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Isocyanide Multicomponent Reactions on Solid-Phase-Coupled DNA Oligonucleotides for Encoded Library Synthesis

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§ Supporting Information

ABSTRACT: Isocyanide multicomponent reactions play a prominent role in drug discovery. This chemistry has hardly been investigated for compatibility with DNA-encoded combinatorial synthesis. The Ugi, Ugi-azide, and Groebke–Blackburn–Bienaymé reactions are well-tolerated by DNA on the solid phase and show a broad scope. However, an oxadiazole-forming variant of the Ugi reaction caused DNA depurination, requiring a more stable hexathymidine DNA for encoded library synthesis. Cheminformatic analysis revealed that isocyanide multicomponent-reaction-based encoded libraries cover a diverse chemical space.

Small-molecule libraries synthesized by DNA-encoded combinatorial chemistry are today a widely used screening technology in drug research.^{1,2} Selection of DNA-encoded libraries (DELs) on diverse targets, among them kinases, proteases, receptors, and epigenetic proteins, has delivered several bioactive compounds, including two clinical candidates.^{3,4} One important challenge in the field of encoded chemistry is the development of a comprehensive toolbox of reactions for encoded library design.⁵ DEL synthesis in solution requires synthesis methods that tolerate aqueous cosolvents and are compatible with DNA.⁶ DNA barcodes for DEL synthesis are synthesized on controlled pore glass (CPG) solid support by phosphoramidite chemistry. Initiation of DEL synthesis strands by amide coupling chemistry on CPG-coupled DNA prior to DNA cleavage is an established alternative to solution-phase DEL synthesis.^{7,8} This solid-phase organic synthesis (SPOS) approach benefits from broad choice of solvents and enhanced DNA stability, e.g., against depurination and deamination. The SPOS approach enabled Boc peptide chemistry on DNA sequences, including protective group removal with trifluoroacetic acid.⁸ DNA barcode sequences tolerated Yb(III)- and Ag(I)-mediated reactions under mild conditions in dry solvents, too.⁹ To translate reactions that require harsh conditions to a barcoded format, we have demonstrated that a hexathymidine adapter “hexT” tolerated Au(I)- and TFA-mediated heterocycle synthesis.¹⁰ Thus, solid-phase-based DEL strategies show potential for greatly expanding the chemistry toolbox in the initial DEL synthesis step. Surprisingly, a systematic study in the scope of chemistry on CPG-bound DNA remains to be shown.

Isocyanide multicomponent reactions (MCRs) play a prominent role in drug discovery due to their robustness and scope. The Ugi four-component reaction gives rise to a diverse substituted peptide-mimetic backbone from abundantly available monofunctionalized building blocks: carboxylic acids, aldehydes, amines, and isocyanides. Tactical application of functionalized building blocks or reactivity in MCR chemistry leads to the rapid creation of molecular diversity. For instance, a broad range of heterocycles can be synthesized either by follow-up reactions or directly at the MCR step. Drugs recently synthesized or discovered by isocyanide MCR include xylocaine, atorvastatin, ivosidenib, levetiracetam, or epelsiban, just to mention a few (Figure 1e).¹¹ To the best of our knowledge, only one account mentioned the use of the Ugi reaction for encoded library synthesis, though not disclosing any experimental details.¹² In our research program toward diverse encoded small-molecule screening collections, we wished to capitalize on the potential that the highly dynamic field of isocyanide chemistry offers for library design.¹³

Here, we investigated the compatibility and scope of four essential isocyanide chemistries with two DNA barcoding strategies initiated on CPG solid support (Figure 1d):^{9,10} the Ugi four-component reaction (U-4CR), the Ugi-azide four-component reaction (UA-4CR), the Ugi four-component/aza-Wittig reaction (U-4CR/aza-Wittig), and the Groebke–Blackburn–Bienaymé three-component reaction (GBB-3CR).

We initiated our studies in the U-4CR with the hexT-aldehyde conjugate 1,¹⁰ *tert*-butyl isocyanide 2a, acetic acid 3a,

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Figure 1. DNA-barcoding strategies for encoded library synthesis. (a) Solution-phase DEL synthesis initiated with a "headpiece". (b) DEL synthesis initiated with the "hexT" adapter. (c) DEL synthesis initiated with the DNA barcode on the solid phase. (d) Exploration of isocyanide MCR chemistry on solid-phase-coupled DNA. (e) Exemplary drugs synthesized by isocyanide MCR chemistry.

and propylamine **4a**. The hexT–aldehyde conjugate **1** was condensed with the amine for 3 h at room temperature; the other two components were added; and the reaction was performed at 50 °C for 16 h. The target hexT conjugate **5** formed neatly without much reaction optimization required (Table S1).

As the reaction proceeded under mild conditions, it should be compatible with a DNA barcode opening up the road to a more efficient barcoding strategy (Figure 1c).⁹ This was tested with the DNA–aldehyde conjugate **6a**. To our delight, the product formed with high conversion and without noticeable DNA degradation. We then explored the reaction scope with a diverse set of isocyanides **2a–d**, carboxylic acids **3a–k**, and amines **4a–l** (Scheme 1, Table S2). *tert*-Butyl **2a**, cyclohexyl **2b**, and benzyl isocyanide **2c** were reacted with DNA–aldehyde **6a**, acetic acid **3a**, and propylamine **4a** and gave the target DNA–dipeptides **7a–c** with full conversion of the aldehyde. Curiously, the Ugi product did not form with ethyl isocyanacetate **2d** in this set of experiments. Keeping *tert*-butyl isocyanide **2a** and propylamine **4a** constant, we next evaluated ten carboxylic acids **3b–k**. Acrylic acid **3b** gave the Ugi product with nearly full conversion, but methylamine was added to the electrophile during DNA cleavage from the CPG (**7d**). This undesired reaction highlights a disadvantage of the SPOS approach: the cleavage conditions limit the choice of starting materials as noticed by others.¹⁴ 4-Biphenylacetic acid **3c** and cinnamic acid **3d** gave the products (**7e/7n**, Table S2) with lower conversions of 27 and 19%, respectively. In the case of cinnamic acid **3d**, we did not detect nucleophile addition.

Scheme 1. Synthesis of DNA–Peptoid Conjugates by Ugi Four-Component Reaction^a

^aCPG-bound conjugate **1** or **6a** (20 nmol) and amine **4** (20 μ mol), MeOH, rt, 3 h, then acid **3** (20 μ mol), and isocyanide **2** (20 μ mol), 50 °C, 16 h. AMA (30% aqueous ammonia/40% aqueous methylamine, 1:1 (v/v)), rt, 0.5 h (hexT) or 4 h (ATGC). ^bBoc removal: 50% TFA, CH₂Cl₂, 1 min.⁸

Aromatic carboxylic acids **3e–k**, including examples with *ortho*-substitution (e.g., **7f**), were generally well tolerated with the exceptions of *meta*-hydroxy- (**3i**) and *meta*-ethynylbenzoic acid **3j** that gave only 32 and 38% conversions (**7r/s**, Table S2). The amine scope was tested with three benzylamines **4b–d**, seven anilines **4e–k**, and 4-amino-1-Boc-piperidine **4l**. The benzylamines and aminopiperidine were all high-yielding (e.g., **7g/h**); *meta*- and *para*-substituted anilines gave moderate to good yields (36–73%, Table S2, e.g., **7j–7l**); whereas *ortho*-*tert*-butylaniline **4e** gave low (**7i**) and *ortho*-nitroaniline **4f** gave no product formation (**7w**, Table S2). During the evaluation of the anilines, we noticed the formation of late-eluting side products which could be removed by HPLC purification. The Ugi reaction was then successfully tested with two additional DNA–aldehydes **6b** and **6c** that both gave the desired products **8** and **9** with high conversions (SI). We could extend the reaction scope to a DNA–carboxylic acid conjugate **10** and 5'-aminolinker DNA **11** that provided different compound connection points to the DNA (**12** and **13a–g** using aldehydes **14a–g**, SI). In the latter case, we observed amide bond formation as a side reaction (Table S3).

Thus, the U-4CR showed in our hands a broad scope of reactants to build up diverse substituted peptoid starting points for encoded library synthesis. Bifunctionalized building blocks for subsequent library synthesis such as the iodobenzylamine **4c** and the 4-amino-1-Boc-piperidine **4l** were well tolerated. The latter could be deprotected as previously described.⁸

Next, we explored the Ugi-azide four-component reaction (UA-4CR). This reaction could be translated to the encoded format in a straightforward manner. The reaction scope was tested with the DNA-coupled aldehyde **6a**, isocyanides **2a–d**, and amines **4a–k** and **4m–o** (Scheme 2, Table S4). Nearly all

Scheme 2. Synthesis of DNA–Tetrazole Conjugates by the Ugi-Azide Four-Component Reaction^a

^aCPG-bound conjugate **6a** (20 nmol) and amine **4** (20 μ mol), MeOH, rt, 3 h, then isocyanide **2** (20 μ mol) and TMSN₃ (20 μ mol), 50 $^{\circ}$ C, 16 h. AMA, rt, 4 h. ^bBoc removal: 50% TFA, CH₂Cl₂, 1 min. ⁸ n.d. = not detected.

these combinations of starting materials gave the target molecules with higher conversions than in the corresponding U-4CR and little to no side product formation. Again, the two *ortho*-substituted anilines **4e** and **4f** were less tolerated or not at all (**15g** and **15h**). Introduction of a position for further library synthesis was achieved with the Boc-protected piperazine **4n** (**15e**).⁸

The oxadiazole core is considered as an attractive scaffold in medicinal chemistry. It has been described as a metabolically more stable amide bioisostere.¹⁵ The Ugi four-component/*aza*-Wittig (U-4CR/*aza*-Wittig) (Scheme 3) reaction gives access to diverse substituted oxadiazoles.¹⁶ We performed this MCR under similar conditions as the U-4CR on a hexT-aldehyde conjugate **1** with benzoic acid **3e**, piperidine **4m**, and

Scheme 3. Synthesis of hexT-1,3,4-Oxadiazole Conjugates by an Ugi Four-Component/*aza*-Wittig Reaction^a

^aCPG-bound conjugate **1** (20 nmol) and amine **4** (20 μ mol), 1,2-dichloroethane, rt, 3 h, then acid **3** (20 μ mol) and (isocyanoimino)-triphenylphosphorane (20 μ mol), 50 $^{\circ}$ C, 16 h. AMA, rt, 0.5 h. ^bBoc removal: 10% TFA, CH₂Cl₂, 4 h.¹⁰

(isocyanoimino)triphenylphosphorane and could observe smooth product formation (**16a**). However, a translation of this reaction to the DNA-aldehyde **6a** failed due to concomitant cleavage of purine bases from the oligomer (**17**, Figure S1). We concluded that the U-4C/*aza*-Wittig MCR requires the “hexT” barcoding strategy.¹⁰ *Meta*- and all *para*-substituted aromatic carboxylic acids (**3h**, **3m–p**) gave high conversions (61–>95%, **16f–j**) and only negligible side product formation. However, all tested *ortho*-substituted benzoic acids (**3f**, **3g**, and **3i**) as well as *meta*-hydroxybenzoic acid **3i** furnished oxadiazoles with low conversions (13–31%, **16b–16e**) and produced several side products that were removed by HPLC purification. The piperidine **4m** could be exchanged by a Boc-protected piperazine **4n** for combinatorial library synthesis (**16k**).

Finally, we investigated the compatibility of the Groebke–Blackburn–Bienaymé three-component reaction (GBB-3CR) with solid-phase-coupled DNA. It gives rise to bicyclic heteroaromatic structures occurring in numerous bioactive molecules.¹⁷ As this reaction is promoted by strong Brønsted and Lewis acids that both could potentially damage DNA,¹⁸ we initiated reaction optimization with the hexT-aldehyde **1**, *tert*-butyl isocyanide **2a**, and 2-aminopyridine **4o** (Table 1).

To our delight, several Brønsted and Lewis acids mediated heterocycle formation. Among them were reaction conditions that appeared DNA-compatible (Table 1, e.g., entry 4). Therefore, we explored translation of the GBB-3CR to a DNA sequence (Scheme 4) and could indeed synthesize several core heterocycles **19a–i** on this DNA. Product

Table 1. Optimization of the Groebke–Blackburn–Bienaymé Three-Component Reaction on a hexT–Aldehyde Conjugate^a

entry	catalyst	conversion [%]
1	1% HClO ₄	20
2	1% TFA	54
3	1% pTsOH	93
4	1% AcOH	97
5	150 equiv of Sc(OTf) ₃	78
6	150 equiv of Yb(OTf) ₃	66
7	150 equiv of InCl ₃	59

^aCPG-bound conjugate **1** (20 nmol) and amine **4o** (20 μmol), MeOH, rt, 6 h, then isocyanide **2a** (20 μmol) and catalyst, rt, 16 h. AMA, rt, 0.5 h.

Scheme 4. Synthesis of DNA–Imidazole Heterocyclic Conjugates by the Groebke–Blackburn–Bienaymé Three-Component Reaction^a

^aCPG-bound conjugate **6a** (20 nmol) and amine **4** (20 μmol), MeOH, rt, 6 h, then isocyanide **2** (20 μmol) and 1% AcOH, rt, 16 h. AMA, rt, 4 h.

conversions were mainly affected by the substitution pattern on the hetaryl amine. 2-Aminopyridine **4o**, aminopyrazine **4q**, and 2-amino-5-methylpyridine **4s** were excellent substrates, but all tested hetaryl amines with *ortho*-substitution (heteroatom, **19e/19g**, or methyl, **19i**) gave lower conversions. In the case of ester-protected isocyano acetic acid **2d**, amidation occurred during DNA cleavage from CPG (**19d**).

Isocyanide MCR chemistry gives access to millions of compounds from thousands of monofunctionalized chemicals

(Figure S2). This vast chemical space requires rational library design. In an encoded library synthesis scenario, the MCR products are reacted with another set of chemicals, e.g., by amide synthesis, necessitating molecular weight (MW) restrictions as a prime library design criterion. Here, we designed two *in silico* libraries, one with more relaxed MW (MW < 460 Da) and a second library with more stringent MW restrictions (MW < 410 Da) so that the latter DEL can be designed not to exceed a MW of 550 Da with, e.g., amide synthesis at a second synthesis stage. These libraries gave insight into the impact of MW restrictions on library diversity. They were designed with aldehydes coupled to aminolinker DNA, a secondary amine for a plausible library synthesis scenario (**7h**, **8e**, **9k**), and a diverse building block selection. In the case of the GBB-3CR, the library was simulated with a piperidine isocyanide. The chemical space of the virtual libraries was characterized by normalized molecular quantum numbers (MQNs, Figure 2a, SI).¹⁹ In both library scenarios all

Figure 2. Cheminformatic analysis of MCR encoded *in silico* libraries. (a) Analysis of library chemical diversity by MQN descriptors and principal component analysis. (b) Analysis of the shape of the *in silico* products by principal moments of inertia analysis. Green: U-4CR, blue: UA-4CR, purple: U-4CR/*aza*-Wittig, red: GBB-3CR.

four reactions cover diverse, only partially overlapping chemical space (Figures S3 and S4 for comparison with a commercial library). The binned pairwise Tanimoto coefficients based on the ECFP4 fingerprints²⁰ of the virtual products further underpin this finding (Figure S5). However, the U-4CR/*aza*-Wittig does not allow for evenly distributed chemical space coverage with the more stringent MW restrictions. The analysis of the principal moments of inertia (Figures 2b, S3, and S4) revealed that the four reactions yield differently shaped molecules.²¹ The U-4CR covers a broad chemical space and leads to highly three-dimensional products. In contrast, the GBB-3CR led to the chemically most diverse set of molecules whose shape is restricted to a smaller, less three-dimensional shape range.

Solid-support-coupled coding DNA tolerated three isocyanide MCRs, while the U-4CR/*aza*-Wittig reaction commanded a stable hexT adapter. The MCRs were mostly high yielding and showed an excellent scope of abundantly available monofunctionalized reactants. Moreover, MCR-based libraries cover diverse, in the case of the Ugi reaction markedly three-dimensional, and only partially overlapping chemical

space. All these features contribute to the appeal of isocyanide MCR chemistry as an entry point into encoded library synthesis.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02448.

Protocols for the synthesis of starting materials, on-DNA multicomponent reactions, and HPLC traces and MALDI MS spectra of all DNA conjugates (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Brenner, S.; Lerner, R. A. *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 5381–5383.
- (2) (a) Kleiner, R. E.; Dumelin, C. E.; Liu, D. R. *Chem. Soc. Rev.* **2011**, *40*, 5707–5717. (b) Franzini, R.; Neri, D.; Scheuermann, J. *Acc. Chem. Res.* **2014**, *47*, 1247–1255. (c) Salamon, H.; Klika Škopić, M.; Jung, K.; Bugain, O.; Brunschweiler, A. *ACS Chem. Biol.* **2016**, *11*, 296–307. (d) Goodnow, R. A., Jr.; Dumelin, C. E.; Keefe, A. D. *Nat. Rev. Drug Discovery* **2017**, *16*, 131–147. (e) Ottl, J.; Leder, L.; Schaefer, J. V.; Dumelin, C. E. *Molecules* **2019**, *24*, 1629. (f) Holenz, J.; Stoy, P. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 517–524.
- (3) Liszczak, G.; Muir, T. W. *Angew. Chem., Int. Ed.* **2019**, *58*, 4144–4162.
- (4) (a) Harris, P. A.; Berger, S. B.; Jeong, J. U.; Nagilla, R.; Bandyopadhyay, D.; Campobasso, N.; Capriotti, C. A.; Cox, J. A.; Dare, L.; Dong, X.; Eidam, P. M.; Finger, J. N.; Hoffman, S. J.; Kang, J.; Kaspárová, V.; King, B. W.; Lehr, R.; Lan, Y.; Leister, L. K.; Lich, J. D.; MacDonald, T. T.; Miller, N. A.; Ouellette, M. T.; Pao, C. S.; Rahman, A.; Reilly, M. A.; Rendina, A. R.; Rivera, E. J.; Schaeffer, M. C.; Sehon, C. A.; Singhaus, R. R.; Sun, H. H.; Swift, B. A.; Totoritis, R. D.; Vossenämper, A.; Ward, P.; Wisnoski, D. D.; Zhang, D.; Marquis, R. W.; Gough, P. J.; Bertin, J. J. *Med. Chem.* **2017**, *60*, 1247–1261. (b) Belyanskaya, S. L.; Ding, Y.; Callahan, J. F.; Lazaar, A. L.; Israel, D. I. *ChemBioChem* **2017**, *18*, 837–842.
- (5) (a) Franzini, R. M.; Randolph, C. J. *Med. Chem.* **2016**, *59*, 6629–6644. (b) Favalli, N.; Bassi, G.; Scheuermann, J.; Neri, D. *FEBS Lett.* **2018**, *592*, 2168–2180. (c) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383–394. (d) Dickson, P.; Kodadek, T. *Org. Biomol. Chem.* **2019**, *17*, 4676–4688.
- (6) (a) Franzini, R. M.; Samain, F.; Abd Elrahman, M.; Mikutis, G.; Nauer, A.; Zimmermann, M.; Scheuermann, J.; Hall, J.; Neri, D. *Bioconjugate Chem.* **2014**, *25*, 1453–1461. (b) Satz, A. L.; Cai, J.; Chen, Y.; Goodnow, R.; Gruber, F.; Kowalczy, A.; Petersen, A.; Naderi-Oboodi, G.; Orzechowski, L.; Strebel, Q. *Bioconjugate Chem.* **2015**, *26*, 1623–1632. (c) Malone, M. L.; Paegel, B. M. *ACS Comb. Sci.* **2016**, *18*, 182–187. (d) Tian, X.; Basarab, G. S.; Selmi, N.; Kogej, T.; Zhang, Y.; Clark, M.; Goodnow, R. A., Jr. *MedChemComm* **2016**, *7*, 1316–1340. (e) Fan, L.; Davie, C. P. *ChemBioChem* **2017**, *18*, 843. (f) Lu, X.; Fan, L.; Phelps, C. B.; Davie, C. P.; Donahue, C. P. *Bioconjugate Chem.* **2017**, *28*, 1625. (g) Lu, X.; Roberts, S. E.; Franklin, G. J.; Davie, C. P. *MedChemComm* **2017**, *8*, 1614. (h) Wang, J.; Lundberg, H.; Asai, S.; Martín-Acosta, P.; Chen, J. S.; Brown, S.; Farrell, W.; Dushin, R. G.; O'Donnell, C. J.; Ratnayake, A. S.; Richardson, P.; Liu, Z.; Qin, T.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, E6404–E6410. (i) Wang, X.; Sun, H.; Liu, J.; Dai, D.; Zhang, M.; Zhou, H.; Zhong, W.; Lu, X. *Org. Lett.* **2018**, *20*, 4764–4768. (j) Ruff, Y.; Berst, F. *MedChemComm* **2018**, *9*, 1188–1193. (k) Kölmel, D. K.; Loach, R. P.; Knauber, T.; Flanagan, M. E. *ChemMedChem* **2018**, *13*, 2159–2165. (l) Phelan, J. P.; Lang, S. B.; Sim, J.; Berritt, S.; Peat, A. J.; Billings, K.; Fan, L.; Molander, G. A. *J. Am. Chem. Soc.* **2019**, *141*, 3723–3732.
- (7) (a) Tse, B. N.; Snyder, T. M.; Shen, Y.; Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611–15626. (b) Franzini, R. M.; Ekblad, T.; Zhong, N.; Wichert, M.; Decurtins, W.; Nauer, A.; Zimmermann, M.; Samain, F.; Scheuermann, J.; Brown, P. J.; Hall, J.; Gräslund, S.; Schüler, H.; Neri, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 3927–3931. (c) Yuen, L. H.; Dana, S.; Liu, Y.; Bloom, S. I.; Thorsell, A.; Neri, D.; Donato, A. J.; Kireev, D. B.; Schüler, H.; Franzini, R. M. *J. Am. Chem. Soc.* **2019**, *141*, 5169–5181.
- (8) Usanov, D. L.; Chan, A. I.; Maianti, J. P.; Liu, D. R. *Nat. Chem.* **2018**, *10*, 704–714.
- (9) Potowski, M.; Kunig, V. B. K.; Losch, F.; Brunschweiler, A. *MedChemComm* **2019**, *10*, 1082–1093.
- (10) Skopic, M. K.; Salamon, H.; Bugain, O.; Jung, K.; Gohla, A.; Doetsch, L. J.; Santos, D. d.; Bhat, A.; Wagner, B.; Brunschweiler, A. *Chem. Sci.* **2017**, *8*, 3356–3361.
- (11) (a) Ugi, I.; Steinbrueckner, C. *Angew. Chem.* **1960**, *72*, 267–268. (b) Zarganes-Tzitzikas, T.; Neochoritis, C. G.; Dömling, A. *ACS Med. Chem. Lett.* **2019**, *10*, 389–392. (c) Popovici-Muller, J.; Lemieux, R. M.; Artin, E.; Saunders, J. O.; Salituro, F. G.; Travins, J.; Cianchetta, G.; Cai, Z.; Zhou, D.; Cui, D.; Chen, P.; Straley, K.; Tobin, E.; Wang, F.; David, M. D.; Penard-Lacronique, V.; Quivoron, C.; Saada, V.; de Botton, S.; Gross, S.; Dang, L.; Yang, H.; Utley, L.; Chen, Y.; Kim, H.; Jin, S.; Gu, Z.; Yao, G.; Luo, Z.; Lv, X.; Fang, C.; Yan, L.; Olaharski, A.; Silverman, L.; Biller, S.; Su, S. M.; Yen, K. *ACS Med. Chem. Lett.* **2018**, *9*, 300–305. (d) Cioc, R. C.; Schaepkens van Riepmst, L.; Schuckman, P.; Ruijter, E.; Orru, R. V. A. *Synthesis* **2017**, *49*, 1664–1674. (e) Borthwick, A. D.; Liddle, J. *Methods and Principles in Medicinal Chemistry: Protein-Protein Interactions in Drug Discovery* **2013**, *56*, 225–256.
- (12) Zimmermann, G.; Rieder, U.; Bajic, D.; Vanetti, S.; Chaikuad, A.; Knapp, S.; Scheuermann, J.; Mattarella, M.; Neri, D. *Chem. - Eur. J.* **2017**, *23*, 8152–8155.
- (13) (a) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083–3135. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (d) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958–2975. (e) Neochoritis, C. G.; Zhao, T.; Dömling, A. *Chem. Rev.* **2019**, *119*, 1970–2042.
- (14) Yuen, L. H.; Franzini, R. M. *Bioconjugate Chem.* **2017**, *28*, 1076–1083.
- (15) (a) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoeregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112–3120. (b) Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, *20*, 65–116. (c) Bostrom, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T. *J. Med. Chem.* **2012**, *55*, 1817–1830.
- (16) Ramazani, A.; Rezaei, A. *Org. Lett.* **2010**, *12*, 2852–2855.
- (17) Shaaban, S.; Abdel-Wahab, B. F. *Mol. Diversity* **2016**, *20*, 233–254.

(18) Skopic, M. K.; Gotte, K.; Gramse, C.; Dieter, M.; Pospich, S.; Raunser, S.; Weberskirch, R.; Brunschweiler, A. *J. Am. Chem. Soc.* **2019**, *141*, 10546–10555.

(19) Nguyen, K. T.; Blum, L. C.; van Deursen, R.; Reymond, J.-L. *ChemMedChem* **2009**, *4*, 1803–1805.

(20) Rogers, D.; Hahn, M. J. *J. Chem. Inf. Model.* **2010**, *50*, 742–754.

(21) Sauer, W. H. B.; Schwarz, M. K. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987–1003.