ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett

Letter

# Development of Highly Potent and Selective Pyrazolopyridine Inhibitor of CDK8/19

John M. Hatcher, Prasanna S. Vatsan, Eric Wang, Jie Jiang, and Nathanael S. Gray*

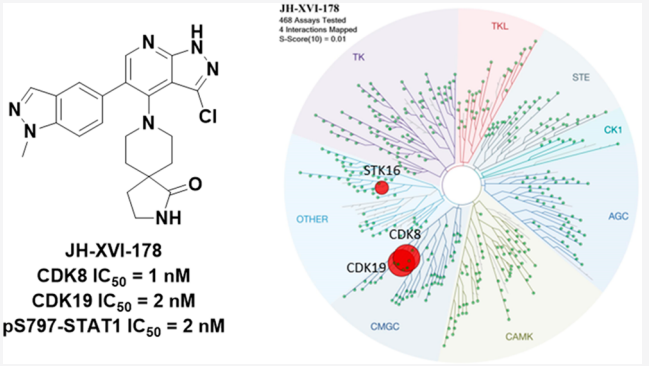
Cite This: ACS Med. Chem. Lett. 2021, 12, 1689−1693

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** CDK8 and its paralog CDK19 are cyclin-dependent kinases that are core components of the so-called Mediator complex that has essential roles as a positive and negative regulator of gene expression. Several efforts to develop inhibitors have yielded natural and synthetic ATP-competitive compounds including cortistatin A, Sel120, BCD-115, CCT251921 (**1**), and MSC2530818 (**2**). Here, we used a hybridization approach starting from CCT251921 and MSC2530818 to derive new inhibitors with the aim of developing highly potent and selective inhibitors of CDK8/19. Initial compounds suffered from rapid aldehyde oxidase-mediated metabolism. This liability was overcome by utilizing a pyrazolopyridine hinge binder with a chlorine at the C-3 position. These efforts resulted in JH-XVI-178 (compound **15**), a highly potent and selective inhibitor of CDK8/19 that displays low clearance and moderate oral pharmacokinetic properties.

**KEYWORDS:** *CDK8, CDK19, Kinase inhibitor, Mediator complex*




CDK8 and its paralog CDK19 are cyclin-dependent kinases that form part of the Mediator complex, a multiprotein assembly composed of at least 30 subunits that functions as a regulator of gene transcription. Mediator complex function has been implicated in multiple contexts including stem cell function, immune response, inflammation, cell adhesion, and epithelial to mesenchymal transition and development.[1−5] Deregulation of CDK8 and its binding partner cyclin C (CCNC) is a common feature of many cancers, including cancers of the colon,[6−8] breast,[9−12] prostate,[13] and pancreas[14] and melanoma[15] and leukemias.[16,17] Several ATP-competitive, small-molecule CDK8/19 inhibitors showed *in vivo* efficacy and two (senexin B and SEL120) have entered clinical trials, with no significant toxicities reported.[18] The results of these trials have not been disclosed at the time of this publication. However, multiple toxicities were observed in rats and dogs treated with compounds **1** and **2**.[19−22] A recent report suggested these toxicities could be due to off-target effects.[18] Based on this report, we set out to develop CDK8/19 inhibitors with narrower selectivity profile that may overcome these toxicities. Herein, we report our initial SAR efforts. Toxicity studies will be reported in due course.

Our strategy was to make a hybrid structure of **1** and **2** since they are known to be potent inhibitors of CDK8/19 with moderate selectivity profiles and promising pharmacokinetic profiles (Figure 1). We imagined that the hybrid of these two compounds should maintain potent CDK8/19 inhibition and might have a narrower selectivity profile. As a starting point, we

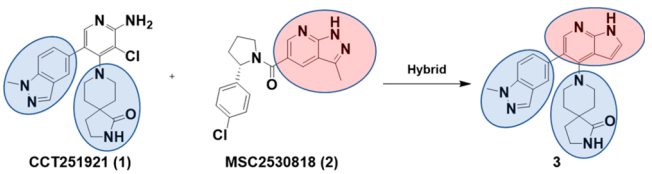
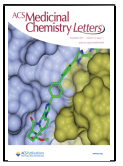



**Figure 1.** Hybridization design strategy leading to the development of this series of CDK8/19 inhibitors.

decided to change the amino-pyridine hinge binder to a variety of hinge binders similar to **2**, including azaindole (**3**), pyrazolopyridine (**4**), imidazopyridine (**5**), and thienopyridine (**6**).

As shown in Table 1, we found that the azaindole (**3**) was extremely potent in the Lanthascreen enzyme assay from Invitrogen with an $IC_{50}$ of 2 nM. The imidazopyridine (**5**) was also potent with an $IC_{50}$ of 10 nM, while the pyrazolopyridine (**4**) and thienopyridine (**6**) lost a great deal of potency with $IC_{50}$ values of 178 and 206 nM, respectively. This was particularly interesting given the similarity in hinge binders

**Received:** May 25, 2021
**Accepted:** October 20, 2021
**Published:** October 22, 2021

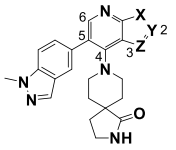






https://doi.org/10.1021/acsmedchemlett.1c00300
ACS Med. Chem. Lett. 2021, 12, 1689−1693

**Table 1. SAR of the Hinge Binding Group**



| compd | X | Y | Z | CDK8 enzyme $IC_{50}$ (nM) | CDK19 enzyme $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **3** | NH | CH | CH | 2 | 7 |
| **4** | NH | N | CH | 178 | 214 |
| **5** | NH | CH | N | 10 | 5 |
| **6** | S | CH | CH | 206 | *a* |

[a]Not determined.

between **4** and MSC2530818 (**2**). However, the reported binding mode of **2**[22] is quite different from the reported binding mode of **1**[21] with the hinge contacts being made at the nitrogens at the 1 and 2 positions with the methyl group at the 3-position directed into a hydrophobic pocket. We undertook a docking study of **3** using the cocrystal structure of **1** in complex with CDK8/cyclin C (Figure 2). The docking study predicts

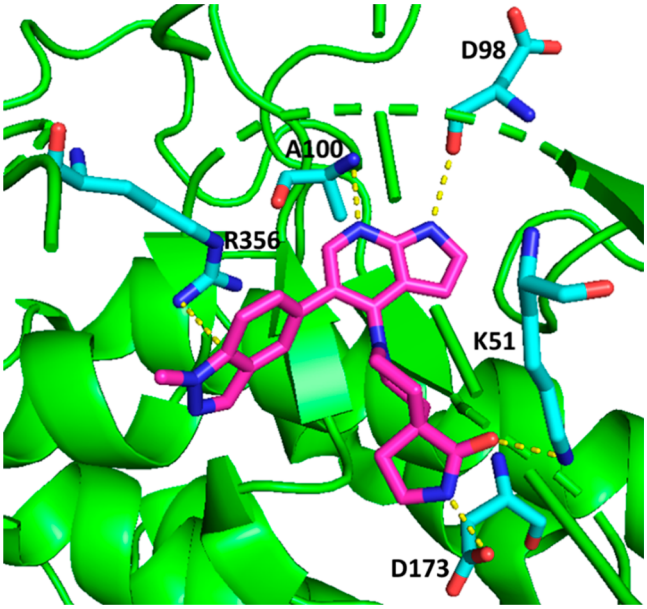
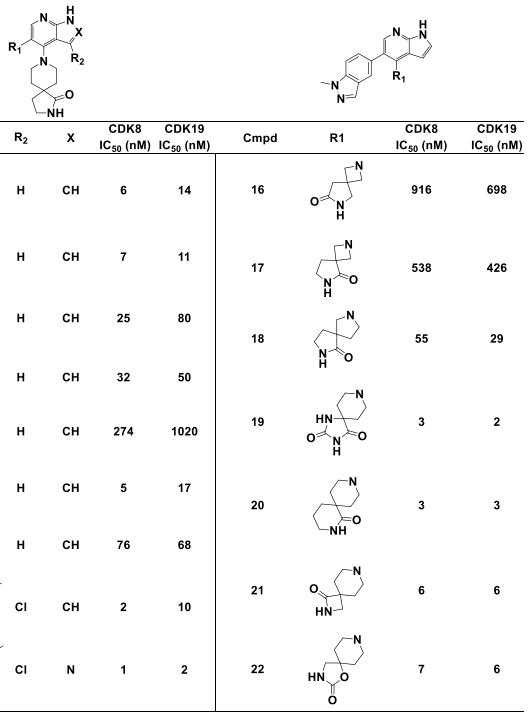



**Figure 2.** Docking study of **3** using the cocrystal structure of **1** in complex with CDK8 (PDB ID 5HBJ). Dashed lines suggest important interactions.

that the azaindole (**3**) maintains the same critical interactions as **1** including hinge contact with A100 and D98, a $\pi$−cation interaction with R356 and the left-hand side indazole, and hydrogen bond interactions with K51 and D173 with the lactam of the spirocycle. In addition, our docking model predicts that **4** could not adopt the same binding mode as **2** described above since the spirocycle is too large to fit in the hydrophobic pocket occupied by the methyl group of **2** and would clash with the backbone of the protein. In this case, the nitrogen at the 2-position of compound **4** is directed into a hydrophobic pocket causing an unfavorable interaction, resulting in the observed loss in potency.

Based on the promising results with azaindole **3**, we decided to pursue this series further by exploring the SAR at the 5 position while keeping the same spirocycle at the 4 position as shown in Table 2. We found that most fused 6−5 ring systems were able to maintain potent inhibition of CDK8 with the

**Table 2. SAR of the 4 and 5 Position of Azaindole 3**



| Cmpd | $R_1$ | $R_2$ | X | CDK8 $IC_{50}$ (nM) | CDK19 $IC_{50}$ (nM) | Cmpd | R1 | CDK8 $IC_{50}$ (nM) | CDK19 $IC_{50}$ (nM) |
|---|---|---|---|---|---|---|---|---|---|
| 7 | | H | CH | 6 | 14 | 16 | | 916 | 698 |
| 8 | | H | CH | 7 | 11 | 17 | | 538 | 426 |
| 9 | | H | CH | 25 | 80 | 18 | | 55 | 29 |
| 10 | | H | CH | 32 | 50 | | | | |
| 11 | | H | CH | 274 | 1020 | 19 | | 3 | 2 |
| 12 | | H | CH | 5 | 17 | 20 | | 3 | 3 |
| 13 | | H | CH | 76 | 68 | | | | |
| 14 | | Cl | CH | 2 | 10 | 21 | | 6 | 6 |
| 15 | | Cl | N | 1 | 2 | 22 | | 7 | 6 |

exception of the triazolopyridine (**11**) and the imidazopyridine (**13**). Our docking model predicted that a chlorine at the 3 position could form an edge-on halogen−$\pi$ interaction with F97. We therefore installed a chlorine at the 3 position of the azaindole (compound **14**, Table 2) and the 3-position of the pyrazolopyridine (compound **15**, Table 2), hoping to improve the potency further. While compound **14** showed similar potency against CDK8 compared to **3**, compound **15** showed a drastic increase in potency (178 nM for **4** compared to 1 nM for **15**). To explain this finding, we docked compound **15** into our model shown in Figure 3 and confirmed that the 2 position of the hinge binder is positioned in a hydrophobic pocket, so having a polar nitrogen in this position results in an unfavorable interaction. However, introduction of a chlorine at the 3 position, could result in a halogen−$\pi$ interaction with F97 as well as a decrease in polarity around that site. Taken together, these modifications result in an increase in potency on CDK8. We then chose to explore various spirocyclic substituents at the 4 position of the azaindole again hoping to further improve potency. We found that a variety of spirocycles (compounds **16**−**22**, Table 2) were quite potent against CDK8; however, none of them showed a significant improvement in potency compared to **3**, so we decided to use the original spirocycle moving forward.

The representative preparation of JH-XVI-178 (**15**) is presented in Scheme 1. Pyrazolopyridine **23** was chlorinated using NCS in $CH_3CN$ at 70 °C followed by SEM protection to give **24**. Compound **24** then underwent nucleophilic substitution with the spirocycle **25** in NMP at 180 °C under microwave conditions to give **26**, which then underwent a Suzuki coupling with the corresponding *N*-methyl indazole



https://doi.org/10.1021/acsmedchemlett.1c00300
ACS Med. Chem. Lett. 2021, 12, 1689−1693

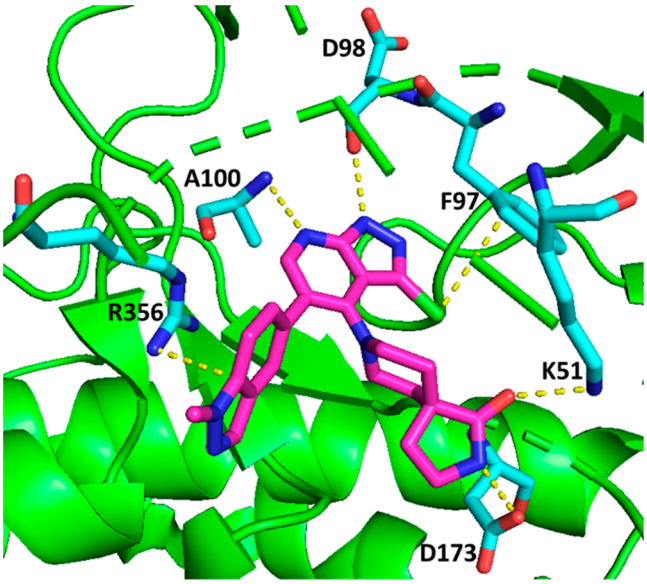
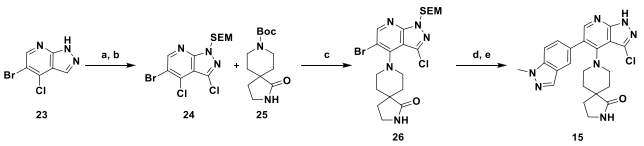



**Figure 3.** Docking study of **15** using the cocrystal structure of **1** in complex with CDK8 (PDB ID 5HBJ). Dashed lines suggest important interactions.

**Scheme 1. Preparation of JH-XVI-178**[a]




[a]Reagents and conditions: (a) NCS, $CH_3CN$, 70 °C; (b) SEM-Cl, NaH, DMF; (c) NMP, TEA, 180 °C $\mu$W; (d) $Pd(dppf)Cl_2$, *t*-BuXPhos, 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole, $Na_2CO_3$, 1,4-dioxane, $H_2O$, 100 °C; (e) HCl, MeOH, 70 °C.

boronic ester followed by removal of the SEM group with HCl to give the desired compound **15**.

We then tested the potency of these compounds in a cellular environment by measuring their inhibition of phosphorylation of S727-STAT1, a known substrate of CDK8, in comparison with **1**. As seen in Figure 4, compound **3** showed much less inhibition of pS727-STAT1 compared to **1** and **2** with an $IC_{50}$ of 46 nM compared to 5 nM for **1** and 3 nM for **2**. Compound **15** showed slightly stronger inhibition of pS727-STAT1 with an $IC_{50}$ of 2 nM. Western blot data for all compounds can be found in the SI, Figure S1. Satisfied with the level of potency of **15** in both biochemical and cellular environments, we then decided to evaluate the kinase selectivity by performing KINOMEscan binding analysis against a near comprehensive panel of 468 kinases at a concentration of 1 $\mu$M as shown in Figure 5. Compound **15** displayed exceptional kinome selectivity as measured by a KINOMEscan selectivity score of S(10) = 0.01 at a concentration of 1 $\mu$M. Compound **15** exhibited off-target inhibition of only two additional kinases, STK16 and FLT3 (D835V). Dose response analysis revealed an $IC_{50}$ of 107 nM for STK16. Biochemical assays for FLT3 (D835V) were not commercially available at the time of writing this manuscript. Full profiling results for **15** can be found in the SI.

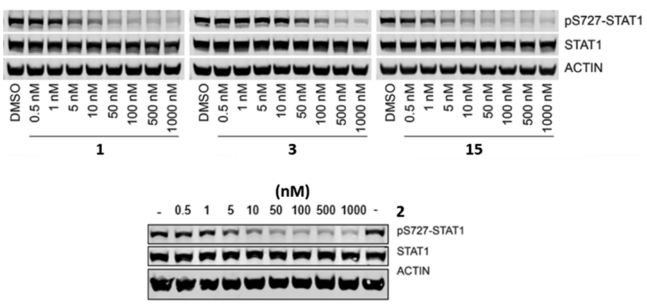



**Figure 4.** Western blot analysis and $IC_{50}$ determination following 24 h treatment of Jurkat cells with **1**, **2**, **3**, or **15** monitoring phosphorylation of s727-STAT1. $IC_{50}$ curves can be found in the Supporting Information section S2.

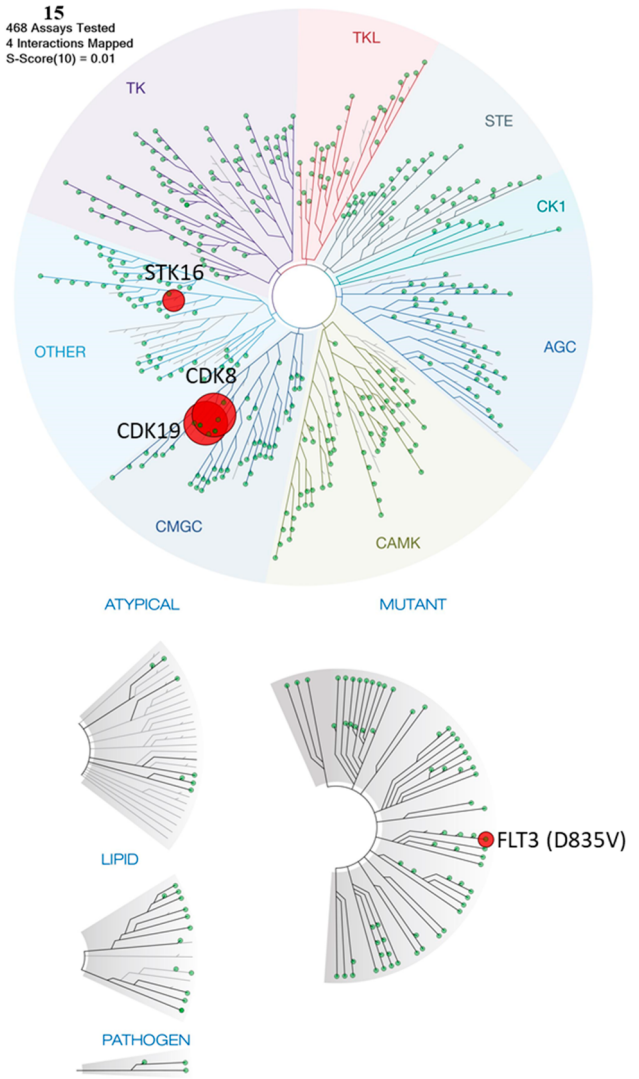



**Figure 5.** KINOMEscan results for **15** at a concentration of 1 $\mu$M with a cutoff of 90% inhibition.

With these promising results, we began investigating the metabolic stability of this series by assessing mouse hepatocyte stability.

As shown in Table 3, compounds **3**, **5**, and **14** suffered from poor metabolic stability. Recent reports in the literature have shown azaindoles to be substrates for aldehyde oxidase (AO).[23] More specifically, the 2-position on the bicyclic ring



https://doi.org/10.1021/acsmedchemlett.1c00300
ACS Med. Chem. Lett. 2021, 12, 1689−1693

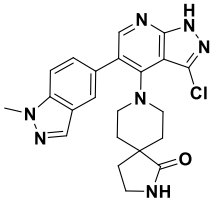
**Table 3. *In Vitro* Metabolic Stability of Representative Hinge Binding Groups**

| compd | $T_{1/2}$ (min) | $Cl_{int}$ ($\mu$L·min$^{-1}$·mg$^{-1}$) | CDK8 $IC_{50}$ (nM) |
|---|---|---|---|
| **3** | 9 | 78 | 2 |
| **4** | 11 | 59 | 178 |
| **5** | 5 | 158 | 10 |
| **14** | 11 | 64 | 2 |
| **15** | 46 | 15 | 1 |

was found to be the labile site. Based on this finding, we tested **4** in mouse hepatocytes since the 2-position is a nitrogen and therefore should not be metabolized by AO. However, **4** was also metabolically unstable. We hypothesized that since we blocked the 2-position, the 3-position could likely become the new labile site. In order to check this possibility, we tested **15** with a nitrogen at the 2-position and a chlorine at the 3-position. Gratifyingly, this substitution greatly improved metabolic stability, and we chose **15** as our lead, and it was progressed to *in vivo* pharmacokinetic studies in C57Bl/6 male mice.

Compound **15** exhibited a reasonable pharmacokinetic profile with a moderate $C_{max}$ of 1.04 $\mu$M following oral dosing, and a low Cl of 17 mL·min$^{-1}$·kg$^{-1}$ (Table 4). Despite having a

**Table 4. Summary of Compound 15**




Compound 15

| In Vitro | |
|---|---|
| CDK8 $IC_{50}$ (nM) | 1 |
| CDK19 $IC_{50}$ (nM) | 2 |
| $Cl_{int}$[a] ($\mu$L·min$^{-1}$·mg$^{-1}$) | 15 |
| **In Vivo Mouse PK[b]** | |
| $C_{Max}$[c] ($\mu$M) | 1.04 |
| $AUC_{last}$ (min × ng/mL)[c] | 51863 |
| $T_{1/2}$[c] (h) | 1.3 |
| Cl (mL·min$^{-1}$·kg$^{-1}$) | 17 |
| $V_{ss}$ (L/kg) | 0.8 |
| *F* (%) | 8 |

[a]Mouse hepatocytes. [b]Formulation: 0.2 mg/mL (IV) and 1 mg/mL (PO) solution in 5/95 DMSO/30% Captisol; 2 mg/kg IV dose and 10 mg/kg PO dose. [c]Following PO dose.

low oral bioavailability, the plasma concentrations of **15** at 4 and 6 h were 200 nM and 20 nM, respectively, which is well in excess of the concentration needed to cover the cellular $IC_{50}$ value.

In summary, we have discovered a highly potent and selective series of CDK8/19 inhibitors based on a hybridization approach starting from CCT251921 and MSC2530818. Compound **15** significantly inhibits phosphorylation of STAT1-S727 with an $IC_{50}$ of 2 nM. In addition, **15** exhibits excellent kinome selectivity, and shows moderate pharmacokinetic properties following oral dosing in mice. Further optimization of this chemotype especially in regard to *in vivo* bioavailability as well as toxicology studies will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00300.

Western blots, $IC_{50}$ curves, full Ambit profiling data for **15**, experimental details, and *in vivo* PK plots of time vs plasma concentration (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Nathanael S. Gray** − *Department of Chemical and Systems Biology, ChEM-H, and Stanford Cancer Institute, Stanford University, Stanford, California 94305, United States;* orcid.org/0000-0001-5354-7403; Phone: 1-617-582-8590; Email: Nathanael_Gray@dfci.harvard.edu

### Authors

**John M. Hatcher** − *Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, United States; Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, United States*

**Prasanna S. Vatsan** − *Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, United States; Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, United States*

**Eric Wang** − *Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, United States; Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, United States*

**Jie Jiang** − *Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, United States; Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.1c00300


### Author Contributions

Conceptualization: J.M.H. and N.S.G. Compound design and synthesis: J.M.H. and P.S.V. Cellular experiments: E.W. and J.J. Molecular modeling: J.H. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare the following competing financial interest(s): Nathanael Gray is a founder, science advisory board member (SAB), and equity holder in Gatekeeper, Syros, Petra, C4, B2S, Aduro, Inception, Allorion, Jengu, Larkspur (board member), and Soltego (board member). The Gray lab receives or has received research funding from Novartis, Takeda, Astellas, Taiho, Janssen, Kinogen, Voronoi, Arbella, Deerfield, and Sanofi.

## ■ REFERENCES

(1) Allen, B. L.; Taatjes, D. J. The Mediator complex: a central integrator of transcription. *Nat. Rev. Mol. Cell Biol.* **2015**, *16* (3), 155−166.

(2) Carlsten, J. O. P.; Zhu, X.; Gustafsson, C. M. The multitalented Mediator complex. *Trends Biochem. Sci.* **2013**, *38* (11), 531−537.
(3) Kim, S.; Xu, X.; Hecht, A.; Boyer, T. G. Mediator is a transducer of Wnt/beta-catenin signaling. *J. Biol. Chem.* **2006**, *281* (20), 14066−14075.
(4) Schiano, C.; Casamassimi, A.; Rienzo, M.; de Nigris, F.; Sommese, L.; Napoli, C. Involvement of Mediator complex in malignancy. *Biochim. Biophys. Acta, Rev. Cancer* **2014**, *1845* (1), 66−83.
(5) Schiano, C.; Casamassimi, A.; Vietri, M. T.; Rienzo, M.; Napoli, C. The roles of Mediator complex in cardiovascular diseases. *Biochim. Biophys. Acta, Gene Regul. Mech.* **2014**, *1839* (6), 444−451.
(6) Firestein, R.; Bass, A. J.; Kim, S. Y.; Dunn, I. F.; Silver, S. J.; Guney, I.; Freed, E.; Ligon, A. H.; Vena, N.; Ogino, S.; Chheda, M. G.; Tamayo, P.; Finn, S.; Shrestha, Y.; Boehm, J. S.; Jain, S.; Bojarski, E.; Mermel, C.; Barretina, J.; Chan, J. A.; Baselga, J.; Tabernero, J.; Root, D. E.; Fuchs, C. S.; Loda, M.; Shivdasani, R. A.; Meyerson, M.; Hahn, W. C. CDK8 is a colorectal cancer oncogene that regulates beta-catenin activity. *Nature* **2008**, *455* (7212), 547−U60.
(7) Adler, A. S.; McCleland, M. L.; Truong, T.; Lau, S.; Modrusan, Z.; Soukup, T. M.; Roose-Girma, M.; Blackwood, E. M.; Firestein, R. CDK8 Maintains Tumor Dedifferentiation and Embryonic Stem Cell Pluripotency. *Cancer Res.* **2012**, *72* (8), 2129−2139.
(8) Liang, J.; Chen, M.; Hughes, D.; Chumanevich, A. A.; Altilia, S.; Kaza, V.; Lim, C.-U.; Kiaris, H.; Mythreye, K.; Pena, M. M.; Broude, E. V.; Roninson, I. B. CDK8 Selectively Promotes the Growth of Colon Cancer Metastases in the Liver by Regulating Gene Expression of TIMP3 and Matrix Metalloproteinases. *Cancer Res.* **2018**, *78* (23), 6594−6606.
(9) Porter, D. C.; Farmaki, E.; Altilia, S.; Schools, G. P.; West, D. K.; Chen, M.; Chang, B.-D.; Puzyrev, A. T.; Lim, C.-u.; Rokow-Kittell, R.; Friedhoff, L. T.; Papavassiliou, A. G.; Kalurupalle, S.; Hurteau, G.; Shi, J.; Baran, P. S.; Gyorffy, B.; Wentland, M. P.; Broude, E. V.; Kiaris, H.; Roninson, I. B. Cyclin-dependent kinase 8 mediates chemotherapy-induced tumor-promoting paracrine activities. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109* (34), 13799−13804.
(10) Broude, E. V.; Gyoerffy, B.; Chumanevich, A. A.; Chen, M.; McDermott, M. S. J.; Shtutman, M.; Catroppo, J. F.; Roninson, I. B. Expression of CDK8 and CDK8-interacting Genes as Potential Biomarkers in Breast Cancer. *Curr. Cancer Drug Targets* **2015**, *15* (8), 739−749.
(11) McDermott, M. S. J.; Chumanevich, A. A.; Lim, C.-u.; Liang, J.; Chen, M.; Altilia, S.; Oliver, D.; Rae, J. M.; Shtutman, M.; Kiaris, H.; Gyorffy, B.; Roninson, I. B.; Broude, E. V. Inhibition of CDK8 mediator kinase suppresses estrogen dependent transcription and the growth of estrogen receptor positive breast cancer. *Oncotarget* **2017**, *8* (8), 12558−12575.
(12) Xu, D.; Li, C.-F.; Zhang, X.; Gong, Z.; Chan, C.-H.; Lee, S.-W.; Jin, G.; Rezaeian, A.-H.; Han, F.; Wang, J.; Yang, W.-L.; Feng, Z.-Z.; Chen, W.; Wu, C.-Y.; Wang, Y.-J.; Chow, L.-P.; Zhu, X.-F.; Zeng, Y.-X.; Lin, H.-K. Skp2-MacroH2A1-CDK8 axis orchestrates G2/M transition and tumorigenesis. *Nat. Commun.* **2015**, *6*, 6641.
(13) Bragelmann, J.; Klumper, N.; Offermann, A.; von Maessenhausen, A.; Boehm, D.; Deng, M.; Queisser, A.; Sanders, C.; Syring, I.; Merseburger, A. S.; Vogel, W.; Sievers, E.; Vlasic, I.; Carlsson, J.; Andren, O.; Brossart, P.; Duensing, S.; Svensson, M. A.; Shaikhibrahim, Z.; Kirfel, J.; Perner, S. Pan-Cancer Analysis of the Mediator Complex Transcriptome Identifies CDK19 and CDK8 as Therapeutic Targets in Advanced Prostate Cancer. *Clin. Cancer Res.* **2017**, *23* (7), 1829−1840.
(14) Xu, W.; Wang, Z.; Zhang, W.; Qian, K.; Li, H.; Kong, D.; Li, Y.; Tang, Y. Mutated K-ras activates CDK8 to stimulate the epithelial-to-mesenchymal transition in pancreatic cancer in part via the Wnt/beta-catenin signaling pathway. *Cancer Lett.* **2015**, *356* (2), 613−627.
(15) Kapoor, A.; Goldberg, M. S.; Cumberland, L. K.; Ratnakumar, K.; Segura, M. F.; Emanuel, P. O.; Menendez, S.; Vardabasso, C.; LeRoy, G.; Vidal, C. I.; Polsky, D.; Osman, I.; Garcia, B. A.; Hernando, E.; Bernstein, E. The histone variant macroH2A suppresses melanoma progression through regulation of CDK8. *Nature* **2010**, *468* (7327), 1105−U509.
(16) Pelish, H. E.; Liau, B. B.; Nitulescu, I. I.; Tangpeerachaikul, A.; Poss, Z. C.; Da Silva, D. H.; Caruso, B. T.; Arefolov, A.; Fadeyi, O.; Christie, A. L.; Du, K.; Banka, D.; Schneider, E. V.; Jestel, A.; Zou, G.; Si, C.; Ebmeier, C. C.; Bronson, R. T.; Krivtsov, A. V.; Myers, A. G.; Kohl, N. E.; Kung, A. L.; Armstrong, S. A.; Lemieux, M. E.; Taatjes, D. J.; Shair, M. D. Mediator kinase inhibition further activates super-enhancer-associated genes in AML. *Nature* **2015**, *526* (7572), 273.
(17) Rzymski, T.; Mikula, M.; Zylkiewicz, E.; Dreas, A.; Wiklik, K.; Golas, A.; Wojcik, K.; Masiejczyk, M.; Wrobel, A.; Dolata, I.; Kitlinska, A.; Statkiewicz, M.; Kuklinska, U.; Goryca, K.; Sapala, L.; Grochowska, A.; Cabaj, A.; Szajewska-Skuta, M.; Gabor-Worwa, E.; Kucwaj, K.; Bialas, A.; Radzimierski, A.; Combik, M.; Woyciechowski, J.; Mikulski, M.; Windak, R.; Ostrowski, J.; Brzozka, K. SEL120-34A is a novel CDK8 inhibitor active in AML cells with high levels of serine phosphorylation of STAT1 and STAT5 transactivation domains. *Oncotarget* **2017**, *8* (20), 33779−33795.
(18) Chen, M.; Li, J.; Liang, J.; Thompson, Z. S.; Kathrein, K.; Broude, E. V.; Roninson, I. B. Systemic Toxicity Reported for CDK8/19 Inhibitors CCT251921 and MSC2530818 Is Not Due to Target Inhibition. *Cells* **2019**, *8* (11), 1413.
(19) Clarke, P. A.; Ortiz-Ruiz, M. J.; TePoele, R.; Adeniji-Popoola, O.; Box, G.; Court, W.; Czasch, S.; El Bawab, S.; Esdar, C.; Ewan, K.; Gowan, S.; De Haven Brandon, A. D.; Hewitt, P.; Hobbs, S. M.; Kaufmann, W.; Mallinger, A.; Raynaud, F.; Roe, T.; Rohdich, F.; Schiemann, K.; Simon, S.; Schneider, R.; Valenti, M.; Weigt, S.; Blagg, J.; Blaukat, A.; Dale, T. C.; Eccles, S. A.; Hecht, S.; Urbahns, K.; Workman, P.; Wienke, D. Assessing the mechanism and therapeutic potential of modulators of the human Mediator complex-associated protein kinases. *eLife* **2016**, *5*, e20722.
(20) Mallinger, A.; Crumpler, S.; Pichowicz, M.; Waalboer, D.; Stubbs, M.; Adeniji-Popoola, O.; Wood, B.; Smith, E.; Thai, C.; Henley, A. T.; Georgi, K.; Court, W.; Hobbs, S.; Box, G.; Ortiz-Ruiz, M. J.; Valenti, M.; De HavenBrandon, A.; TePoele, R.; Leuthner, B.; Workman, P.; Aherne, W.; Poeschke, O.; Dale, T.; Wienke, D.; Esdar, C.; Rohdich, F.; Raynaud, F.; Clarke, P. A.; Eccles, S. A.; Stieber, F.; Schiemann, K.; Blagg, J. Discovery of Potent, Orally Bioavailable, Small-Molecule Inhibitors of WNT Signaling from a Cell-Based Pathway Screen. *J. Med. Chem.* **2015**, *58* (4), 1717−1735.
(21) Mallinger, A.; Schiemann, K.; Rink, C.; Stieber, F.; Calderini, M.; Crumpler, S.; Stubbs, M.; Adeniji-Popoola, O.; Poeschke, O.; Busch, M.; Czodrowski, P.; Musil, D.; Schwarz, D.; Ortiz-Ruiz, M. J.; Schneider, R.; Thai, C.; Valenti, M.; De Haven Brandon, A.; Burke, R.; Workman, P.; Dale, T.; Wienke, D.; Clarke, P. A.; Esdar, C.; Raynaud, F. I.; Eccles, S. A.; Rohdich, F.; Blagg, J. Discovery of Potent, Selective, and Orally Bioavailable Small-Molecule Modulators of the Mediator Complex-Associated Kinases CDK8 and CDK19. *J. Med. Chem.* **2016**, *59* (3), 1078−1101.
(22) Czodrowski, P.; Mallinger, A.; Wienke, D.; Esdar, C.; Poschke, O.; Busch, M.; Rohdich, F.; Eccles, S. A.; Ortiz-Ruiz, M. J.; Schneider, R.; Raynaud, F. I.; Clarke, P. A.; Musil, D.; Schwarz, D.; Dale, T.; Urbahns, K.; Blagg, J.; Schiemann, K. Structure-Based Optimization of Potent, Selective, and Orally Bioavailable CDK8 Inhibitors Discovered by High-Throughput Screening. *J. Med. Chem.* **2016**, *59* (20), 9337−9349.
(23) Bandarage, U. K.; Clark, M. P.; Perola, E.; Gao, H.; Jacobs, M. D.; Tsai, A.; Gillespie, J.; Kennedy, J. M.; Maltais, F.; Ledeboer, M. W.; Davies, I.; Gu, W.; Byrn, R. A.; Nti Addae, K.; Bennett, H.; Leeman, J. R.; Jones, S. M.; O'Brien, C.; Memmott, C.; Bennani, Y.; Charifson, P. S. Novel 2-Substituted 7-Azaindole and 7-Azaindazole Analogues as Potential Antiviral Agents for the Treatment of Influenza. *ACS Med. Chem. Lett.* **2017**, *8* (2), 261−265.


https://doi.org/10.1021/acsmedchemlett.1c00300
ACS Med. Chem. Lett. 2021, 12, 1689−1693