OL Organic Letters

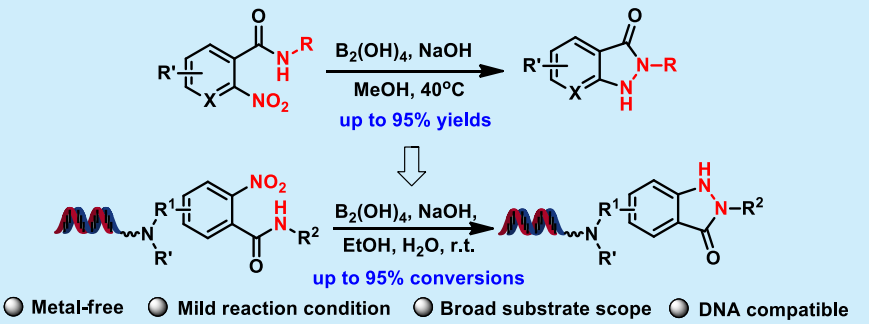
pubs.acs.org/OrgLett Letter

A $B_2(OH)_4$-Mediated Synthesis of 2-Substituted Indazolone and Its Application in a DNA-Encoded Library

Yapeng Bao,[†] Zongfa Deng,[†] Jing Feng,* Weiwei Zhu, Jin Li, Jinqiao Wan,* and Guansai Liu*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02032 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Indazolone cores are among the most common structural components in medicinal chemistry and can be found in many biologically active molecules. In this report, a mild and efficient approach to 2-substituted indazolones via $B_2(OH)_4$-mediated reductive *N*−*N* bond formation is developed. This strategy features mild conditions, no request for a metal catalyst, and a wide scope for both aliphatic and aromatic amines. Meanwhile, this method was further successfully applied on DNA to construct indazolone cores for a DNA-encoded library. This will enable the production of a very attractive indazolone-cored library from simple amines and scaffolds, which will provide considerable diversity.

The chemical space of biological compounds and natural products contains a large variety of heterocyclic structures. Indazolone cores are among the most common heterocyclic skeletons in medicinal chemistry and can be found in many biologically active molecules. Their tremendous importance can be exemplified by the presence of a great number of applications in the drug development field, such as antihyperlipidemia,[1a] analgesic,[1b] anti-inflammatory,[1c] antitumor,[1d] and antidiabetic.[1e]

Due to their versatility in pharmaceutical applications, many synthetic attempts to construct indazolone cores have been made (Figure 1).[1b,2] These methods are complementary, providing avenues to access various substitution patterns. However, these methods still have some potential limitations at some levels. Some of them relied on the requirements for a transition-metal catalyst (routes a and b),[2a−c,e] while the others still suffered from harsh reaction conditions such as high reaction temperatures (routes c−e).[1b,2d,j] In 2019, a mild and efficient synthetic method for 2-*N*-substituted indazolone derivatives via a photochemical cyclization was reported by Kambe and co-workers (route g).[2h] The photochemical cyclization reaction was rapid and halide compatible for the synthesis of halogenated indazolones. Unfortunately, it seemed that the reaction conditions were most likely applied for aliphatic amines. To build indazolone derivatives that are tolerant of both aliphatic and aromatic groups at 2-*N* positions,

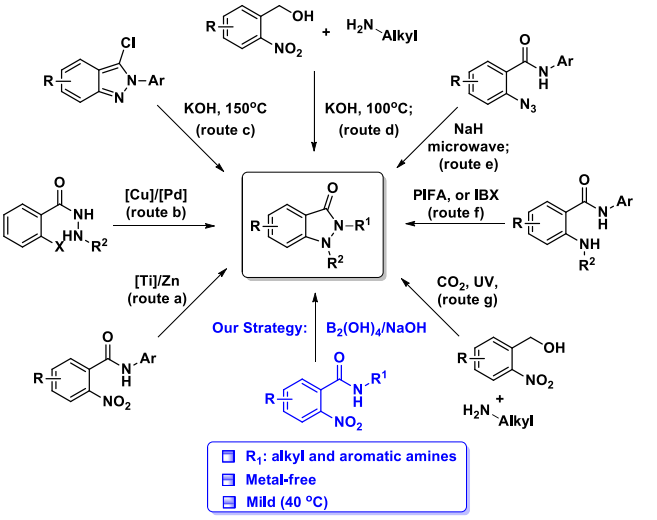
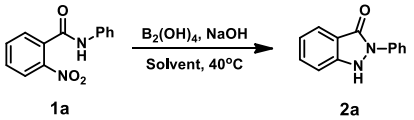


Figure 1. Approaches to indazolone derivatives.

Received: June 19, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02032
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimizations of the Conditions for $B_2(OH)_4$-Mediated Cyclization



entry[a]	solvent	$B_2(OH)_4$ (equiv)	NaOH (equiv)	yield (%[b])
1	MeOH	5	10	49[c]
2	MeOH	5	10	90 (89[d])
3	MeOH	5	0	0
4	EtOH	5	10	85
5	DMA	5	10	trace
6	DMSO	5	10	trace
7	9:1 MeOH/H_2O	5	10	89
8[e]	MeOH	5	10	0
9[e]	MeOH	100	200	91
10[e]	9:1 MeOH/H_2O	100	200	90

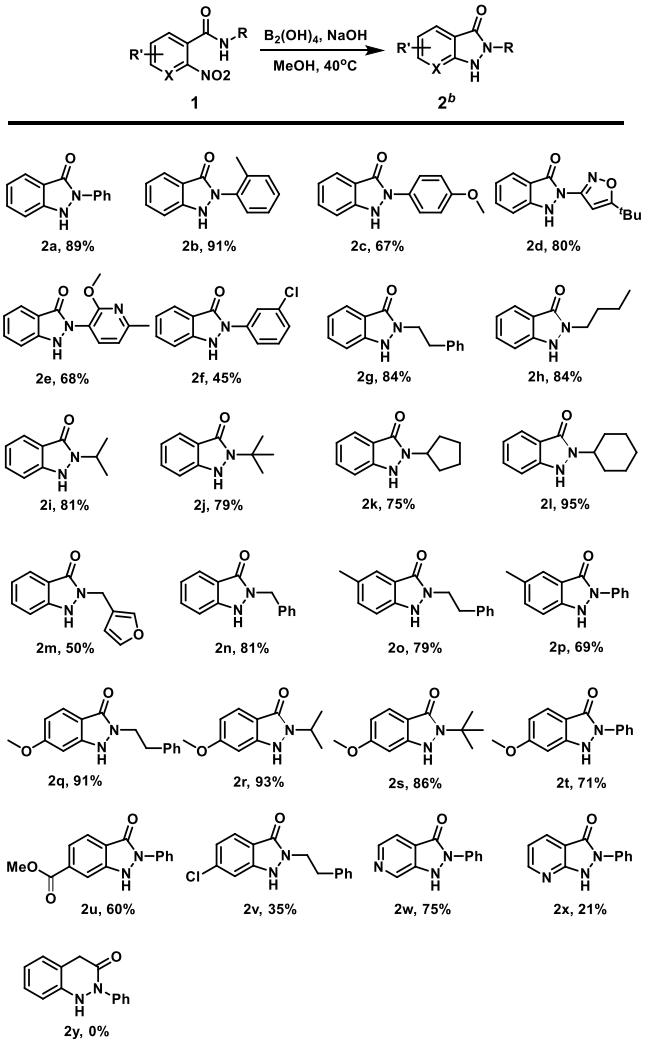
[a]To the solution of compound **1a** (0.040 mmol in 0.5 mL of solvent, 1.0 equiv) was added $B_2(OH)_4$. The mixture was then cooled to 0 °C. The NaOH solution (0.8 M in solvent) was added dropwise. After being stirred at 0 °C for 10 min, the mixture was warmed to 40 °C and reacted at 40 °C overnight. [b]Conversion was determined by LC-MS. [c]Reaction at 40 °C for 2 h. [d]Isolated yield (1.0 mmol scale). [e]The final concentration of compound **1a** was 0.002 M.

we report a new strategy for the synthesis of 2-substituted indazolone derivatives.

Diboronic acid was previously reported as a novel reducing agent for converting nitro aromatics into aromatic amines with good functional group tolerance in excellent yields.[3] In the transformation, the nitro aromatics were converted into nitroso intermediates,[3a] which were further reduced to aromatic amines. We envisioned that the nitroso intermediates can be captured by nucleophilic groups in *ortho* positions of aromatic rings to generate heterocycles. Inspired by this idea, we treated compound **1a** as a starting material with the $B_2(OH)_4$/NaOH condition (Table 1). To our delight, the reaction worked very well and gave the desired indazolone with a 90% LC-MS yield. The reaction was performed very well at 1 mmol scale, giving **2a** in an 89% isolated yield (entry 2). Then the roles of NaOH and solvents were further investigated. When NaOH was removed, this reaction did not work (entry 3). Protic solvents (MeOH and EtOH) were extremely important for this transformation. By comparison, there were only trace amounts of the desired compound observed when the solvent was changed to DMA or DMSO (entry 5 or 6, respectively). Furthermore, we found the reaction was aqueous compatible. An 89% LC-MS yield was obtained when using MeOH and water as co-solvents (entry 7). We next further investigated the kinetics of the transformations by adjusting the concentrations of reaction materials. We found that the reaction did not proceed if the concentration of compound **1a** was decreased to only 0.002 M (entry 8). However, the reaction gave an up to 91% LC-MS yield when 100 equiv of diboronic acid was used (entries 9 and 10). The information about aqueous compatibility and kinetic features implied to us that it is highly possible to develop this reaction on DNA and to apply it in the synthesis of a DNA-encoded library (DEL).

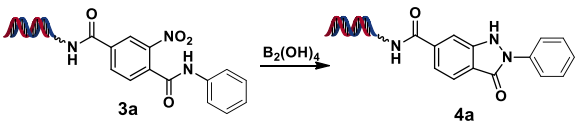
With the well-developed conditions in hand, we further studied the substrate scope by introducing various amines and substitutions on 2-nitro benzamide derivatives (Scheme 1). To

Scheme 1. Substrate Scope of 2-Substituted Indazolone Formation[a]



[a]To the solution of compound **1** (0.08 M in MeOH, 1.0 equiv) was added $B_2(OH)_4$ (5.0 equiv). The mixture was then cooled to 0 °C. The NaOH solution (0.8 M in MeOH, 10.0 equiv) was added dropwise. After being stirred at 0 °C for 10 min, the mixture was warmed to 40 °C and reacted at 40 °C overnight. [b]Isolated yields.

Table 2. Optimizations of Conditions for On-DNA Indazolone Formation



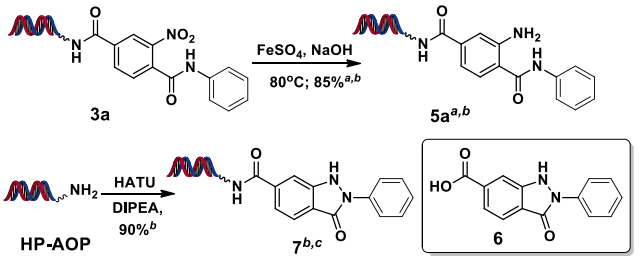
entry[a]	$B_2(OH)_4$ (equiv)	NaOH (equiv)	EtOH (v/v) (%)	**4a** (%[b])
1	80	300	0	87
2	80	300	6	95

[a]NaOH (6 μmol in 6 μL of H_2O, 300 equiv) and conjugate **3a** (20 nmol in 20 μL of H_2O, 1.0 equiv) were premixed together. EtOH and $B_2(OH)_4$ (1.6 μmol in 16 μL of H_2O, 80 equiv) were then added sequentially. The mixture was vortexed and reacted at room temperature for 2 h. [b]Conversion was determined by LC-MS.

our delight, both aliphatic amines and aromatic amines were tolerable, giving good to excellent yields, even for some hindered amines (**2j**) and heterocyclic amines (**2d** and **2e**).

https://dx.doi.org/10.1021/acs.orglett.0c02032
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. On-DNA Synthesis of Conjugate 5a[a,c] and 7[b]



[a]NaOH (4 μmol in 4 μL of H_2O, 200 equiv) and conjugate **3a** (20 nmol in 20 μL of H_2O, 1.0 equiv) were premixed together. $FeSO_4$ (2 μmol in 10 μL of H_2O, 100 equiv) was then added. The mixture was vortexed and reacted at 80 °C for 2 h. [b]Conversion was determined by LC-MS. [c]Compound **6** (5.0 μmol in 25 μL of DMA, 25 equiv), HATU (5.0 μmol in 12.5 μL of DMA, 25 equiv), and DIPEA (5.0 μmol in 12.5 μL of DMA, 25 equiv) were premixed and reacted at 0 °C for 5 min. The obtained crude mixture was added to HP-AOP {200 nmol in 200 μL of borate buffer [250 mM in H_2O (pH 9.4)]} and reacted at room temperature for 16 h.

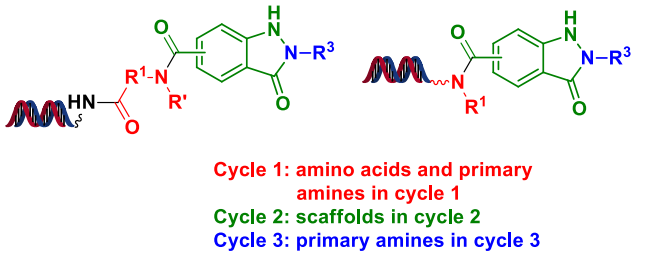
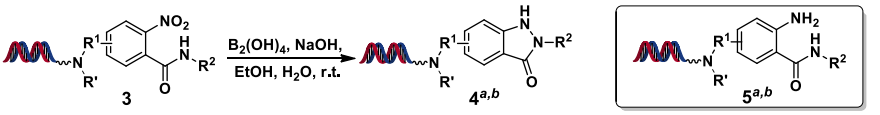
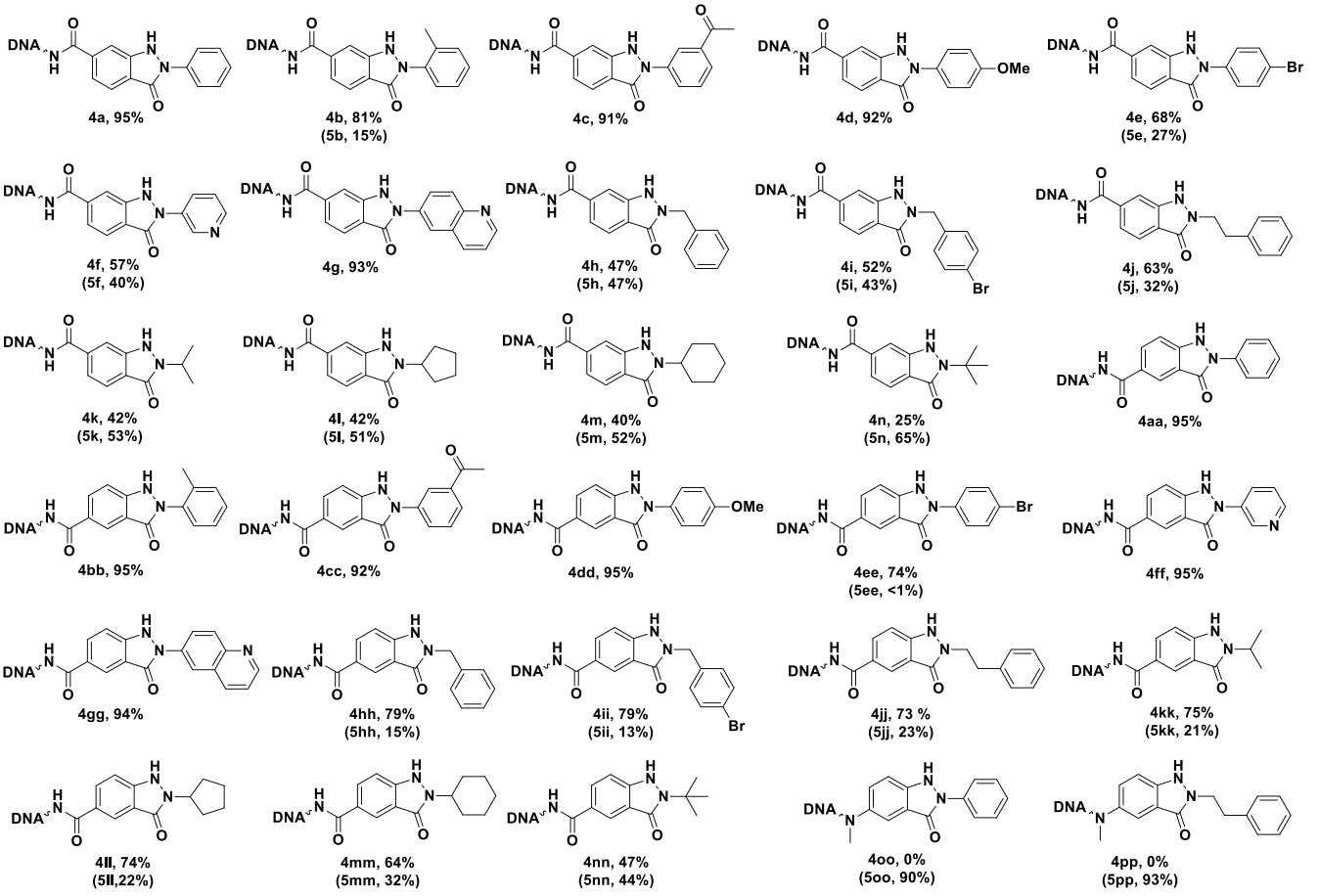


Figure 2. DNA-encoded library with indazolone cores.

This is one of the advantages of this strategy over other previously reported approaches. However, it seemed that the method was not so efficient for halogen-containing substrates. Besides the desired products, significant dehalogenation byproducts were obtained in the reactions (**2f** and **2v**). Furthermore, we screened substitutions on 2-nitro benzamide derivatives. Both electron-donating and electron-withdrawing groups are tolerable, as well, giving acceptable yields (**2o**–**2v**). Pyridine rings instead of phenyl rings were also investigated. A

Scheme 3. Substrate Scope of On-DNA Indazolone Formation





[a]NaOH (6 μmol in 6 μL of H_2O, 300 equiv) and conjugate **3** (20 nmol in 20 μL of H_2O, 1.0 equiv) were premixed together, and then EtOH [2.6 μL, 6% (v/v)] was added, which was followed by the addition of $B_2(OH)_4$ (1.6 μmol in 16 μL of H_2O, 80 equiv). The mixture was vortexed and reacted at room temperature for 2 h. [b]Conversion was determined by LC-MS.

https://dx.doi.org/10.1021/acs.orglett.0c02032
Org. Lett. XXXX, XXX, XXX−XXX

75% yield was obtained when nitrogen was at the *meta* position of nitro groups (**2w**). By comparison, an only 21% yield was achieved for the substrate with nitrogen at the *ortho* position of the nitro group (**2x**). Finally, this method was also tested to construct 1,4-dihydrocinnolin-3(2*H*)-one (**2y**). Unfortunately, we did not observe any proposed product, and the corresponding amine was produced instead.

DNA-encoded libraries have emerged in the pharmaceutical industry as one of the most powerful hit generation sources for early drug discovery.[4,5] One key attribute for a DEL to provide useful chemical starting points for medicinal chemistry is the structural diversity of accessible structures displayed by DNA. Its success is dependent not only on the number and diversity of the building blocks or scaffolds used for the DEL construction but also on a chemical methodology for assembling these building blocks and scaffolds.[6] On the basis of the studies presented above, we then decided to develop chemistry to furnish indazolone cores on DNA. Once the chemistry was proven to be DNA compatible, it would be interesting to use this approach to construct indazolone-cored DEL with millions of library compounds because tens of thousands of amines are commercially available.

On our end, there are several pieces of information giving us enormous confidence to realize this chemistry on DNA and apply it to DEL synthesis. First, this reaction was proven to be aqueous compatible. There was no obvious yield loss when using aqueous MeOH instead of MeOH solely. Second, the chemistry kinetically met criteria of on-DNA chemistry development upon dilution of one reactant while increasing the number of equivalents or concentrations of other reactants.[6k] Third, amines are largely commercially available, which will provide a huge diversity of DEL compounds. Finally, diboronic acid was previously reported to reduce nitro aromatics to aromatic amines on DNA by Simmons and co-workers in 2019.[3b] The naïve sequencing data implied to us that reduction reactions mediated by diboronic acid [150 equiv of $B_2(OH)_4$, 500 equiv of NaOH, aqueous EtOH] were DNA compatible, maintaining DNA integrity and ligation efficiency. As expected, conjugate **4a** was obtained from conjugate **3a** with excellent conversion (95% in entry 2 of Table 2) under conditions similar to those reported by Simmons and co-workers.[3b] Ethanol as the co-solvent was crucial for improving the conversion that is proven in the work of Simmons, as well (additional optimizations of conditions are provided in the Supporting Information).

To further validate on-DNA indazolone formation, on-DNA nitro-reduction product **5a** was synthesized via an $FeSO_4$/NaOH system that was commonly used in nitro reduction in DEL synthesis (Scheme 2). Meanwhile, small molecule compound **6** was synthesized and then attached to amine-modified DNA via simple amide coupling. Co-injection experiments (LC-MS and HPLC) of conjugates **4a**, **5a** and **7** were carried out. Conjugates **4a** and **7** gave identical LC-MS and HPLC traces (see the detailed information in the Supporting Information). This method indirectly confirmed the characterization of conjugate **4a**.

With the established conditions in hand, we further explored the scope of the on-DNA reactions with a range of substrates by (1) studying the effects of R^2 (**4a**−**4n**) and (2) studying DNA linking positions (**4aa**−**4nn**) and linking methods (**4oo** and **4pp**) (Scheme 3). The results showed that the on-DNA ring closures were efficient at room temperature. Both aromatic and aliphatic amines are tolerable in the transformations while aromatic amines perform slightly better. Interestingly, nearly no dehalogenation product was observed with bromide on amines (**4e**, **4ee**, **4i**, and **4ii**). This is different from what we observed in small molecule synthesis. Trifunctional 2-nitro benzamides are not widely commercially available; hence, we tested only some of them to see how tolerable they are. The acid-linked conjugate (**4aa**−**4nn**) gave the desired products in satisfactory conversions. However, the *N*-linked conjugates (**4oo** and **4pp**) gave reduction by-products, without giving the desired products.

With this on-DNA chemistry and scope study in hand, an indazolone-cored DEL was proposed to be synthesized with a split and pool approach (Figure 2). Upon introduction of three cycles of diversity, one library with millions of compounds was expected using commercially available building blocks as shown in Figure 2.

In summary, we report a mild and efficient approach to 2-substituted indazolones via $B_2(OH)_4$-mediated reductive *N*−*N* bond formation, which features mild conditions, no request of metal catalyst, and a wide scope for both aliphatic and aromatic amines. This method was further successfully applied on DNA to construct indazolone cores for DELs. Considerable diversity would be enabled by simple amines and commercially available scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02032.

Details of experimental procedures, copies of HPLC traces, and MS and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Guansai Liu − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*; orcid.org/0000-0001-8925-6093; Email: gs.liu@hitgen.com

Jing Feng − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*; Email: jing.feng@hitgen.com

Jinqiao Wan − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*; Email: jq.wan@hitgen.com

Authors

Yapeng Bao − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*

Zongfa Deng − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*

Weiwei Zhu − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*

Jin Li − *Discovery Chemistry Unit, HitGen Inc., Chengdu 610200, Sichuan, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02032

Author Contributions

†Y.B. and Z.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

https://dx.doi.org/10.1021/acs.orglett.0c02032
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

The authors acknowledge Jianrong Chen (HitGen Inc.) for assistance with HPLC purification.

■ REFERENCES

(1) (a) Kawanishi, N.; Sugimoto, T.; Shibata, J.; Nakamura, K.; Masutani, K.; Ikuta, M.; Hirai, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122. (b) Fletcher, S. R.; McIver, E.; Lewis, S.; Burkamp, F.; Leech, C.; Mason, G.; Boyce, S.; Morrison, D.; Richards, G.; Sutton, K.; Jones, A. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2872. (c) Yu, W.; Guo, Z.; Orth, P.; Madison, V.; Chen, L.; Dai, C.; Feltz, R. J.; Girijavallabhan, V. M.; Kim, S. H.; Kozlowski, J. A.; Lavey, B. J.; Li, D.; Lundell, D.; Niu, X.; Piwinski, J. J.; Popovici-Muller, J.; Rizvi, R.; Rosner, K. E.; Shankar, B. B.; Shih, N. Y.; Arshad Siddiqui, M.; Sun, J.; Tong, L.; Umland, S.; Wong, M. K.; Yang, D. Y.; Zhou, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1877. (d) Wang, H.; Han, H. Y.; Von Hoff, D. D. *Cancer Res.* **2006**, *66*, 9722. (e) Qian, Y.; Bolin, D.; Conde-Knape, K.; Gillespie, P.; Hayden, S.; Huang, K. S.; Olivier, A. R.; Sato, T.; Xiang, Q.; Yun, W.; Zhang, X. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2936.

(2) (a) Bird, C. W.; Chng, J. C. W.; Rama, N. H.; Saeed, A. *Synth. Commun.* **1991**, *21*, 545. (b) Dou, G.; Shi, D. *J. Comb. Chem.* **2009**, *11*, 1073. (c) Tanimori, S.; Ozaki, Y.; Iesaki, Y.; Kirihata, M. *Synlett* **2008**, *2008*, 1973. (d) Zhu, J. S.; Kraemer, N.; Shatskikh, M. E.; Li, C. J.; Son, J.-H.; Haddadin, M. J.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2018**, *20*, 4736. (e) Cappelli, A.; Nannicini, C.; Gallelli, A.; Giuliani, G.; Valenti, S.; Mohr, G. P.; Anzini, M.; Mennuni, L.; Ferrari, F.; Caselli, G.; Giordani, A.; Peris, W.; Makovec, F.; Giorgi, G.; Vomero, S. *J. Med. Chem.* **2008**, *51*, 2137. (f) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501. (g) Park, S. W.; Choi, H.; Lee, J.-H.; Lee, Y.-J.; Ku, J.-M.; Lee, S. Y.; Nam, T.-G. *Arch. Pharmacal Res.* **2016**, *39*, 302. (h) Yang, T.; Lu, H.; Qiu, R.; Hong, L.; Yin, S.-F.; Kambe, N. *Chem. - Asian J.* **2019**, *14*, 1436. (i) Zhu, J. S.; Kraemer, N.; Li, C. J.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2018**, *83*, 15493. (j) Shaw, A. Y.; Chen, Y. R.; Tsai, C. H. *Synth. Commun.* **2009**, *39*, 2647.

(3) (a) Chen, D.; Zhou, Y.; Zhou, H.; Liu, S.; Liu, Q.; Zhang, K.; Uozumi, Y. *Synlett* **2018**, *29*, 1765. (b) Du, H.-C.; Simmons, N.; Faver, J. C.; Yu, Z.; Palaniappan, M.; Riehle, K.; Matzuk, M. M. *Org. Lett.* **2019**, *21*, 2194.

(4) For selected recent reviews of DNA-encoded chemical libraries, see: (a) Neri, D.; Lerner, R. A. *Annu. Rev. Biochem.* **2018**, *87*, 479. (b) Lerner, R. A.; Brenner, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 1164. (c) Goodnow, R. A., Jr.; Dumelin, C. E.; Keefe, A. D. *Nat. Rev. Drug Discovery* **2017**, *16*, 131. (d) Zimmermann, G.; Neri, D. *Drug Discovery Today* **2016**, *21*, 1828. (e) Franzini, R. M.; Randolph, C. *J. Med. Chem.* **2016**, *59*, 6629. (f) Dickson, P.; Kodadek, T. *Org. Biomol. Chem.* **2019**, *17*, 4676. (g) Götte, K.; Chines, S.; Brunschweiger, A. *Tetrahedron Lett.* **2020**, *61*, 151889.

(5) For selected research papers on hit discovery using DEL technologies, see: (a) Harris, P. A.; King, B. W.; Bandyopadhyay, D.; Berger, S. B.; Campobasso, N.; Capriotti, C. A.; Cox, J. A.; Dare, L.; Dong, X.; Finger, J. N.; Grady, L. C.; Hoffman, S. J.; Jeong, J. U.; et al. *J. Med. Chem.* **2016**, *59*, 2163. (b) Maianti, J. P.; McFedries, A.; Foda, Z. H.; Kleiner, R. E.; Du, X. Q.; Leissring, M. A.; Tang, W. J.; Charron, M. J.; Seeliger, M. A.; Saghatelian, A.; Liu, D. R. *Nature* **2014**, *511*, 94. (c) Ding, Y.; O'Keefe, H.; DeLorey, J. L.; Israel, D. I.; Messer, J. A.; Chiu, C. H.; Skinner, S. R.; Matico, R. E.; Murray-Thompson, M. F.; Li, F.; Clark, M. A.; Cuozzo, J. W.; Arico-Muendel, C.; Morgan, B. A. *ACS Med. Chem. Lett.* **2015**, *6*, 888. (d) Lewis, H. D.; Liddle, J.; Coote, J. E.; Atkinson, S. J.; Barker, M. D.; Bax, B. D.; Bicker, K. L.; Bingham, R. P.; Campbell, M.; Chen, Y. H.; Chung, C.; Craggs, P. D.; Davis, R. P.; et al. *Nat. Chem. Biol.* **2015**, *11*, 189. (e) Samain, F.; Ekblad, T.; Mikutis, G.; Zhong, N.; Zimmermann, M.; Nauer, A.; Bajic, D.; Decurtins, W.; Scheuermann, J.; Brown, P. J.; Hall, J.; Gräslund, S.; Schüler, H.; Neri, D.; Franzini, R. M. *J. Med. Chem.* **2015**, *58*, 5143. (f) Li, Y. Z.; De Luca, R.; Cazzamalli, S.; Pretto, F.; Bajic, D.; Scheuermann, J.; Neri, D. *Nat. Chem.* **2018**, *10*, 441. (g) Cuozzo, J. W.; Centrella, P. A.; Gikunju, D.; Habeshian, S.; Hupp, C. D.; Keefe, A. D.; Sigel, E. A.; Soutter, H. H.; Thomson, H. A.; Zhang, Y.; Clark, M. A. *ChemBioChem* **2017**, *18*, 864. (h) Brown, D. G.; Brown, G. A.; Centrella, P.; Certel, K.; Cooke, R. M.; Cuozzo, J. W.; Dekker, N.; Dumelin, C. E.; Ferguson, A.; Fiez-Vandal, C.; Geschwindner, S.; et al. *SLAS Discovery* **2018**, *23*, 429. (i) Richter, H.; Satz, A. L.; Bedoucha, M.; Buettelmann, B.; Petersen, A. C.; Harmeier, A.; Hermosilla, R.; Hochstrasser, R.; Burger, D.; Gsell, B.; Gasser, R.; Huber, S.; Hug, M. N.; Kocer, B.; Kuhn, B.; Ritter, M.; Rudolph, M. G.; Weibel, F.; Molina-David, J.; Kim, J.-J.; Santos, J. V.; Stihle, M.; Georges, G. J.; Bonfil, R. D.; Fridman, R.; Uhles, S.; Moll, S.; Faul, C.; Fornoni, A.; Prunotto, M. *ACS Chem. Biol.* **2019**, *14*, 37. (j) Petersen, L. K.; Blakskjær, P.; Chaikuad, A.; Christensen, A. B.; Dietvorst, J.; Holmkvist, J.; Knapp, S.; Kořínek, M.; Larsen, L. K.; Pedersen, A. E.; Röhm, S.; Sløk, F. A.; Hansen, N. J. V. *MedChemComm* **2016**, *7*, 1332. (k) Ahn, S.; Kahsai, A. W.; Pani, B.; Wang, Q. T.; Zhao, S.; Wall, A. L.; Strachan, R. T.; Staus, D. P.; Wingler, L. M.; Sun, L. D.; Sinnaeve, J.; Choi, M.; Cho, T.; Xu, T. T.; Hansen, G. M.; et al. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 1708. (l) Kazmierski, W. M.; XIA, B.; Miller, J.; De la Rosa, M.; Favre, D.; Dunham, R.; Washio, Y.; Zhu, Z.; Wang, F.; Mebrahtu, M.; Deng, H.; Basilla, J.; Wang, L.; Evindar, G.; Fan, L.; Olszewski, A.; Prabhu, N.; Davie, C.; Messer, J. A.; Samano, V. *J. Med. Chem.* **2020**, *63* (7), 3552.

(6) For selected research papers on the development of DNA compatible reactions, see: (a) Li, X.; Liu, D. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4848. (b) Chouikhi, D.; Ciobanu, M.; Zambaldo, C.; Duplan, V.; Barluenga, S.; Winssinger, N. *Chem. - Eur. J.* **2012**, *18*, 12698. (c) 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. (d) Ding, Y.; Clark, M. A. *ACS Comb. Sci.* **2015**, *17*, 1. (e) MacConnell, A. B.; McEnaney, P. J.; Cavett, V. J.; Paegel, B. M. *ACS Comb. Sci.* **2015**, *17*, 518. (f) Satz, A. L.; Cai, J.; Chen, Y.; Goodnow, R.; Gruber, F.; Kowalczyk, A.; Petersen, A.; Naderi-Oboodi, G.; Orzechowski, L.; Strebel, Q. *Bioconjugate Chem.* **2015**, *26*, 1623. (g) Li, Y.; Gabriele, E.; Samain, F.; Favalli, N.; Sladojevich, F.; Scheuermann, J.; Neri, D. *ACS Comb. Sci.* **2016**, *18*, 438. (h) Ding, Y.; Franklin, G. J.; DeLorey, J. L.; Centrella, P. A.; Mataruse, S.; Clark, M. A.; Skinner, S. R.; Belyanskaya, S. *ACS Comb. Sci.* **2016**, *18*, 625. (i) Fan, L.; Davie, C. P. *ChemBioChem* **2017**, *18*, 843. (j) Thomas, B.; Lu, X.; Birmingham, W. R.; Huang, K.; Both, P.; Reyes Martinez, J. E.; Young, R. J.; Davie, C. P.; Flitsch, S. L. *ChemBioChem* **2017**, *18*, 858. (k) 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. Q.; Qin, T.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, E6404. (l) Wang, X.; Sun, H.; Liu, J.; Dai, D.; Zhang, M.; Zhou, H.; Zhong, W.; Lu, X. *Org. Lett.* **2018**, *20*, 4764. (m) Lu, X.; Roberts, S. E.; Franklin, G. J.; Davie, C. P. *MedChemComm* **2017**, *8*, 1614. (n) Lu, X.; Fan, L.; Phelps, C. B.; Davie, C. P.; Donahue, C. P. *Bioconjugate Chem.* **2017**, *28*, 1625. (o) Satz, A. L.; Cai, J.; Chen, Y.; Goodnow, R.; Gruber, F.; Kowalczyk, A.; Petersen, A.; Naderi-Oboodi, G.; Orzechowski, L.; Strebel, Q. *Bioconjugate Chem.* **2015**, *26*, 1623. (p) Kölmel, D. K.; Loach, R. P.; Knauber, T.; Flanagan, M. E. *ChemMedChem* **2018**, *13*, 2159. (q) Du, H.-C.; Simmons, N.; Faver, J. C.; Yu, Z.; Palaniappan, M.; Riehle, K.; Matzuk, M. M. *Org. Lett.* **2019**, *21*, 2194. (r) Phelan, J. P.; Lang, S. B.; Sim, J.; Berritt, S.; Peat, A. J.; Billings, K.; Fan, L. J.; Molander, G. A. *J. Am. Chem. Soc.* **2019**, *141*, 3723. (s) Flood, D. T.; Asai, S.; Zhang, X. J.; Wang, J.; Yoon, L.; Adams, Z. C.; Dillingham, B. C.; Sanchez, B. B.; Vantourout, J. C.; Flanagan, M. E.; Piotrowski, D. W.; Richardson, P. F.; Green, S. A.; Shenvi, R. A.; Chen, J. S.; Baran, P. S.; Dawson, P. E. *J. Am. Chem. Soc.* **2019**, *141*, 9998. (t) Kölmel, D. K.; Ratnayake, A. S.; Flanagan, M. E.; Tsai, M.-H.; Duan, C.; Song, C. *Org. Lett.* **2020**, *22* (8), 2908. (u) Westphal, M. V.; Hudson, L.; Mason, J. W.; Pradeilles, J.; Zecri, F. J.; Briner, K.; Schreiber, S. L. *J. Am. Chem. Soc.* **2020**, *142* (17), 7776. (v) Cai, P. W.; Yang, G. Y.; Zhao, L. Z.; Wan, J. Q.; Li, J.; Liu, G. S. *Org. Lett.* **2019**, *21*, 6633. (w) Su, L. Q.; Feng, J.; Peng, T.; Wan, J. Q.; Fan, J.; Li, J.; O'Connell,

https://dx.doi.org/10.1021/acs.orglett.0c02032
Org. Lett. XXXX, XXX, XXX−XXX

J.; Lancia, D. R., Jr.; Franklin, G. J.; Liu, G. S. *Org. Lett.* **2020**, *22*, 1290.

https://dx.doi.org/10.1021/acs.orglett.0c02032
Org. Lett. XXXX, XXX, XXX−XXX