ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

pubs.acs.org/acsmedchemlett

The Role of Enhancer of Zeste Homologue 2 Inhibitors in Controlling Epigenetics and Their Potential for Cancer Treatment

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Title:	Enhancer of Zeste Homologue 2 Inhibitors		
Patent Application Number:	WO 2014/195919 A1	**Publication date:**	11 December 2014
Priority Application:	US 61/831,649	**Priority date:**	6 June 2013
	US 61/949,399		7 March 2014
	US 61/977,666		10 April 2014
Inventors:	Knight, S. D; Lafrance, L. V., III; Mcnulty, K. C.; Romeril, S. P.; Seefeld, M. A.		
Assignee Company:	GlaxoSmithkline Intellectual Property (N0. 2) Limited; 980 Great West Road, Brentford, Middlesex TW89GS (GB)		
Disease Area:	Cancer	**Biological Target:**	Enhancer of Zeste Homologue 2 (EZH2)

Summary:

The invention in this patent application relates to macrocyclic amide derivatives represented generally by formula (I), which inhibit the Enhancer of Zeste Homologue 2 (EZH2). These compounds may potentially be useful for treating different types of cancer.

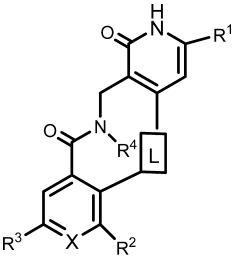
The Enhancer of Zeste Homologue 2 (EZH2) is the catalytic subunit of the Polycomb Repressor Complex 2 (PRC2), which is a hestone methyltransferase. Histone H3 is one of five main histone protein constituents of chromatin, a complex macromolecule found in cells. Chromatin contains DNA, protein, and RNA and is composed of basic units called nucleosomes made of DNA and histones. Histone H3 is trimethylated at its lysine 27 fragment by the PRC2. Histone H3 is the most extensively modified histone, and it is an important protein in the emerging field of epigenetics.

Epigenetics refers to biological modifications of DNA, RNA, or proteins without changing their primary structural sequences. Epigenetic modifications regulate many cellular processes such as proliferation, differentiation, survival, gene expression, DNA replication, and recombination. Epigenetic modifications are also common in cancer and include DNA and/or histone methylations, dysregulation of noncoding RNAs, and nucleosome remodeling. They cause aberrant activation or inactivation of oncogenes, tumor suppressors and signaling pathways. Unlike genetic mutations, epigenetic modifications are reversible processes. Several methylases that affect histone or DNA methylation are known to be dysregulated in cancer. Many cancerous tumors such as prostate, breast, skin, bladder, liver, and pancreas are characterized by elevated levels of EZH2. The higher levels of EZH2 correlate with cancer aggressiveness, metastasis, and poor outcome.

The ubiquitously transcribed tetratricopeptide repeats X (UTX) is an H3K27 demethylase, which reverses the function to EZH2 to remove the methyl groups on lysine 27 of histone H3. Recent studies have identified inactivating mutations of UTX in multiple solid and hematological tumor types. Low levels of UTX correlate with poor survival in breast cancer. The loss of UTX function may lead to increased trimethylation of histone H3 and repression of target genes, which in turn contribute to cancer aggressiveness in many tumor types.

These studies and observations provide strong evidence suggesting that selective inhibition of EZH2 activity may decrease cellular proliferation and invasion. Therefore, selective inhibitors of EZH2 activities, such as the compounds presented in this patent application, would be potentially useful for the treatment of cancer.

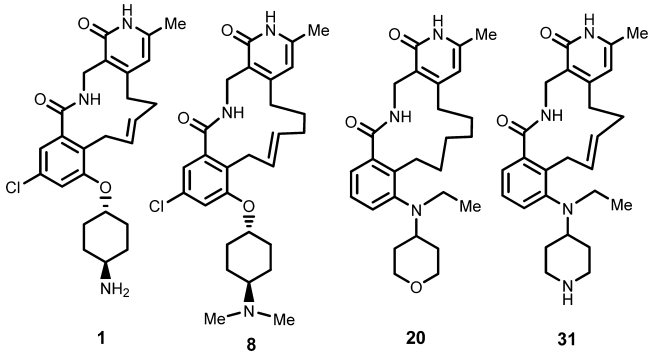
Important Compound Classes:



(Formula (I))

Received: December 31, 2014
Published: January 08, 2015

Key Structures: The inventors described the structures and syntheses of 86 examples of formula (I) including the following four examples:



Biological Assay: The ability of the compounds to inhibit the methyltransferase activity of EZH2 within the Polycomb Repressor Complex 2 (PRC2) was evaluated using two protocols:

Assay Protocol 1: Enzyme activity was measured in a scintillation proximity assay (SPA) where a tritiated methyl group is transferred from ^{3}H−S-adenosyl-methionine (^{3}H-SAM) to a lysine residue on Histone H3 of a mononucleosome, purified from HeLa cells.

Assay Protocol 2: Enzyme activity was measured in a scintillation proximity assay (SPA) where a tritiated methyl group is transferred from ^{3}H-SAM to a lysine residue on a biotinylated, unmethylated peptide substrate derived from histone H3.

Biological Data: The assay data for the above representative examples:

Example	**Assay Protocol 1** EZH2 IC_{50} (nM)	**Assay Protocol 2** EZH2 IC_{50} (nM)
1	32	100
8	63	251
20	25	1000
31	13	200

Recent Review Articles:

1. McCabe, M. T.; Creasy, C. L. *Epigenomics* **2014**, *6* (3), 341−351.
2. Deb, G.; Singh, A. K.; Gupta, S. *Mol. Cancer Res.* **2014**, *12* (5), 639−653.
3. Tan, J.-z.; Yan, Y.; Wang, X.-x.; Jiang, Y.; Xu, H. E. *Acta Pharmacol. Sin.* **2014**, *35* (2), 161−174.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.