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Patent Highlight

Novel PRMT5 Inhibitors for Treating Cancer

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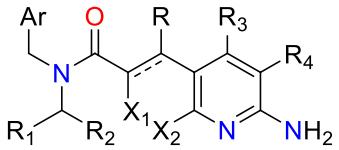
Important Compound Classes.



Title. Novel PRMT5 Inhibitors

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Priority Date. February 12, 2020

Inventors. Allen, J. R.; Amegadzie, A.; Beylkin, D. J.; Booker, S.; Bourbeau, M. P.; Butler, J. R.; Frohn, M. J.; Glad, S. O. S.; Husemoen, B. W.; Kaller, M. R.; Kohn, T. J.; Lanman, B. A.; Li, K.; Liu, Q.; Lopez, P.; Ma, V. V.; Manoni, F.; Medina, J.; Minatti, A. E.; Peiro Cadahia, J.; Pettus, L.; Pickrell, A. J.; Sarvary, I.; Tamayo, N. A.; Vestergaard, M.

Assignee Company. Amgen, Inc., USA

Disease Area. Cancer

Biological Target. PRMT5

Summary. Epigenetic regulation of gene expression is an important biological determinant of protein production, cellular differentiation and plays a significant pathogenic role in several human diseases. Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification. (e.g., methylation) of DNA and proteins (e.g., histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (e.g., protein arginine *N*-methyltransferase 5 (PRMT5)), many of which are associated with specific genetic alterations that can cause human disease. PRMT5 plays a role in diseases such as proliferative disorders, metabolic disorders, and blood disorders.

The homozygous deletion of tumor suppressor genes is a key driver of cancer, frequently resulting in the collateral loss of passenger genes located in close genomic proximity to the tumor suppressor. Deletion of these passenger genes can create therapeutically tractable vulnerabilities that are specific to tumor cells. Deletion of MTAP (methylthioadenosine phosphorylase), a key enzyme in the methionine and adenine salvage pathways, results in accumulation of its substrate, methylthioadenosine (MTA). MTA shares close structural similarity to S-adenosylmethionine (SAM), the substrate methyl donor for the type II methyltransferase PRMT5. Targeting PRMT5 with an MTA-cooperative small molecule inhibitor could preferentially target the MTA bound state of PRMT5, enriched in MTAP null tumor cells, while providing an improved therapeutic index over normal cells where MTAP is intact and MTA levels are low.

The present application describes a series of novel PRMT5 inhibitors for the treatment of cancer. Further, the application discloses compounds, their preparation, use, pharmaceutical composition, and treatment.

Definitions. = ⎓ represents a single or double bond;

X_1 and X_2 = N or C, wherein if X_1 is C, it can be optionally substituted with halo or C_{1-6}alkyl;

Ar = six membered aromatic ring having 0−2 N atoms, wherein each Ar is independently substituted with 0−2 R_a groups;

R = H or methyl;

R_1 and R_2 = H, optionally substituted with C_{1-6}alkyl, C_{1-6}alkynyl, -C(OR_c), single and double cyclyl having 0−3 N, S or O atoms, wherein substituents are selected from halo, optionally substituted with C_{1-6}alkyl, −C(O)NR_fR_g, OH and 5-membered ring having 0−3 N atoms; and

R_3 and R_4 = H, halogen, alkynyl, cyano and C_{1-6}alkyl, optionally substituted with halo or deuterium.

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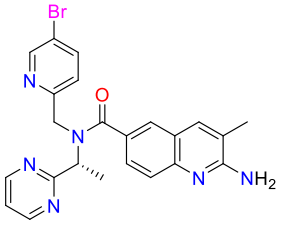
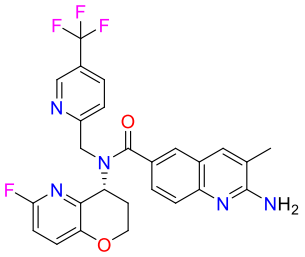
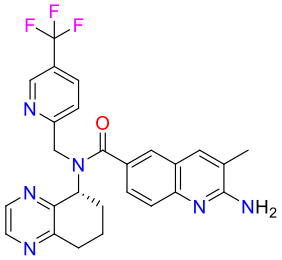
Key Structures.



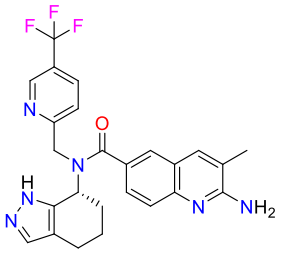
Compound 402



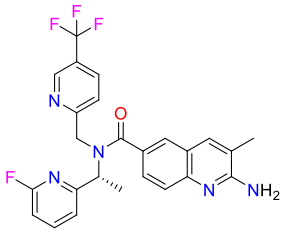
Compound 451



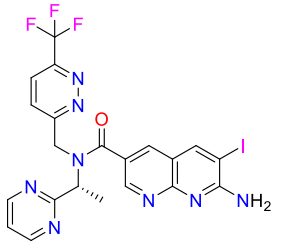
Compound 521



Compound 527



Compound 799



Compound 808

Biological Assay. The HTC116 MTAP null proliferation assay was performed. The compounds described in this application were tested for their ability to inhibit PRMT5. The PRMT5 IC_{50} (μM) are shown in the following table.

Biological Data. The table below shows representative compounds were tested for PRMT5 inhibition. The biological data obtained from testing representative examples are listed in the following table.

Example No.	Prolif. HCT116 MTAP null IC_{50} (μM)
402	0.015
451	0.013
521	0.012
527	0.010
799	0.013
808	0.015

Claims. Total claims: 25
Compound claims: 19
Pharmaceutical composition claims: 2
Method of treatment claims: 4

Recent Review Articles.

1. Guccione, E.; Schwarz, M.; Di Tullio, F.; Mzoughi, S. *Curr. Opin. Pharmacol.* **2021**, *59*, 33.
2. Lei, Y.; Han, P.; Tian, D. *Transl. Oncol.* **2021**, *14*, 101194.
3. Tang, Z.; Xu, Z.; Zhu, X.; Zhang, J. *Cancer Commun.* **2021**, *41*, 16.
4. Pellarin, I.; Belletti, B.; Baldassarre, G. *Med. Res. Rev.* **2021**, *41*, 586.
5. Verheul, T. C. J.; Trinh, V. T.; Vazquez, O.; Philipsen, S. *ChemMedChem.* **2020**, *15*, 2436.
6. Sengupta, S.; Kennemer, A.; Patrick, K.; Tsichlis, P.; Guerau-de-Arellano, M. *Trends Immunol.* **2020**, *41*, 918.

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Notes

The author declares no competing financial interest.

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