EXPERT OPINION

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# Substituted purine and 7-deazapurine compounds as modulators of epigenetic enzymes: a patent evaluation (WO2012075381)

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The patent presents 140 purine and 7-azapurine derivatives as potent inhibitors of DOT1L histone methyltransferase that might be useful in the treatment of leukemia with *MLL* rearrangements. It is becoming more and more evident that the deregulation of chromatin modifiers such as DOT1L plays a critical role in tumorigenesis. As yet, the number of pharmaceutical agents targeting chromatin modifiers is still limited. The market for such compounds has been estimated to be potentially as large as one third of all cancer patients. Overall, the prospective of a targeted product (i.e., a drug targeting a commonly affected chromatin modifier) is very promising, and exponentially growing investments into this market are anticipated.

**Keywords:** cancer, DOT1L histone methyltransferase, epigenetic modulator, leukemia

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## 1. Introduction

The term "epigenetics" refers to modifications in gene expression caused by heritable, but potentially reversible, changes in DNA methylation and chromatin structure [1]. An important level of regulation is embedded in the accessibility of genomic regions controlled by the chromatin structure. Epigenetic mechanisms that modulate chromatin accessibility include DNA methylation and post-translational modifications of amino acid residues in histone tails, such as acetylation, phosphorylation, methylation and others [2]. The methylation of certain lysine residues is mediated by histone lysine methyltransferases (HMTs) that transfer a methyl group from *S*-adenosyl-L-methionine (SAM) to histone lysine residues. HMTs can be classified as proteins containing either a catalytic SET domain or the *Dot1* (*disruptor of telomeric silencing*)-*like* (DOT1L, also known as KMT4) histone H3 methyltransferase that does not contain a SET domain [3]. DOT1L is the only known methyltransferase that methylates lysine 79 of histone 3 (H3K79) [4], generally related to transcriptional activation [5].

DOT1L plays an important role in the oncogenesis of leukemias associated with rearrangements of MLL (Mixed Lineage Leukemia, KTM2A) [6,7]. The *MLL* gene is located on chromosome 11q23, where rearrangements are found in >70% of infant leukemias and in about 10% of adult acute myeloid leukemias (AML) [8]. As a member of the trithorax group of proteins MLL normally acts in protein complexes that exhibit histone 3 lysine 4 (H3K4) methyltransferase activities. In case of rearranged *MLL*, fusion proteins are formed [9,10] that mediate a novel physical interaction with DOT1L. Consequently, transformation of hematopoietic progenitors by the fusion protein MLL-AF10 were shown to depend on aberrant H3K79 methylation mediated by DOT1L [7,11].

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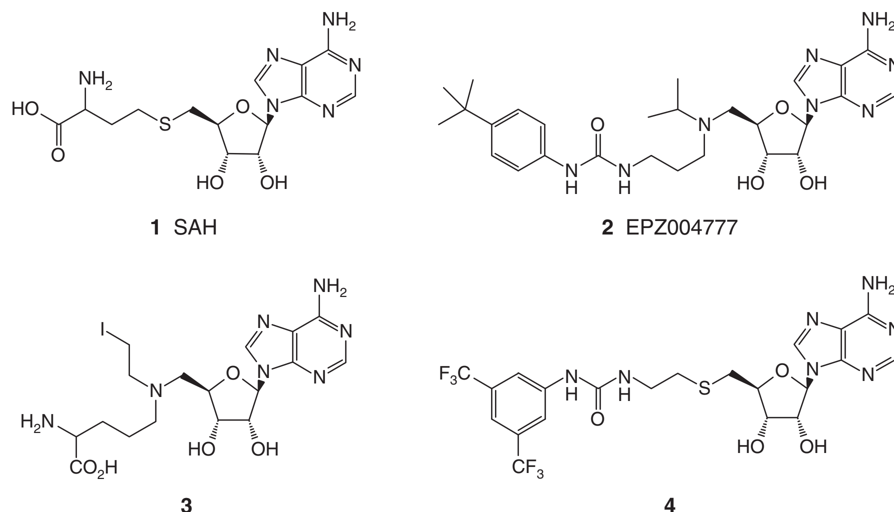


**Figure 1. Chemical structures of published DOT1L inhibitors EPZ004777 (2) from Ref. [13], (3) from Ref. [15] and (4) from Ref. [17], in comparison with *S*-adenosyl homocysteine (1).**

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Children with *MLL*-rearranged acute lymphoblastic leukemia (ALL) exhibit poor clinical outcome due to a high relapse rate on conventional chemotherapy, and there is an urgent clinical need for novel therapeutic approaches targeting this high-risk patient population. Therefore, DOT1L could provide an important therapeutic target in *MLL*-rearranged leukemias. Development and use of inhibitors of DOT1L activity is subject of the present patent application [12].

## 2. Chemistry

Recent crystallographic studies have revealed that in comparison to SET-domain HMTs binding of SAM to DOT1L is unique [3,4]. This provides means of designing drugs that specifically inhibit DOT1L activity, but not other SET-domain HMTs. Several earlier studies have reported the synthesis and characterization of small molecule inhibitors of DOT1L partly active at subnanomolar concentrations, including the development of EPZ004777 first described by Daigle *et al.* [13,14], *S*-adenosyl-L-homocysteine (SAH) mimetics synthesized by Yao *et al.* [15], aminonucleoside inhibitors by Basavapathruni *et al.* [16] and a series of 58 adenosine-containing compounds (examples in **Figure 1**) [17].

The present patent application describes the synthesis of substituted purine and 7-deazapurine compounds containing ribose or cyclopentane moieties as shown in the generic structure of Claim 1 (**Figure 2**). With this generic structure, the authors stake a claim to the chemical space of interest. To confirm the structures as to be patentable the syntheses of 140 compounds are presented. This includes the preparation of required starting material as well as the detailed descriptions for several compounds including analytical data. As an example, the synthesis of compound 2 is outlined in **Figure 3**. It starts with a reductive amination of the cyclobutane spacer yielding a cis/trans mixture, which has to be separated through chiral HPLC. The cis compound is then N alkylated. Reduction and elongation of the side chain, reduction of the double bond and cleavage of the ester is straight forward. The benzoimidazol ring is formed in a two-step synthesis without isolation of the amide. Finally compound 2 is isolated after acidic cleavage of the acetal of the ribose. Overall, this synthesis takes nine steps with an overall yield of less than 0.5 % which might be disadvantageous in terms of bulk synthesis.

The International Search Report for the application cites only one document defining the general state of the art. Thus, the application seems to be new and inventive. Epizyme, Inc. (Cambridge, MA, USA) has filed a series of related patent applications [18-20]. They differ in extend of the covered chemical space, but describe similar nucleoside moieties that might be the active part of the molecules.

## 3. Biology and action

The applicants provide two examples related to biological activities of the described compounds. To determine DOT1L inhibitory potential, recombinant human DOT1L is incubated with $^3$[H]-labeled SAM, nucleosomes and serial dilutions of inhibitors in a standard assay as described previously [13]. Incorporated radioactivity is measured to compute half maximal inhibitory concentrations ($IC_{50}$ values). In total, 133 compounds are tested in a dose-dependent manner (**Table 1**). Compound 2 (**Figure 3**) showing an *in vitro* $IC_{50}$ of 0.74 nM for DOT1L is further investigated for its effects on cell proliferation of various human leukemia cell lines. Cell viability is determined by cell counting in the presence of two fluorescent dyes that discriminate non-viable and viable cells [13]. Compound 2 potently inhibits viability of three out of four *MLL*-rearranged leukemia cell lines at nanomolar concentrations. In



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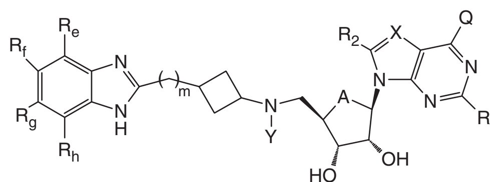


A is O or $CH_2$;

Q is H, $NH_2$, $NHR_b$, $NR_bR_e$, OH, Rb, or $OR_b$, in which each of $R_b$ and $R_e$ independently is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 7-membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -$M_1$-$T_1$ in which $M_1$ is a bond or $C_1$-$C_6$ alkyl linker optionally substituted with halo, CN, OH or $C_1$-$C_6$ alkoxyl and $T_1$ is $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, or $R_b$ and $R_e$, together with the N atom to which they attach, form 4 to 7-membered heterocycloalkyl having 0 or 1 additional heteroatoms to the N atom optionally substituted with $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, halo, OH, carboxyl, C(O)OH, C(O)O-$C_1$-$C_6$ alkyl, OC(O)-$C_1$-$C_6$ alkyl, CN, $C_1$-$C_6$ alkoxyl, $NH_2$, mono-$C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and each of $R_b$, $R_e$, and $T_1$ is optionally substituted with one or more substituents selected from the group consisting of $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, halo, OH, C(O)OH, CN, $C_1$-$C_6$ alkoxyl, $NH_2$, mono $C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, and 5 to 6-membered heteroaryl;

X is N or $CR_x$, in which $R_x$ is H, halo, OH, C(O)OH, CN, or $R_{S1}$, $R_{S1}$ being amino, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and $R_{S1}$ being optionally substituted with one or more substituents selected from the group consisting of halo, OH, C(O)OH, CN, $C_1$-$C_6$ alkoxyl, $NH_2$, mono-$C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, and 5 to 6-membered heteroaryl;

Y is H, $R_d$, $SO_2R_d$, or $COR_d$, $R_d$ being $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, or 5 to 6-membered heteroaryl, and $R_d$ being optionally substituted with one or more substituents selected from the group consisting of $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, halo, OH, C(O)OH, CN, $C_1$- $C_6$ alkoxyl, $C_1$-$C_6$ alkylsulfonyl, $NH_2$, mono-$C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, and 5 to 6-membered heteroaryl and each of which $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, and 5 to 6-membered heteroaryl substituents on $R_d$ is further optionally substituted with $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, halo, OH, carboxyl, C(O)OH, C(O)O-$C_1$-$C_6$ alkyl, OC(O)-$C_1$-$C_6$ alkyl, cyano, $C_1$-$C_6$ alkoxyl, amino, mono-$C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, or 5 to 6-membered heteroaryl;

each of $R_1$ and $R_2$ independently, is H, halo, OH, C(O)OH, CN, $R_{S2}$, $R_{S2}$ being $NH_2$, $C_1$-$C_6$ alkoxyl, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, and each $R_{S2}$ being optionally substituted with one or more substituents selected from the group consisting of halo, OH, C(O)OH, CN, $C_1$-$C_6$ alkoxyl, $NH_2$, mono-$C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, and 5 to 6-membered heteroaryl;

each of $R_e$, $R_f$, $R_g$, and $R_h$, independently is -$M_2T_2$, in which $M_2$ is a bond, $SO_2$, SO, S, CO, $CO_2$, O, O-$C_1$-$C_4$ alkyl linker, $C_1$-$C_4$ alkyl linker, NH, or N($R_t$), $R_t$ being $C_1$-$C_6$ alkyl, and $T_2$ is H, halo, or $R_{S4}$, $R_{S4}$ being $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 8-membered heterocycloalkyl, or 5 to 10-membered heteroaryl,

and each of O-$C_1$-$C_4$ alkyl linker, $C_1$-$C_4$ alkyl linker, $R_t$, and $R_{S4}$ being optionally substituted with one or more substituents selected from the group consisting of halo, OH, C(O)OH, CN, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_1$-$C_6$ alkoxyl, amino, mono-$C_1$-$C_6$ alkylamino, di-$C_1$-$C_6$ alkylamino, $C_3$-$C_8$ cycloalkyl, $C_6$-$C_{10}$ aryl, 4 to 6-membered heterocycloalkyl, and 5 to 6-membered heteroaryl, and
m is 0, 1, or 2.

**Figure 2. Generic structure with a description of substituents accounting for the variation of attached moieties A, Q, X, Y, $R_1$, $R_2$, $R_e$ to $R_h$ and m to the core structure.**

contrast, $IC_{50}$ values for the RS4; 11 cell line harboring a *MLL-AF4* rearrangement and five non-*MLL*-rearranged cell lines are at least 1–3 orders of magnitude higher.

Compound 2 is further tested in an *in vivo* xenograft model with the MV4-11 *MLL*-rearranged cell line essentially as described previously [13]. Animals bearing small tumors of about 100 $mm^3$ size are treated in groups of 20 animals, except for one control group with only 8 animals. The compound is constantly delivered subcutaneously (sc) by minipumps at two doses of 112 and 56 mg/kg bodyweight/day over a period of 21 days. One group exposed to 112 mg/kg/day received an additional 20 mg/kg three times a day intraperitoneally (ip; total dose 172 mg/kg/day). The highest dose of compound 2 (172 mg/kg/day) significantly inhibits tumor growth by about 67%. Average steady state plasma concentrations of compound 2 after continuous sc application are in the range of 99–152 ng/ml for the 112 mg/kg/day group and 52–238 ng/ml for the 56 mg/kg/day dose group. Additional ip injections significantly increase plasma levels in a time-dependent manner.

Overall, the examples demonstrate as a proof of principle that substituted purine and 7-deazapurine compounds potently



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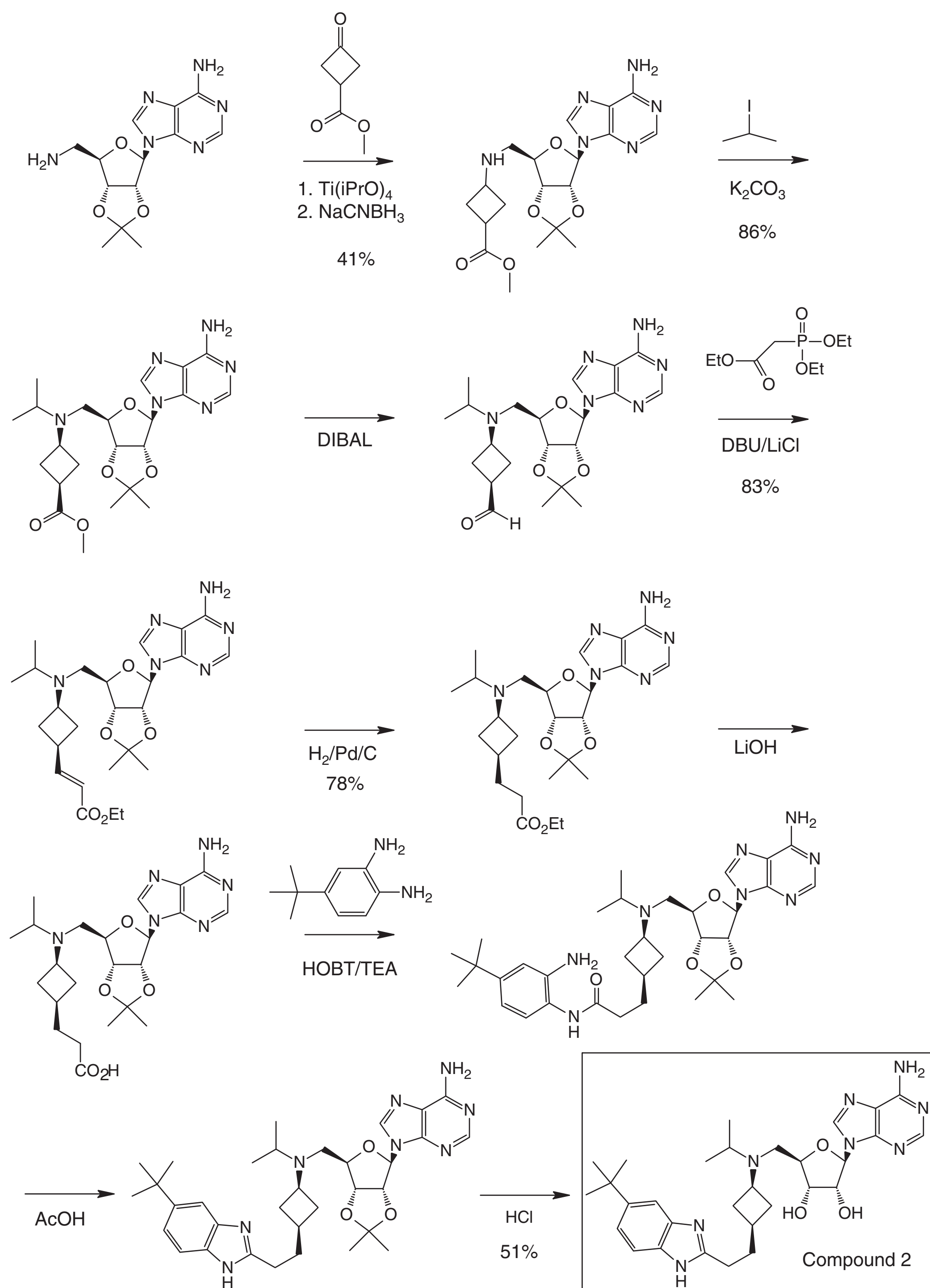


**Figure 3. Synthesis of compound 2.**

inhibit DOT1L activity *in vitro*. Further, it is shown that compound 2 (selected as a representative) inhibits proliferation of leukemia cell lines with DOT1L-activating *MLL* rearrangements *in vitro* and *in vivo* comparable to EPZ004777 [13,16].

There might be theoretical concerns with respect to inhibiting DOT1L pharmacologically: since DOT1L is the only known H3K79 methyltransferase, its inhibition might have detrimental effects not only on cancer cells but also on the surrounding healthy cells. According to published data on the DOT1L-inhibitor lead-compound EPZ004777 this does not seem to be the case [13], and the fact that non-*MLL*-rearranged tumor cell lines are not sensitive to compound

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**Table 1. Summary of DOT1L inhibitory activity.**

| Potency category | No of compounds tested |
|---|---|
| $IC_{50}$ < 0.1 µM | 107 |
| 0.1 µM < $IC_{50}$ < 1.0 µM | 16 |
| 1.0 µM < $IC_{50}$ < 10 µM | 8 |
| $IC_{50}$ > 10 µM | 2 |
| Total | 133 |

2 further supports this view. Notably, Epizyme has recently initiated a phase 1 clinical trial (ID: NCT01684150) in advanced hematologic malignancies, including acute leukemia with *MLL* rearrangements using a related compound called EPZ-5676 [21]. The trial started recruitment in September 2012, and as of now, no results are publicly available. Data on preclinical characteristics including rat and dog pharmacokinetics and efficacy data in a nude rat xenograft leukemia model have been presented at the Annual Meeting of the American Society of Hematology 2012 [22].

At present, there are no published data available that support anti-proliferative activity of DOT1L inhibitors in non-leukemic cancers not harboring a *MLL*-rearrangement or alternative genetic aberrations leading to activation of DOT1L. This needs to be kept in mind when considering that the majority of 'cell proliferative disorders' addressed in the application refer to solid tumors and neurological disorders.

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## 4. Expert opinion

It is becoming more and more evident that the deregulation of chromatin modifiers plays a critical role in tumorigenesis [23]. Therefore, it is not surprising that this field attracts increasing attention of academic and pharmaceutical research to investigate potential exploitation as drug targets and/or biomarkers [23,24]. A competitor analysis of published documents by SciFinder [25] revealed that HMTs as drug targets seem to represent yet a middlingly competitive field [when compared to the histone deacetylase (HDAC) field], which is so far mainly investigated by academia with at least 142 published documents versus 14 from industry. The numbers of publications are constantly rising over the past six years. A patent search in the WIPO (World Intellectual Property Organization) database, Patentscope [26] revealed that OncoTherapy Science, Inc. (OTS, Kawasaki-shi Kanagawa, Japan) and Sangamo BioSciences, Inc. (Richmond, CA, USA) are the most active applicants in this field with 50, respectively, 38 patent applications.

As yet, the number of pharmaceutical agents targeting chromatin modifiers is still small. The first to-market drug was a pan HDAC inhibitor from Merck, suberoylanilide hydroxamic acid (SAHA, vorinostat), which is FDA approved for cutaneous T cell lymphoma and is now in several Phase III trials for wider approval [2]. Currently, only one additional chromatin modifier is approved for clinical use: romidepsin from Celgene, which is a class I histone deacetylase inhibitor used for the treatment of CTCL [2], but there are more than 13 other HDAC inhibitors in the clinical pipeline, highlighting the potential of epigenetic drugs [2].

Epizyme has recently formed strategic partnerships with GlaxoSmithKline [27] and Celgene (Summit, NJ, USA) [28] to systematically discover, develop and commercialize HMT inhibitors. In addition, 'Transcription and Chromatin Modulation' is currently a major focus area of Bayer HealthCare for new drug development in oncology [29]. Overall, the potential of drugs targeting commonly affected chromatin modifiers is expected to be very high, and exponentially growing investments into this market are anticipated. Products targeting chromatin modifiers are potentially applicable to different tumor entities such as high-grade gliomas [30], aromatase-inhibitor resistant breast cancer [31] or other solid tumors [32], clearly illustrating their enormous market potential for commercialization (billions of Euros).

Compared to the HDAC inhibitor field, the development of HMT inhibitors is still emerging. So far only one compound targeting HMTs, the above mentioned EPZ-5676, has entered clinical trials [21]. However, growing evidence indicates several HMTs as promising drug targets in numerous cancer types. Since multiple companies are now developing such inhibitors, targeting HMTs will be a promising new frontier for anticancer drug discovery.

*MLL/AF4* rearrangements that lead to 'activation' of DOT1L are present in about 5% of all ALL patients and are associated with poor prognosis (median overall survival < 12 months) [33]. In the USA, approximately 2500–3500 new cases of ALL are diagnosed in children/year, with high incidence of *MLL* rearrangements in 70% of infant ALL patients. In case that use of DOT1L inhibitors is only beneficial for leukemias with *MLL* rearrangements, their market potential might be limited, but in terms of 'years of life gained', the clinical value is expected to be very high.

## Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.



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