (s, 6H), 4.33 (d, J = 5.6 Hz, 1H), 6.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.5, 37.6, 43.3, 55.7, 110.8, 110.9, 119.8, 130.1, 148.1, 148, 8, 156.5, 168.2.

***N*-(1H-Indol-6-ylmethyl)-2-isocyanoacetamide (5).** 78% yield; $C_{12}H_{11}N_3O$ 213.24. HPLC/MS (ESI-TOF): t_R = 2.58

min; $m/z = 236$ $[M + Na]^+$. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 4.35-4.41$ (m, 4H), 6.40 (s, 1H), 7.03 (d, 1H), 7.32−7.36 (m, 2H), 8.59 (t, 1H), 11.06 (s, br, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 43.2$, 44.8, 100.9, 111.27, 119.0, 121.1, 125.6, 127.5, 128.7, 135.1, 158.0, 162.6.

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-2-isocyanoacetamide (6).** 85% yield; $C_{13}H_{13}N_3O$ 227.27. HPLC/MS (ESI-TOF): $t_R = 2.96$ min; $m/z = 228$ $[M + H]^+$, 250 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 2.85$ (tr, $J = 7.2$ Hz, 2H), 3.40 (m, 2H), 4.33 (s, 2H), 6.99 (tr, $J = 7.6$ Hz, 1H), 7.09 (tr, $J = 7.2$ Hz, 2H), 7.17 (s, 1H), 7.34 (d, $J = 8$, 1H), 7.53 (d, $J = 7.6$, 1H), 8.28 (s, 1H), 10.84 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 12.9$, 14.7, 23.6, 24.3, 27.3, 27.9, 37.9, 38.0, 41.1, 42.0, 44.8, 47.1, 58.6, 161.4, 161.5, 171.2, 171.6.

***N*-[2-(5-Benzyloxy-1*H*-indol-3-yl)-ethyl]-2-isocyanoacetamide (7).** 70% yield; $C_{20}H_{19}N_3O_2$ 333.39. HPLC/MS (ESI-TOF): $t_R = 3.44$ min; $m/z = 334$ $[M + H]^+$, 356 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 2.91-2.70$ (m, 2H), 3.56−3.21 (m, 4H), 4.35−4.33 (m, 2H), 5.25−4.97 (m, 2H), 6.90−6.74 (m, 1H), 7.18−7.12 (m, 1H), 7.29−7.23 (m, 1H), 7.35−7.29 (m, 1H), 7.43−7.36 (m, 1H), 7.52−7.47 (m, 1H), 10.89−10.52 (m, 1H), 8.31−8.24 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 24.9$, 44.8, 69.7, 69.9, 101.7, 111.2, 112.0, 123.5, 127.4, 127.6, 127.7, 128.3, 131.5, 137.7, 151.9, 158.1, 162.8.

***N*-{[2-(1*H*-Indol-3-yl)-ethylcarbamoyl]-methyl}-2-isocyanoacetamide (8).** 43% yield; $C_{15}H_{16}N_4O_2$ 284.32. HPLC/MS (ESI-TOF): $t_R = 2.76$ min; $m/z = 285$ $[M + H]^+$, 307 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 2.85$ (dd, $J = 14.50$, 6.90 Hz, 2H), 3.37 (m, 2H), 3.75 (d, $J = 5.69$ Hz, 1H), 4.43 (d, $J = 5.45$ Hz, 1H), 7.23−6.92 (m, 1H), 7.35 (d, $J = 8.06$ Hz, 1H), 7.54 (d, $J = 7.77$ Hz, 1H), 8.09 (t, $J = 5.64$, 5.64 Hz, 1H), 8.44 (t, $J = 5.65$, 5.65 Hz, 1H), 10.82 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 25.2$, 42.3, 44.8, 111.4, 118.2, 120.9, 122.7, 127.1, 136.2, 158.2, 163.4, 168.1.

2-Isocyano-*N*-methyl-*N*-phenethylacetamide (9). 65% yield; $C_{12}H_{14}N_2O$ MW 202.26 g/mol. HPLC/MS (ESI-TOF): $t_R = 3.53$ min; $m/z = 203$ $[M + H]^+$, 225 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 4.19$ (m, 4H), 4.39 (s 1H), 4.78 (m, 1H), 4.98 (tr, $J = 7.3$ Hz, 1H), 5.10 (s, 1H), 5.63 (s, 1H), 8.50−8.70 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 33.3$, 31.0, 44.5, 50.6, 126.4, 128.5, 128.9, 138.3, 160.6, 162.3.

2-Isocyano-*N*-methyl-*N*-(2-pyridin-2-yl-ethyl)-acetamide (10). 98% yield; $C_{11}H_{13}N_3O$ MW 203.25 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.46$ min; $m/z = 204$ $[M + H]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.81-3.00$ (m, 5H), 3.59−3.73 (m, 2H), 4.21−4.23 (m, 2H), 7.07−7.15 (m, 2H), 7.56 (m, 1H), 8.45−8.49 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 33.2$, 35.7, 44.4, 48.1, 121.5, 123.7, 136.8, 149.1, 158.3, 160.3, 162.3.

2-Isocyano-*N*-methyl-*N*-prop-2-ynyl-acetamide (11). 56% yield; $C_7H_8N_2O$ MW 136.15 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.84$ min; $m/z = 137$ $[M + H]^+$, 159 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.26$ (s, 1H), 3.03 (s, 5H), 3.81 (s, 1H), 3.96 (m, 1H), 4.22 (m, 3H), 4.31 (s, 2H), 4.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 33.9$, 37.0, 44.4, 53.3, 72.7, 160.9, 162.1.

***N*-(3-Dimethylaminopropyl)-2-isocyano-*N*-methylacetamide (12).** 76% yield (red oil); $C_9H_{176}N_3O$ 183.26. HPLC/MS (ESI-TOF): $t_R = 0.57$ min; $m/z = 184$ $[M + H]^+$, 206 $[M + Na]^+$. See NMR spectra in Supporting Information as purity control.

***N*-(3-Hydroxy-3-phenylpropyl)-2-isocyano-*N*-methylacetamide (13).** 98% yield; $C_{13}H_{16}N_2O_2$ MW 232.28 g/mol. HPLC/MS (ESI-TOF): $t_R = 2.82$ and 3.12 min; $m/z = 233$ $[M + H]^+$, 255 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.80-1.90$ (m, 2H), 2.83−2.85 (m, 3H), 3.12−3.40 (m, 2H), 3.68−3.75 (m, 1H), 4.09−4.55 (m, 3H), 7.17−7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 33.3$, 35.9, 44.4, 45.7, 70.6, 125.5, 127.3, 127.8, 128.3, 128.6, 143.7, 162.7, 163.2.

***N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-2-isocyano-*N*-methylacetamide (14).** Yield 75%; $C_{14}H_{18}N_2O_3$ 263.31. HPLC/MS (ESI-TOF): $t_R = 2.95$ min; $m/z = 263$ $[M + H]^+$, 285 $[M + Na]^+$. See NMR spectra in Supporting Information as purity control.

***N*-Benzyl-*N*-(2-hydroxyethyl)-2-isocyanoacetamide (15).** 82% yield; $C_{12}H_{14}N_2O_2$ MW 218.26 g/mol. HPLC/MS (ESI-TOF): $t_R = 2.71$ and 2.94 min; $m/z = 219$ $[M + H]^+$, 241 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 3.22-3.24$ (m, 2H), 3.59−3.80 (m, 3H), 4.34 (s, 1H), 4.55−4.68 (m, 3H), 7.14−7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 44.7$, 48.7, 51.9, 60.3, 125.9, 127.7, 127.9, 128.7, 129.2, 136.1, 159.2, 164.2.

2-Isocyano-*N*,*N*-bis-(2-methoxyethyl)-acetamide (16). 76% yield (red oil); $C_9H_{16}N_2O_3$ 200.24. HPLC/MS (ESI-TOF): $t_R = 1.79$; $m/z = 201.2$ $[M + H]^+$, 223.2 $[M + Na]^+$. See NMR spectra in Supporting Information as purity control.

1-(3-Hydroxypyrrolidin-1-yl)-2-isocyanoethanone (17). 97% yield; $C_7H_{10}N_2O_2$ MW 154.17 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.39$ min; $m/z = 155$ $[M + H]^+$, 177 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.95-2.06$ (m, 2H), 3.33−3.50 (m, 2H), 3.56−3.60 (m, 2H), 3.94 (br, 1H), 4.20−4.35 (m, 2H, 4.45−4.52 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 34.0$, 44.6, 54.2, 68.6, 70.5, 159.3, 161.5.

1-(2-Hydroxymethylpyrrolidin-1-yl)-2-isocyanoethanone (18). 73% yield; $C_8H_{12}N_2O_2$ MW 168.20 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.66$ min; $m/z = 169$ $[M + H]^+$, 191 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.75-2.03$ (m, 4H), 3.37−3.88 (m, 4H), 4.11−4.44 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.7$, 27.6, 45.1, 47.3, 61.6, 65.0, 161.2, 162.8.

1-(2-Isocyanoacetyl)-pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester (19). 49% yield; $C_{12}H_{18}N_2O_3$ MW 238,29 g/mol. HPLC/MS (ESI-TOF): $t_R = 3.07$ and 3.41 min; $m/z = 239$ $[M + H]^+$, 261 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.42$ (s, 9H), 1.83−2.23 (m, 4H), 3.40−3.46 (m, 1H), 3.50−3.60 (m, 1H), 4.08−4.26 (m, 2H), 4.36−4.39 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 22.1$, 24.5, 27.8, 28.8, 31.3, 44.7, 46.5, 60.0, 81.7, 152.1, 160.8, 170.5.

1-(2-Isocyanoacetyl)-pyrrolidine-2-carboxylic Acid Amide (20). 96% yield (brown oil); $C_8H_{11}N_3O_2$ MW 181.20 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.37$ min; $m/z = 182$ $[M + H]^+$, 204 $[M + Na]^+$. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 1.68-2.26$ (m, 3H), 3.31−3.42 (m, 2H), 3.71 (m, 1H), 4.05−4.27 (m, 1H), 4.64−4.68 (m, 2H), 7.01−7.60 (m 2H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 24.6, 29.6, 46.4, 53.5, 60.6, 158.6, 162.5, 173.8.

1-(2-Isocyanoacetyl)-piperidine-4-carboxylic Acid Methyl Ester (21). 69% yield; $C_{10}H_{14}N_2O_3$ MW 210.23 g/mol. HPLC/MS (ESI-TOF): t_R = 2.29 and 2.94 min; m/z = 211 [M + H]$^+$, 233 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.64−1.74 (m, 2H), 1.94−1.96 (m, 2H), 2.54−2.59 (m, 1H), 2.93 tr, J = 13.1 Hz, 1H), 3.15 (tr, J = 13.2 Hz, 1H), 3.58 (d, J = 13.2 Hz, 1H), 3.67 (s, 3H), 4.26−4.29 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.4, 27.8, 40.2, 41.7, 44.5, 44.6, 51.8, 160.6, 173.9.

1-(2-Isocyanoacetyl)-piperidine-4-carboxylic Acid Ethyl Ester (22). 84% yield; $C_{11}H_{16}N_2O_3$ MW 224.26 g/mol. HPLC/MS (ESI-TOF): t_R = 3.25 min; m/z = 225 [M + H]$^+$, 247 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (s, 3H), 1.56−1.71 (m, 2H), 1.81−2.10 (m, 2H), 2.46−2.58 (m, 1H), 2.98−3.14 (m, 1H), 3.40−3.69 (m, 3H), 4.13−4.53 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 23.1, 26.4, 26.9, 40.5, 42.8, 44.4, 46.6, 61.1, 161.1, 172.4.

1-(2-Isocyanoacetyl)-piperidine-3-carboxylic Acid Diethylamide (23). 75% yield; $C_{13}H_{21}N_3O_2$: 251.33. HPLC/MS (ESI-TOF): t_R = 2.63 min; m/z = 252 [M + H]$^+$, 274 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.17 (dtr, J = 6.8 Hz, J = 1.2 Hz, 2H), 0.29 (tr, J = 6.8 Hz, 2H), 0.52−0.83 (m, 2H), 0.95 (tr, J = 13.6 Hz, 1H), 1.68−1.93 (m, 2H), 2.10−2.15 (m, 1H), 2.24−2.70 (m, 4H), 3.43 (tr, J = 10.8, 1H), 3.91 (s, 2H), 3.93 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 12.9, 14.7, 23.6, 24.3, 27.3, 27.9, 37.9, 38.0, 41.1, 42.0, 44.8, 47.1, 58.6, 161.4, 161.5, 171.2, 171.6.

8-(2-Isocyanoacetyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (24). 86% yield; $C_{16}H_{18}N_4O_2$ 298.35. HPLC/MS (ESI-TOF): t_R = 2.90 min; m/z = 299 [M + H]$^+$, 321 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.63−1.67 (m, 2H), 2.27−2.32 (m, 1H), 2.48−2.52 (m, 2H), 3.15 (s, 1H), 3.47−3.50 (m, 1H), 3.66−3.72 (m, 1H), 4.27−4.31 (m, 1H), 4.58 (s, 2H), 4.70 (d, J = 17.6 Hz, 1H), 4.89 (d, J = 17.6 Hz, 1H), 6.74−6.77 (m, 3H), 7.18−7.22 (m, 2H), 8.80 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 27.9, 28.8, 58.4, 114.5, 118.1, 129.1, 143.1, 161.5, 175.5.

1-[4-Phenyl-4-hydroxypiperidin-1-yl]-2-isocyanoethanone (25). 87% yield; $C_{14}H_{16}N_2O_2$ 244.29. HPLC/MS (ESI-TOF): t_R = 2.75 min; m/z = 245 [M + H]$^+$, 267 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.60 (tr, J = 14.4 Hz, 2H), 1.80 (dtr, J = 13.2 Hz, J = 4.8 Hz, 1H), 1.97 (dtr, J = 12.4 Hz, J = 5.6 Hz, 1H), 3.02 (dtr, J = 12.8 Hz, J = 1.6 Hz, 1H), 3.40 (s, 1H), 3.66−3.72 (m, 1H), 4.28 (d, J = 12.8 Hz, 1H), 4.77 (m, 2H), 5.16 (s, 1H), 7.32 (m, 2 H), 7.48 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 37.3, 37.6, 38.3, 40.9, 44.5, 69.8, 124.6, 126.4, 127.8, 149.0, 158.2, 161.3.

1-[4-(4-Bromophenyl)-4-hydroxypiperidin-1-yl]-2-isocyanoethanone (26). 83% yield; $C_{14}H_{15}BrN_2O_2$ 323.19. HPLC/MS (ESI-TOF): t_R = 3.15 min; m/z = 325 [M + H]$^+$, 347 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.60 (tr, J = 16 Hz, 2H), 1.77 (dtr, J = 13.2 Hz, J = 4.8 Hz, 1H), 1.96 (dtr, J = 12.4 Hz, J = 4.8 Hz, 1H), 2.96 (dtr, J = 12.8 Hz, J = 2.4 Hz, 1H), 3.32 (s, 1H), 3.38−3.44 (m, 1H), 4.27 (d, J = 10.8 Hz, 1H), 4.76 (s, 2H), 5.27 (s, 1H), 7.42−7.45 (m, 2 H), 7.49−7.53 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 37.1, 38.2, 40.8, 44.5, 69.8, 119.5, 127.1, 130.7, 148.6, 158.2, 161.3.

1-(4-Hydroxypiperidin-1-yl)-2-isocyanoethanone (27). 96% yield; $C_8H_{12}N_2O_2$ MW 168.2 g/mol. HPLC/MS (ESI-TOF): t_R = 0.38 min; m/z = 169 [M + H]$^+$, 191 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.50−1.63 (m, 2H), 1.84−1.92 (m, 2H), 3.15−3.21 (m, 1H), 3.31−3.38 (m, 1H), 3.43 (m, 1H), 3.53−3.59 (m, 1H), 3.89−3.99 (m, 2H), 4.30 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 33.2, 33.8, 39.7, 42.5, 44.4, 50.5, 65.9, 160.4, 160.7.

1-(3-Hydroxypiperidin-1-yl)-2-isocyanoethanone (28). 66% yield; $C_8H_{12}N_2O_2$ 168.20. HPLC/MS (ESI-TOF): t_R = 0.51 min; m/z = 169 [M + H]$^+$, 191 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.26−1.49 (m), 1.61−1.62 (m), 2.69−2.74 (m), 2.90−3.00 (m), 3.25−3.45 (m), 3.59 (m), 3.95−4.00 (m), 4.62−4.75 (m), 4.87−4.93 (m). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 21.2, 22.8, 31.8, 32.4, 42.3, 44.4, 48.8, 51.2, 64.3, 64.4, 64.6, 64.7, 158.2, 161.5, 161.8.

1-(2-Hydroxymethylpiperidin-1-yl)-2-isocyanoethanone (29). 89% yield; $C_9H_{14}N_2O_2$ MW 182.22 g/mol. HPLC/MS (ESI-TOF): t_R = 1.34 min; m/z = 183 [M + H]$^+$, 205 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40−1.71 (m, 6H), 2.76 (tr, J = 11.9 Hz, 1H), 3.18−3.21 (m, 1H), 3.28−3.32 (m, 1H), 3.44−3.47 (m, 1H), 3.65−3.67 (m, 1H), 3.72−3.75 (m, 1H), 4.02 (m, 1H), 4.32−4.42 (m, 2H), 4.65−4.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.4, 24.6, 25.8, 37.6, 44.6, 54.9, 60.4, 159.2, 163.1.

1-(3-Hydroxymethylpiperidin-1-yl)-2-isocyanoethanone (30). 90% yield; $C_9H_{14}N_2O_2$ MW 182.22 g/mol. HPLC/MS (ESI-TOF): t_R = 0.90 min; m/z = 183 [M + H]$^+$, 205 [M + Na]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22−1.39 (m, 1H), 1.42−1.59 (m, 1H), 1.62−1.86 (m 3H), 2.70−2.91 (m, 1H), 2.95−3.18 (m, 2H), 3.37−3.61 (m 2H), 3.94−4.05 (m, 1H), 4.24−4.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.4, 24.5, 38.4, 46.4, 46.7, 48.1, 64.0, 159.7, 161.1

1-[2-(2-Hydroxyethyl)-piperidin-1-yl]-2-isocyanoethanone (31). 66% yield; $C_{10}H_{16}N_2O_2$ 196.25. HPLC/MS (ESI-TOF): t_R = 1.43 min; m/z = 197 [M + H]$^+$, 219 [M + Na]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18−1.28 (m), 1.33−1.46 (m), 1.48−1.64 (m), 1.72−1.81 (m), 1.88−1.96 (m), 2.55−2.62 (m), 2.96−3.03 (m), 3.17−3.26 (m), 3.33 (s), 3.35 (s), 3.42−3.48 (m), 3.72−3.74 (m), 4.23−4.27 (m), 4.32 (tr), 4.61−4.71 (m), 4.83 (s), 4.88 (s). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 19.1, 19.2, 25.7, 26.1, 28.5, 29.3, 32.3, 32.8, 37.2, 37.3, 46.7, 48.9, 49.0, 57.4, 58.8, 158.9, 162.2, 162.3.

1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-2-isocyanoethanone (32). 81% yield; $C_{10}H_{16}N_2O_3$ 212.25. HPLC/MS (ESI-TOF): t_R = 1.61 min; m/z = 211 [M + H]$^+$, 233 [M + Na]$^+$. See NMR spectra in Supporting Information as purity control.

1-[1,4′]Bipiperidinyl-1′-yl-2-isocyanoethanone (33). 22% yield; $C_{13}H_{21}N_3O$ MW 235.33 g/mol. HPLC/MS (ESI-TOF): t_R = 0.38 min; m/z = 236 [M + H]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.50 (m, 10H), 1.88 (m, 2H), 2.47 (m, 6H), 3.44 (m, 2H), 3.65 (m 1H), 4.28 (s, 2H), 4.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.5, 26.2, 27.2, 28.2, 39.7, 41.9, 42.3, 44.4, 45.2, 50.1, 62.0, 160.4, 160.9.

2-Isocyano-1-thiomorpholin-4-yl-ethanone (34). 62% yield; $C_7H_{10}N_2OS$ 170.23. HPLC/MS (ESI-TOF): $t_R = 1.22$ min; $m/z = 171$ $[M + H]^+$, 193 $[M + Na]^+$. ^1H NMR (400 MHz, CD_3OD): $\delta = 2.62 - 2.68$ (m, 4H), 3.61−3.63 (m, 2H), 3.84−3.87 (m, 2H), 4.66 (s, 2H). ^{13}C NMR (CD_3OD, 100 MHz): $\delta = 27.9, 28.3, 46.4, 49.1, 160.8, 163.8$.

1-(2-Isocyanoacetyl)-piperidine-4-carboxylic Acid Amide (35). 96% yield; $C_9H_{13}N_3O_2$ 195.22. HPLC/MS (ESI-TOF): $t_R = 0.38$ min; $m/z = 196$ $[M + H]^+$, 218 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 1.36$ (dq, $J = 12.4$ Hz, $J = 4.4$ Hz, 1H), 1.50 (dq, $J = 12$ Hz, $J = 4$ Hz, 1H), 1.67−1.73 (m, 2H), 2.32 (dtr, $J = 11.2$ Hz, $J = 7.6$ Hz, 1H), 2.66 (dtr, $J = 12.4$ Hz, $J = 2.4$ Hz, 1H), 2.96 (dtr, $J = 12.6$ Hz, $J = 2.4$ Hz, 1H), 3.51 (d, $J = 14$ Hz, 1H), 4.25 (d, $J = 13.2$ Hz, 1H), 4.68 (d, $J = 18$ Hz, 1 H), 4.76 (d, $J = 18$ Hz, 1H), 6.80 (s, 1H), 7.27 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 28.6, 29.1, 41.7, 42.1, 44.6, 45.2, 159.9, 162.1, 176.5$.

1-(2-Isocyanoacetyl)-piperidine-3-carboxylic Acid Amide (36). 87% yield; $C_9H_{13}N_3O_2$ MW 195.22 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.37$ min; $m/z = 196$ $[M + H]^+$, 218 $[M + Na]^+$. ^1H NMR (DMSO, 400 MHz): $\delta = 1.47-1.85$ (m, 4H), 2.16−2.31 (m, 1H), 2.85 (m, 2H), 3.43 (m, 1H), 3.98−4.29 (m, 1H), 4.74 (m, 2H), 6.90 (d, 1H), 7.36 (d, 1H). ^{13}C NMR (DMSO, 100 MHz): $\delta = 24.6, 27.2, 41.5, 44.5, 46.7, 158.2, 161.4, 174.4$

2-Isocyano-1-[4-(2-methoxyphenyl)-piperazin-1-yl]-ethanone (37). 76% yield; $C_{14}H_{17}N_3O_2$: 259.31. HPLC/MS (ESI-TOF): $t_R = 3.30$ min; $m/z = 260$ $[M + H]^+$; 282 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.00$ (s, br), 3.22 (s, br), 3.48, (s, br), 3.80 (s, br), 4.29 (s, br, 2H), 6.84 (s, br, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 42.5, 44.3, 45.6, 48.7, 50.0, 55.3, 111.2, 118.3, 120.8, 123.6, 140.0, 152.0, 160.8, 160.9$.

2-Isocyano-1-[4-(3-methoxyphenyl)-piperazin-1-yl]-ethanone (38). 85% yield; $C_{14}H_{17}N_3O_2$ 259.31. HPLC/MS (ESI-TOF): $t_R = 3.22$ min; $m/z = 260$ $[M + H]^+$; 282 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 3.11-3.17$ (m, 4H), 3.38−3.40 (m, 2H), 3.58−3.60 (m, 2H), 3.72 (s, 3H), 4.79 (s, 2H), 6.40−6.41 (dd, $J = 2$ Hz, $J = 8$ Hz, 1H), 6.46−6.47 (tr, $J = 2.4$ Hz, 1H), 6.52−6.54 (dd, $J = 1.6$ Hz, $J = 8.4$ Hz, 1H), 7.10−7.15 (tr, $J = 8$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 41.5, 44.0, 44.4, 44.6, 47.9, 48.1, 54.7, 54.9, 101.8, 102.0, 104.5, 104.7, 108.2, 108.4, 129.6, 129.7, 151.9, 158.4, 160.1, 161.7$.

2-Isocyano-1-[4-(4-methoxyphenyl)-piperazin-1-yl]-ethanone (39). 68% yield; $C_{14}H_{17}N_3O_2$ 259.31. HPLC/MS (ESI-TOF): $t_R = 2.88$ min; $m/z = 260$ $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 2.94-3.00$ (m, 4H), 3.07−3.38 (m, 2H), 3.56−3.59 (m, 2H), 3.66 (3, 3H), 3.88−3.80 (m, 1H), 4.77 (s, 2H), 6.79−6.82 (m, 2H), 6.88−6.90 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 41.7, 44.3, 49.7, 55.1, 114.1, 118.0, 144.9, 153.3, 158.4, 161.7$.

1-(4-Benzo-1,3-dioxol-5-ylmethylpiperazin-1-yl)-2-isocyanoethanone (40). 88% yield; $C_{15}H_{17}N_3O_3$ 287.32. HPLC/MS (ESI-TOF): $t_R = 0.66$ min $m/z = 288$ $[M + H]^+$, 310 $[M + Na]^+$. ^1H NMR (400 MHz, CD_3OD): $\delta = 2.37$ (s, 4H), 3.30 (s, 2H), 3.36 (s, 2H), 3.55 (s, 2H), 4.22 (s, 2H), 5.87 (s, 2H), 6.66 (s, 2H), 6.76 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 42.7, 44.6, 45.7, 52.5, 62.6, 101.2, 108.1, 109.5, 122.4, 131.4, 147.0, 147.9, 161.0, 161.2$.

4-(2-Isocyanoacetyl)-piperazine-1- carboxylic Acid *tert*-Butyl Ester (41). 44% yield; $C_{12}H_{19}N_3O_3$ MW 253.30 g/mol. HPLC/MS (ESI-TOF): $t_R = 3.41$ min; $m/z = 254$ $[M + H]^+$, 276 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.41$ (s, 9H), 3.32−3.55 (m, 8H), 4.31 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 28.1, 42.1, 44.3, 45.0, 80.4, 154.2, 161.1$.

2-Isocyano-1-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-ethanone (42). 31% yield; $C_{13}H_{20}N_2O$ 220.32. HPLC/MS (ESI-TOF): $t_R = 3.34$ min; $m/z = 221$ $[M + H]^+$, 243 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 0.86-090$ (m), 1.02 (s), 1.25−1.75 (m), 2.92 (d, $J = 10.8$ Hz), 4.05 (tr, $J = 4.4$ Hz), 4.25−4.28 (m), 4.48−4.60 (m), 4.75 (s), 4.80 (s). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 24.3, 24.4, 29.3, 30.4, 37.3, 40.7, 41.8, 41.9, 43.3, 50.4, 50.8, 54.9, 56.0, 160.0, 160.2$.

1-(4-Acetyl-1,4-diazepan-1-yl)-2-isocyanoethanone (43). 72% yield; $C_{10}H_{15}N_3O_2$ MW 209.25 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.41$ min; $m/z = 210$ $[M + H]^+$, 232 $[M + Na]^+$, ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.79-1.90$ (m, 2H), 2.01−2.07 (m, 3H), 3.35−3.68 (m, 8H), 4.29−4.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 20.8, 26.6, 43.6, 45.7, 46.3, 47.2, 49.9, 162.3, 170.6$.

2-Isocyano-1-(4-methyl-1,4-diazepan-1-yl)-ethanone (44). 96% yield; $C_9H_{15}N_3O$ MW 181.24 g/mol. HPLC/MS (ESI-TOF): $t_R = 0.36$ min; $m/z = 182$ $[M + H]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.77-1.88$ (m, 2H), 2.25−2.28 (m, 3H), 2.47−2.58 (m, 4H), 3.31−3.36 (m, 2H), 3.54−3.60 (m, 2H), 4.27 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 26.7, 44.9, 46.3, 46.8, 56.5, 57.3, 57.5, 160.1, 161.8$.

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-2-isocyano-3-phenylpropionamide (45).** 61% yield; $C_{20}H_{19}N_3O$ 317.39. HPLC/MS (ESI-TOF): $t_R = 3.58$ min; $m/z = 318$ $[M + H]^+$; 340 $[M + Na]^+$. ^1H NMR (400 MHz, CD_3OD): $\delta = 2.85-2.88$ (tr, $J = 7.2$ Hz, 2H), 2.97−3.10 (m, 2H), 3.45 (tr, $J = 7.2$ Hz, 2H), 4.42 (tr, $J = 14$ Hz, 1H), 6.95 (s, 1H), 7.01 (m, 1H), 7.18−7.27 (m, 5H), 7.32 (d, $J = 8$ Hz, 1H), 7.53 (d, $J = 8$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 24.8, 39.0, 40.5, 59.1, 111.1, 111.6, 118.1, 118.6, 121.2, 122.4, 127.3, 1128.4, 129.3, 135.3, 137.0, 159.0, 166.5$.

***N*-Cyclohexyl-2-isocyano-3-phenylpropionamide (46).** 82% yield; $C_{16}H_{20}N_2O$ 256.35. HPLC/MS (ESI-TOF): $t_R = 3.63$ min; $m/z = 257$ $[M + H]^+$, 279 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.89-1.31$ (m, 5H), 1.50−1.79 (m, 5H), 3.08−3.19 (m, 2H), 3.65 (s, br, 1H), 4.31 (s, br, 1H), 6.00 (s, br, 1H), 7.17−7.25 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.5, 25.2, 32.4, 48.7, 59.7, 127.5, 128.5, 134.4, 162.0, 163.5$.

***N*-Benzyl-2-isocyano-3-phenylpropionamide (47).** 83% yield; $C_{17}H_{16}N_2O$ 264.33. HPLC/MS (ESI-TOF): $t_R = 3.53$ min; $m/z = 265$ $[M + H]^+$, 287 $[M + Na]^+$. See NMR spectra in Supporting Information as purity control.

***N*-Allyl-2-isocyano-*N*-methylacetamide (48).** 83% yield; $C_7H_{10}N_2O$ MW 138.17 g/mol. HPLC/MS (ESI-TOF): $t_R = 1.06$ min; $m/z = 139$ $[M + H]^+$, 161 $[M + Na]^+$. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 2.89-2.97$ (m, 3H), 3.81 (m, 1H),

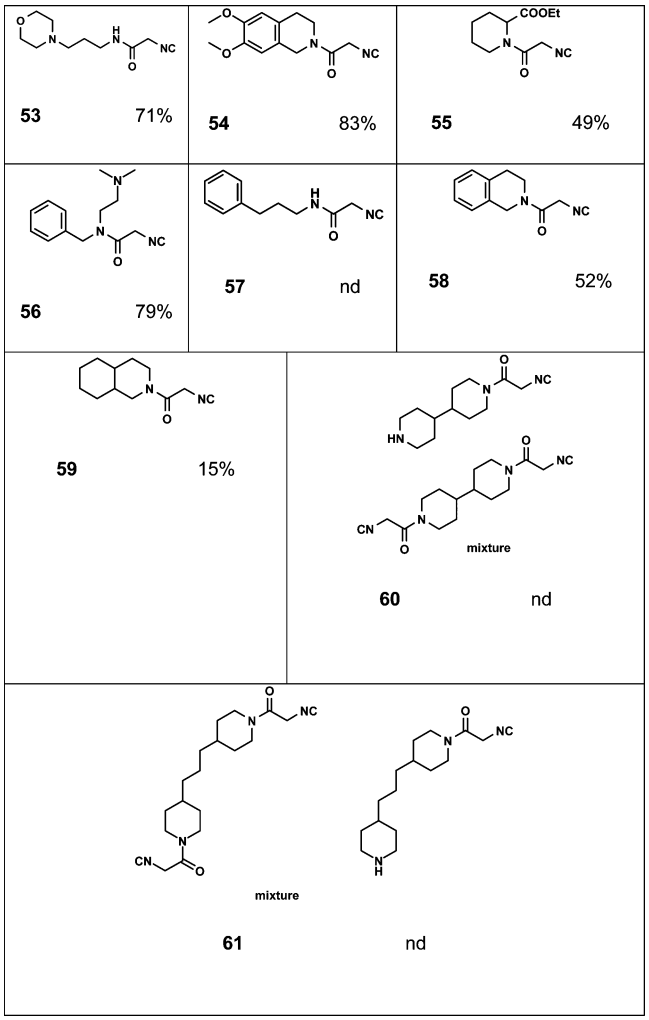
3.97 (m, 1H) 4.28−4.315 (m, 2H), 5.15−5.28 (m, 2H), 5.64−5.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 34.4$, 44.4, 50.7, 117.5, 131.6, 160.5, 162.5.

***N*-Benzhydryl-2-isocyanoacetamide (49).** 81% yield; $C_{16}H_{14}N_2O$ 250.30. HPLC/MS (ESI-TOF): $t_R = 3.42$ min; $m/z = 251$ $[M + H]^+$, 273 $[M + Na]^+$. See NMR spectra in Supporting Information as purity control.

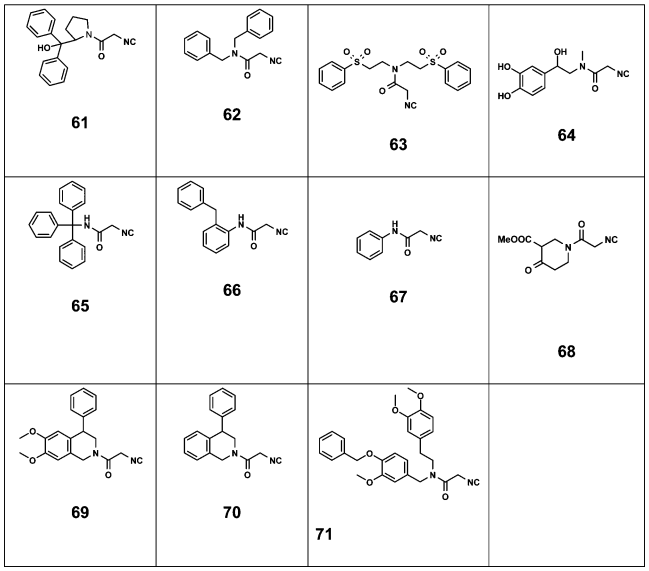
***N*-(3,3-Diphenylpropyl)-3-isocyanopropionamide (50).** 50% yield; $C_{19}H_{20}N_2O$ 292.38. HPLC/MS (ESI-TOF): $t_R = 3.53$ min; $m/z = 393$ $[M + H]^+$, 315 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2{,}26-2{,}16$ (m, 4H), 3.13 (m, 2H), 3.52 (m, 2H), 3.86 (m, 1H), 5.75 (s, br, 1H), 7.21−7.7 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 34.8$, 35.6, 37.7, 38.5, 48.9, 126.3, 127.5, 128.4, 143.9, 156.6, 168.0.

***N*-(3,3-Diphenylpropyl)-4-isocyanobutyramide (51).** 25% yield; $C_{20}H_{22}N_2O$ 306.41. HPLC/MS (ESI-TOF): $t_R = 3.60$ min; $m/z = 329$ $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17-1.19$ (m, 1H), 1.84−2.41 (m, 8H), 3.13 (m, 2H), 3.33 (m, 2H), 3.86 (m, 1H), 5.64 (m, 1H), 7.10−7.20 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.2$, 32.0, 35.0, 38.5, 40.9, 49.1, 126.2, 127.58, 144.1, 170.8.

4. Other successful examples of isocyanoamide synthesis (structure, number, yield; nd = not determined).



5. Examples of reactions failed, presumably for steric, electronic or solubility reasons.



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Supporting Information Available. ^{1}H and ^{13}C NMR and exemplary IR spectra of the new isocyanoamides are available. Tabular enlisting of further isocyanoamides is given. This material is available free of charge via the Internet at http://pubs.acs.org.

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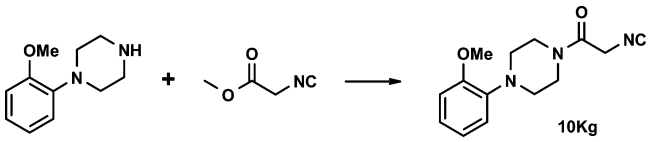

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