ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett

Patent Highlight

Novel CDK2 Inhibitors for Treating Cancer

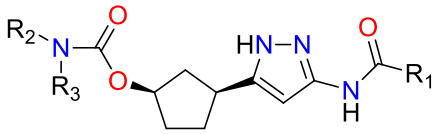
Ram W. Sabnis*

Cite This: ACS Med. Chem. Lett. 2020, 11, 2346−2347

Read Online

ACCESS | Metrics & More | Article Recommendations

Important Compound Classes.



Title. CDK2 Inhibitors

Patent Publication Number. WO 2020/157652 A2

Publication Date. August 6, 2020

Priority Application. US 62/799,455 and US 62/959,042

Priority Date. January 31, 2019 and January 9, 2020

Inventors. Behenna, D. C.; Freeman-Cook, K. D.; Hoffman, R. L.; Nagata, A.; Ninkovic, S.; Sutton, S. C.

Assignee Company. Pfizer Inc., USA

Disease Area. Cancer

Biological Target. CDK2

Summary. Cyclin-dependent kinases (CDKs) and related serine/threonine protein kinases are important cellular enzymes that perform essential functions in regulating cell division and proliferation. CDKs 1−4, 6, 10, and 11 have been reported to play a direct role in cell cycle progression, while CDKs 3, 5, and 7−9 may play an indirect role. The CDK catalytic units are activated by binding to regulatory subunits, known as cyclins, followed by phosphorylation. Cyclins can be divided into four general classes (G_1, G_1/S, S, and M cyclins) whose expression levels vary at different points in the cell cycle.

Overexpression of CDK2 is associated with abnormal regulation of the cell-cycle. Cyclin E, the regulatory cyclin for CDK2, is frequently overexpressed in cancer. Cyclin E amplification or overexpression has long been associated with poor outcomes in breast cancer. Amplification or overexpression of cyclin E1 (CCNE1) is associated with poor outcomes in ovarian, gastric, endometrial, and other cancers.

The small molecule inhibitor dinaciclib inhibits CDK1, CDK2, CDK5, and CDK9 and is currently in clinical development for breast and hematological cancers. Seliciclib, which inhibits CDK2, CDK7, and CDK9 was studied in nasopharyngeal cancer. CYCO65, which inhibits CDK2 and CDK9, is in early clinical development. Despite significant efforts, there are no approved agents selectively targeting CDK2 to date. The present application describes a series of novel CDK2 inhibitors that are useful for treatment of cancer. Further, the application discloses compounds, their preparation, use, pharmaceutical composition, and treatment.

Definitions. R_1 = -L_1-(5−10 membered heteroaryl) or -L_1-(C_6−C_{12} aryl), where 5−10 membered heteroaryl or C_6−C_{12} aryl is optionally substituted by one or more R_4;

R_2 and R_3 are independently H, C_1−C_6 alkyl, C_1−C_6 fluoroalkyl, -L_2-(C_3−C_7 cycloalkyl) or -L_2-(4−7 membered heterocyclyl), where each C_1−C_6 alkyl and C_1−C_6 fluoroalkyl is optionally substituted by one or more R_5 and C_3−C_7 cycloalkyl and 4−7 membered heterocyclyl is optionally substituted by one or more R_6; or

R_2 and R_3 are taken together with the N atom to which they are attached to form a 4−6 membered heterocyclyl optionally containing an additional heteroatom selected from O, N(R_7), and S(O)$_q$ as a ring member, where 4−6 membered heterocyclyl is optionally substituted by one or more R_8;

L_1 and L_2 is independently a bond or a C_1−C_2 alkylene optionally substituted by one or more R_9;

R_4 = F, Cl, OH, CN, $NR_{10}R_{11}$, C_1−C_4 alkyl, C_1−C_4 fluoroalkyl, C_1−C_4 alkoxy, C_1−C_4 fluoroalkoxy, C_3−C_8 cycloalkyl, $C(O)NR_{10}R_{11}$, SO_2R_{12}, $SO(=NH)R_{12}$ or $SO_2NR_{10}R_{11}$, where each C_1−C_4 alkyl and C_1−C_4 fluoroalkyl is optionally substituted by one or more R_{13};

R_5 = OH, C_1−C_4 alkoxy or $NR_{10}R_{11}$;

R_6 = F, OH, C_1−C_4 alkyl, C_1−C_4 fluoroalkyl, C_1−C_4 alkoxy, C_1−C_4 fluoroalkoxy or $NR_{10}R_{11}$ where each C_1−C_4 alkyl, C_1−C_4 fluoroalkyl is optionally substituted by one or more R_{13};

R_7 = H, C_1−C_4 alkyl or C(O)-C_1−C_4 alkyl;

R_8 = F, OH, C_1−C_4 alkyl, C_1−C_4 alkoxy or CN;

R_9 = F, OH, or C_1−C_2 alkyl;

R_{10} and R_{11} are independently H, or C_1−C_2 alkyl;

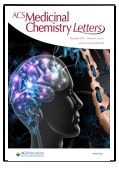
R_{12} = C_1−C_4 alkyl or C_3−C_6 cycloalkyl;

R_{13} = OH, C_1−C_4 alkoxy or $NR_{14}R_{15}$;

R_{14} and R_{15} are independently H, or C_1−C_2 alkyl; and

q = 0, 1 or 2.

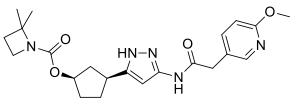
Received: September 14, 2020
Published: October 1, 2020



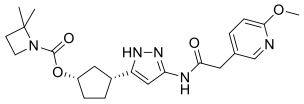
https://dx.doi.org/10.1021/acsmedchemlett.0c00500
ACS Med. Chem. Lett. 2020, 11, 2346−2347

Key Structures.

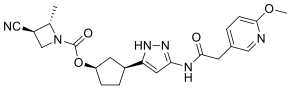
Key Structures:



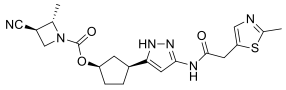
Compound 144



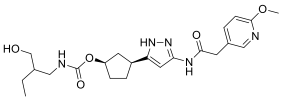
Compound 145



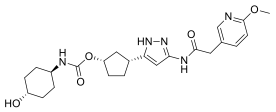
Compound 158



Compound 160



Compound 533



Compound 556

Biological Assay. The CDK2/cyclin E1 and GSK3β assays were performed. The compounds described in this application were tested using a fluorescence-based microfluidic mobility shift assays to test the ability of the compounds to inhibit CDK2/cyclin E1 and GSK3β. The CDK2/cyclin E1 K_i (nM) and GSK3β K_i (nM) inhibition are shown in the following Table.

Biological Data. The Table below shows representative compounds were tested for CDK2/cyclin E1 and GSK3β inhibition. The biological data obtained from testing representative examples are listed in the following table.

Example No.	CDK2/cyclin E1 Ki (nM)	GSK3β Ki (nM)
144	0.10	1.26
145	0.12	0.95
158	0.17	0.78
160	0.15	1.72
533	0.77	1.41
556	0.46	1.85

Claims. Total claims: 20
Compound claims: 18
Pharmaceutical composition claims: 1
Method of treatment claims: 1

Recent Review Articles.

1. Tadesse, S.; Anshabo, A. T.; Portman, L.; Lim, E.; Tilley, W.; Caldon, C. E.; Wang, S. *Drug Discovery Today* **2020**, *25*, 406.
2. Liu, Q.; Gao, J.; Zhao, C.; Guo, Y.; Wang, S.; Shen, F.; Xing, X.; Luo, Y. *DNA Repair* **2020**, *85*, 102702.
3. Marak, B. N.; Dowarah, J.; Khiangte, L.; Singh, V. P. *Eur. J. Med. Chem.* **2020**, *203*, 112571.
4. Leal-Esteban, L. C.; Fajas, L. *Biochim. Biophys. Acta, Mol. Basis Dis.* **2020**, *1866*, 165715.

AUTHOR INFORMATION

Corresponding Author

Ram W. Sabnis − *Smith, Gambrell & Russell LLP, Atlanta, Georgia 30309, United States;* orcid.org/0000-0001-7289-0581; Email: ramsabnis@yahoo.com

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.0c00500

Notes

The author declares no competing financial interest.

https://dx.doi.org/10.1021/acsmedchemlett.0c00500
ACS Med. Chem. Lett. 2020, 11, 2346−2347