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(54) Title: COMPOUNDS AND COMPOSITIONS FOR MODULATING HISTONE METHYLTRANSFERASE ACTIVITY

(57) Abstract: The invention provides DOT1L inhibitors, and also methods and use of the compounds of the invention, by themselves or in combination with other therapies, for treating a disease, disorder, or condition.

DESCRIPTION
COMPOUNDS AND COMPOSITIONS FOR MODULATING HISTONE METHYLTRANSFERASE ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to, and the benefit of, U.S. provisional application No. 61/694,892, filed August 30, 2012, the content of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to certain compounds which can modulate the activity of a particular histone methyltransferase, a process for preparing them, pharmaceutical compositions containing them as an active ingredient, and their use as medicaments.

BACKGROUND OF THE INVENTION

Histone methyltransferases are a family of enzymes that selectively add methyl groups to specific amino acids on histones, which can often result in increased activity of a gene influenced by the methyl group at a relevant histone site. Disruptor of Telomere Silencing 1-like ("DOT1L") is responsible for methylation of histone H3 at lysine 79. DOT1L is a histone methyltransferase that is uniquely and specifically targetable for modulation, in that it does not contain an enzymatic domain common to all other histone methyltransferases. DOT1L is involved in normal cellular processes, including DNA damage repair, cardiac muscle function, intestinal homeostasis, WNT signaling, and erythropoiesis.

DOT1L activity is also involved in disease processes. For example, transcriptional activation by DOT1L-mediated methylation is exploited by leukemias that originate with chromosomal re-arrangements involving the mixed lineage leukemia (*MLL*) gene. Translocation of the *MLL* gene results in the expression of oncogenic fusion proteins, some of which recruit DOT1L activity to gene targets of

MLL fusion proteins, such as *Hoxa* cluster, and *Meis1*. Resulting aberrant methylation by DOT1L leads to transcriptional activation of these and other genes, leading to precancerous transformation of affected white blood cells, and leukemic transformation of affected cells, including leukemogenesis and uncontrolled proliferation. Translocation of the *MLL* gene is a common cause of acute leukemia, accounting for between 5% and 10% of adult acute leukemias and between 60% and 80% of infant acute leukemias. Inhibiting DOT1L activity, and/or disrupting the interaction between DOT1L and MLL fusion proteins may inhibit precancerous or leukemic transformation, but may also affect DOT1L's role in normal hematopoiesis and cardiac function.

SUMMARY OF THE INVENTION

The invention includes compounds comprising a C-nucleoside that selectively inhibits the activity of the histone methyltransferase DOT1L. The compounds of the present invention surprisingly may be more chemically stable in body under physiological conditions, as compared to N-nucleoside compounds (e.g., C-C bond chemically more stable than C-N bond), as well as more stable to purine nucleoside phosphorylase enzyme activity.

It is an object of the present invention to provide novel compounds which are effective as DOT1L inhibitor.

It is another object of the present invention to provide a pharmaceutical composition for preventing or treating precancerous transformation or cancer.

It is yet another object of the present invention to provide a method for preventing or treating precancerous transformation or cancer in a mammal.

It is still another object of the present invention to provide a use of the inventive compound.

In accordance with one aspect of the present invention, there is provided a compound of Formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof, wherein formula **I** is as defined herein.

In accordance with another aspect of the present invention, there is provided a pharmaceutical composition for preventing or treating precancerous transformation or cancer, comprising as an active ingredient the compound of formula **I**, or a

pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof, and a pharmaceutically acceptable carrier.

In accordance with yet another aspect of the present invention, there is provided a method for preventing or treating precancerous transformation or cancer in a mammal, which comprises administering the compound of formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof to the mammal.

In accordance with a further aspect of the present invention, there is provided a use of the compound of formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof for the manufacture of a medicament for preventing or treating precancerous transformation or cancer.

Other aspects, objects and features of the invention will be apparent from the following description.

DETAILED DESCRIPTION OF THE INVENTION

While the terms used in the description of the invention are believed to be well understood by one of ordinary skill in the pharmaceutical arts, definitions, where provided herein, are set forth to facilitate description of the invention, and to provide illustrative examples for use of the terms.

The terms "a," "an," and "the" may mean one or more, and may be used to reference both the singular and the plural.

The terms “purified” or “isolated” for a compound according to Formula **I** refers to the physical state of the compound following isolation from a synthetic process or purification step described herein or well known to those in the art, and in sufficient purity to be characterizable by standard analytical methods described herein or well known in the art.

The terms “treat,” “treats,” or “treating,” as used herein, embrace one or more of preventative (prophylactically) or palliative (therapeutically).

The term “alkyl” is used herein to refer to a hydrocarbon containing normal, secondary, tertiary, or cyclic carbon atoms (e.g., linear saturated aliphatic hydrocarbon groups, branched saturated aliphatic hydrocarbon groups, or a saturated or unsaturated non-aromatic hydrocarbon mono or multi- ring system (e.g., cycloalkyl)).

When the term "alkyl" is used without reference to a number of carbon atoms, it is to be understood to refer to a C_{1-10} alkyl; e.g., a C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 or C_{10} alkyl.

The term "aryl" is used herein to refer to cyclic, aromatic hydrocarbon groups which have 1 to 3 aromatic rings, for example phenyl or naphthyl. The aryl group may have fused thereto a second or third ring which is a heterocyclo, cycloalkyl, or heteroaryl ring, provided in that case the point of attachment will be to the aryl portion of the ring system. "Heteroaryl" refers to an aryl group in which at least one of the carbon atoms in the aromatic ring has been replaced by a heteroatom selected from oxygen, nitrogen and sulfur. The nitrogen and/or sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heteroaryl group may be a 5 to 6 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 16 membered tricyclic ring system.

The term "alkenyl" is used herein to refer to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens.

The term "alkynyl" is used herein to refer to a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond.

The term "alkoxy" is used herein to refer to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term "aralkyl" is used herein to refer to an aryl-alkyl group in which the aryl and alkyl are as defined herein. Preferred aralkyls comprise a lower alkyl group.

The term "alkyloxy" is used herein to refer to an alkyl group, as defined herein, attached via an oxygen linkage to the rest of the molecule.

The term "aryloxy" is used herein to refer to an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term "aralkyloxy" is used herein means an aralkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term "alkylcarbonyl" is used herein to refer to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

The term "alkylcarbonyloxy" is used herein to refer to an alkylcarbonyl, as

defined herein, appended to the parent molecular moiety through an oxygen atom.

The term "carbocyclyl" (alone or in combination with another term(s)) is used herein to refer to a saturated cyclic (i.e., "cycloalkyl"), partially saturated cyclic (i.e., "cycloalkenyl"), or completely unsaturated (i.e., "aryl") hydrocarbyl substituent containing from 3 to 14 carbon ring atoms ("ring atoms" being the atoms bound together to form the ring or rings of a cyclic substituent). A carbocyclyl may be a single ring, which typically contains from 3 to 6 ring atoms.

The term "cycloalkyl" is used herein to refer to monocyclic or multicyclic (e.g., bicyclic, tricyclic, etc.) hydrocarbons containing from 3 to 12 carbon atoms that is completely saturated or has one or more unsaturated bonds but does not amount to an aromatic group.

The term "cyano" as used herein means a -CN group.

The term "halo" or "halogen" means -Cl, -Br, -I, or -F.

The term "haloalkyl" is used herein to refer to an alkyl, as defined herein, wherein at least one hydrogen atom is replaced with halogen atoms.

The term "heterocyclyl" is used herein to include a saturated (e.g., "heterocycloalkyl"), partially unsaturated (e.g., "heterocycloalkenyl" or "hetercycloalkynyl") or completely unsaturated (e.g., "heteroaryl) ring system, which have 3 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur.

The term "silyl" as used herein to include hydrocarbyl derivatives of the silyl ($H_{(3)}Si$-) group (i.e., (hydrocarbyl)$_{(3)}Si$-), wherein hydrocarbyl groups are univalent groups formed by removing a hydrogen atom from a hydrocarbon, e.g., ethyl, phenyl. The hydrocarbyl groups can be combinations of different groups which can be varied in order to provide a number of silyl groups.

The term "silyloxy" is used herein to refer to a silyl group, as defined herein, appended to the parent molecule through an oxygen atom.

The terms "first" and "second" are used herein for purposes of distinguishing between two compounds, or between two compositions, as will be clearer from the description.

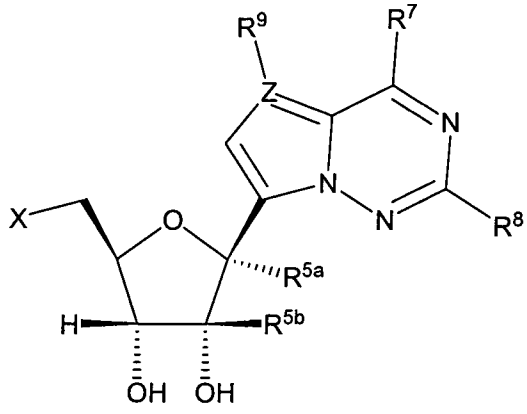
The phrase "medically effective amount" means an amount of a composition or compound that treats the particular disease, condition or disorder; ameliorates, relieves, or decreases one or more symptoms associated with the particular disease, condition or

disorder; and/or delays or prevents the onset of symptoms of, or a pathological process associated, with the particular disease, condition or disorder described herein in more detail.

The term "pharmaceutically acceptable carrier" is used herein to mean any compound or composition or carrier medium useful in any one or more of administration, delivery, storage, stability of a composition or compound described herein. These carriers are known in the art to include, but are not limited to, a diluent, water, saline, suitable vehicle (e.g., liposome, microparticle, nanoparticle, emulsion, capsule), buffer, medical parenteral vehicle, excipient, aqueous solution, suspension, solvent, emulsions, detergent, chelating agent, solubilizing agent, salt, colorant, polymer, hydrogel, surfactant, emulsifier, adjuvant, filler, preservative, stabilizer, oil, binder, disintegrant, absorbent, flavor agent, and the like as broadly known in the pharmaceutical art.

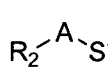
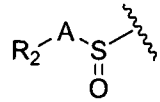
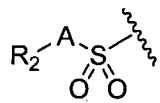
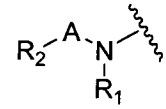
Hereinafter, the present invention is described in detail.

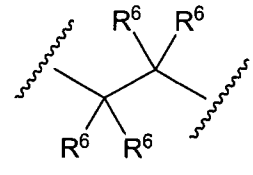
The present invention provides a compound of Formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof:

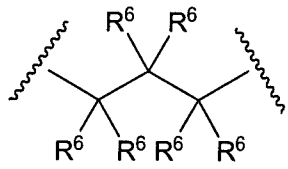
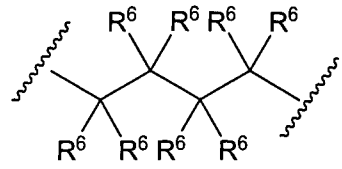


I

wherein,

X is  ,  ,  or  ;

A being alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,  ,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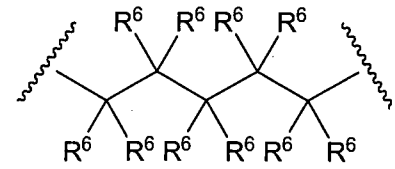
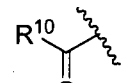
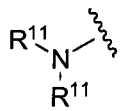
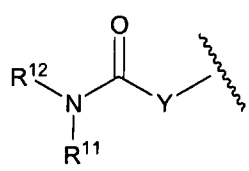
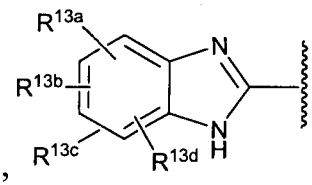
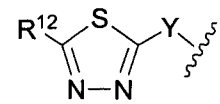


R_1 being hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, alkylaryl, haloalkyl, formyl, heterocyclyl, heterocyclylalkyl,  or C_{2-4} alkyl substituted with  , and

R_2 being  ,  or 

R^6 being hydrogen, alkyl or halogen, or two geminal R^6 taken together are ethyl, propyl or butyl,

R^{10} being alkyl, cycloalkyl, cycloalkylalkyl or haloalkyl,

R^{11} being hydrogen, alkyl or cycloalkyl,

R^{12} being alkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heteroarylaryl, fused bicyclyl, biaryl, aryloxyaryl, heteroaryloxyaryl, aryloxyheteroaryl or heteroaryloxyheteroaryl,

R^{13a}, R^{13b}, R^{13c} and R^{13d} being each independently $-M_2-T_2$ or $-T_2$, in which M_2 is a bond, SO_2, SO, S, CO, CO_2, O, O-C_{1-4} alkyl linker, C_{1-4} alkyl linker, NH, or N(R_t), R_t being C_1-C_6 alkyl, and T_2 is H, halogen, alkyl, heterocycloalkyl, heteroaryl or haloalkyl, and

Y being –NH, -N(alkyl) or –N(haloalkyl);

Z is nitrogen or carbon;

R^{5a} is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl or CN;

R^{5b} is hydrogen, halogen or hydroxyl;

R^7 is halogen, NR^3R^4, $N(R^3)OR^3$, NO, NO_2, CHO, CN, -CH(=NR^3), -CH=NNHR^3, -CH=N(OR^3), -$CH(OR^3)_2$, -C(=O)NR^3R^3, -C(=S)NR^3R^3, -C(=O)OR^3,

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl, heteroaryl, -C(=O)-C_{1-8} alkyl, -$S(O)_n$-C_{1-8} alkyl, aryl-C_{1-8} alkyl, OR^3 or SR^3; and

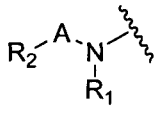
R^8 and R^9 are each independently H, halogen, alkyl, haloalkyl, NR^3R^4, $N(R^3)OR^3$, NO, NO_2, CHO, CN, -CH(=NR^3), -CH=NNHR^3, -CH=N(OR^3), -$CH(OR^3)_2$, -C(=O)NR^3R^3, -C(=S)NR^3R^3, -C(=O)OR^3, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl, heteroaryl, -$S(O)_n$-C_{1-8} alkyl, aryl-C_{1-8} alkyl, OR^3 or SR^3;

R^3 being hydrogen, alkyl, alkyloxy, aryl, aralkyloxy, alkylcarbonyloxy or silyloxy,

R^4 being hydrogen, alkyloxy or alkyl, and

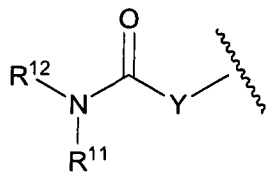
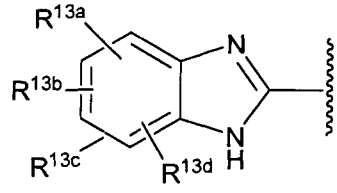
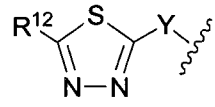
n being an integer of 0 to 2.

In a preferred embodiment of the present invention, there is provided the compound of Formula **I**, as defined below:

X is  ;

A being alkyl, cycloalkyl, cycloalkylalkyl or heterocyclyl,

R_1 being hydrogen, alkyl, cycloalkyl or alkylcycloalkyl, and

R_2 being  ,  or 

R^{11} being hydrogen, alkyl or cycloalkyl,

R^{12} being alkyl, aryl, heteroaryl, aralkyl or heteroarylalkyl,

R^{13a}, R^{13b}, R^{13c} and R^{13d} being each independently H, halogen, alkyl, heterocycloalkyl, heteroaryl or haloalkyl, and

Y being –NH;

Z is nitrogen or carbon;

R^{5a} is hydrogen, C_{1-8} alkyl or CN;

R^{5b} is hydrogen, halogen or hydroxyl;

R^7 is halogen, NR^3R^4, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl or heteroaryl; and

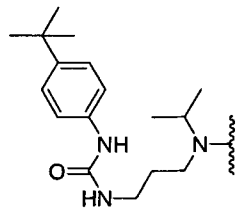
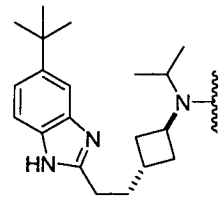
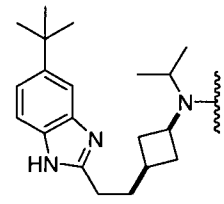
R^8 and R^9 are each independently H, halogen, alkyl, haloalkyl, NR^3R^4, CN, C_{2-}

$_8$ alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl, heteroaryl, OR^3 or SR^3;

R^3 being hydrogen, alkyl, alkyloxy, aryl, aralkyloxy, alkylcarbonyloxy or silyloxy, and

R^4 being hydrogen, alkyloxy or alkyl.

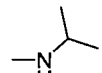
In a more preferred embodiment of the present invention, there is provided the compound of Formula **I**, as defined below:

X is  ,  , or  ;

Z is nitrogen or carbon;

R^{5a} is hydrogen;

R^{5b} is hydrogen;

R^7 is $-NH_2$ or  ;

R^8 is hydrogen; and

R^9 is hydrogen or bromo.

Compounds especially useful in the present invention are selected from the group consisting of:

(1) 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea;

(2) 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea;

(3) 1-(3-((((*2R,3S,4R,5S*)-5-(4-amino-5-bromopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea;

(4) 1-(4-(tert-butyl)phenyl)-3-(3-((((*2R,3S,4R,5S*)-3,4-dihydroxy-5-(4-

(isopropylamino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)tetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)urea;

(5) (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol; and

(6) (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*s*,3*R*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol.

The compounds of Formula **I** can form salts, and salts of the compounds are included within the scope of the invention. The terms "salt" or "pharmaceutically acceptable salt", as used herein, refers to inorganic or organic salts of a compound. These salts can be prepared, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, and in a medium such as one in which the salt formed then precipitates, or in an aqueous medium followed by lyophilization. Representative salts include bisulfate, sulfate, benzene sulfonate, camphorsulfonate, laurylsulphonate, methanesulfonate, naphthalenesulformate, toluenesulfonate, acetate, trifluoracetate, benzoate, borate, butyrate, citrate, formate, fumarate, hydorbromide, hydrochloride, hydroiodide, lactate, laurate, maleate, malonate, mesylate, nitrate, oxalate, phosphate, hexafluorophosphate, propionate, salicylate, stearate, succinate, tartrate, thiocyanate, and the like. The salts may include base salts based on the alkali and alkaline earth metals, such as calcium, sodium, lithium, magnesium, and potassium; or with organic bases such as with organic amines (e.g., dicyclohexylamine, t-butyl amine, methylamine, dimethylamine, triethylamine, ethylamine, procaine, morpholine, N-methylpiperidine, dibenzylamine, and the like); or as an ammonium salt.

The compounds of Formula **I** may be used in the form of prodrugs, which are included within the scope of the invention. The term "prodrug", as used herein, refers to a compound that is transformed *in vivo* (e.g., by a metabolic, physiological, or chemical process) to yield a compounds of Formula **I**, or a pharmaceutically acceptable salt, hydrate or solvate of the compound. Prodrugs, made by synthesizing one or more prodrug moieties as part of an active compound, can serve to enhance one or more of solubility, absorption, lipophilicity, pharmacodynamics, pharmacokinetics,

and efficacy, as compared to the active compound without the one or more prodrug moieties. Various forms of prodrugs are known in the art. Examples of prodrugs of the compounds of the invention include an *in vivo* cleavable ester of a carboxy group (e.g., lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono-or di-substituted lower alkyl esters, and the like); or *S*-acyl and *O*-acyl derivatives of thiols, alcohols, or phenols. "Prodrug moiety" refers to a labile functional group, including but not limited to a protective group, which can be removed or reduced from the active compound during a process elected from one or more of metabolism, systemic circulation, intracellular, hydrolysis, or enzymatic cleavage. Enzymes which are capable of an enzymatically activating a phosphonate prodrug include, but are not limited to, amidases, esterases, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself. Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^3$ and acyloxymethyl carbonates esters $-CH_2OC(=O)OR^3$ where R^3 is C_{1-6} alkyl, C_{1-6} substituted alkyl, C_{1-20} aryl or C_{1-20} substituted aryl. Phosphonate prodrug moieties may include, but are not limited, to groups such as phosphate esters, phosphonate esters, phosphonamidate esters, wherein the ester may be further substituted with groups that confer a pharmaceutical advantage such as one or more of improved solubility in aqueous solutions, or prolonged *in vivo* exposure, or enhanced absorption through a mucosa of a compound according to Formula **I**. Thio-containing prodrug moieties, reported to be useful for the intracellular delivery of drugs, contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Following deesterification or reduction of the disulfide, generated is a free thio intermediate which, in turn, breaks down.

The compounds of Formula **I** may exist in a solvated form or unsolvated form. Solvates of a compound of the invention may be formed in the synthetic process in which the compound becomes physically associated with one or more solvent molecules (e.g., such as by ionic and/or covalent bonding) or, optionally, may be converted to a solvate such as by dissolving the compound in desired amounts of a solvent of choice (e.g., organic solvent, water, or mixtures thereof) in forming a

solution, heating the solution to a temperature higher that ambient temperature, and cooling the solution at a rate sufficient to form crystals of the solvate, which may then be further isolated using methods known the art. Examples of suitable solvents include methanolates, ethanolates, hydrates (where the solvent molecule is water), and the like.

The compounds of Formula **I** may contain asymmetric or chiral centers, and thus exist in different isomeric forms. All stereoisomers (e.g., geometric isomers, optical isomers, and the like), enantiomeric forms, diastereomeric forms, tautomeric forms, positional isomers, of the compounds of the invention are embraced within the scope of the invention. A first conformational form of a compound can be separated from a second and different conformational form of the compound using methods well known in the chemical arts such as by chromatography, crystallization, and methods of synthesis which selectively result in a particular desired conformational form.

Further, the present invention provides a pharmaceutical composition for preventing or treating precancerous transformation or cancer, comprising as an active ingredient the compound of formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof, and a pharmaceutically acceptable carrier.

The composition according to the invention may be administered once, or multiple times, as needed, to deliver a medically effective amount of the composition, e.g., an amount effective to mediate modulation of a disease, disorder, or condition by inhibiting DOT1L in the individual receiving the composition. For example, a medically effective amount of a composition comprising a compound of the invention may be an amount that enters into cells which are contacted with the compound, and which results in inhibiting DOT1L within the cells. Such a medically effective amount of the composition will depend on such factors as the mode of administration, the formulation for administration, disease to be modulated, the size and health of the individual to receive such a composition, and other factors which can be taken into consideration by a medical practitioner whom is skilled in the art of determining appropriate dosages for treatment. An amount of compound of the invention in a composition to be administered may vary from 0.01 milligrams to about 500 milligrams, and more typically from about 1 milligram per day to about 200 milligram per day. One skilled in the art can apply known principles and models of drug

delivery and pharmacokinetics to ascertain a likely range of dosages to be tested in preclinical and clinical studies for determining a medically effective amount of a compound of the invention. A pharmaceutically acceptable carrier, used in a composition of the invention, may facilitate one or more of storage, stability, administration, and delivery, of the composition. The carrier may be particulate, so that the composition may be in, for example, powder or solid form. The carrier may be in a semi-solid, gel, or liquid formula, so that the composition may be ingested, injected, applied, or otherwise administered. The carrier may be gaseous, so that the composition may be inhaled.

For oral administration of a composition containing a compound of the invention, suitable formulations may be presented in the form of tablets, caplets, capsules, and the like, in which typically the compound of the invention may be present in a predetermined amount as a powder, granules, solution, or suspension as the sole active agent, or in combination with an additional one or more pharmaceutical agents. As known in the art, such oral formulations typically involve one or more of a binder (e.g., syrup, sorbitol, gum, corn starch, gelatin, acacia), a filler (e.g., lactose, sugar, starch, calcium phosphate), an excipient (e.g., dicalcium phosphate), a disintegrating agent (e.g., vegetable starch, alginic acid), a lubricant (e.g., magnesium stearate), a flavoring agent (sweetening agent, natural or artificial flavors). Such oral formulations may be coated or uncoated to modify their disintegration and/or absorption. Coating may be performed using conventional coating agents and methods known in the art.

The mode of administration of a compound or composition of the invention to an individual (such as a human) in need of such composition or compound may be any mode known in the art to be suitable for delivering a pharmaceutical composition, and particularly suitable for treating a disease, disorder or condition by inhibiting DOT1L, and may include but is not limited to, intravenously, intraperitoneally, orally, subcutaneously, intramuscularly, intranasally, transdermally, by perfusion, and by peristaltic techniques. The compositions of the invention may also be combined with other therapies, such as one or more additional pharmaceutical agents, to treat a disease, disorder or condition. Such combination therapy may be administered in concurrently, sequentially, or in regimen alternating between the composition of the invention and the other therapy. Such combination therapies may include the following

treatments: a compound of Formula **I** with one or more allergy medications. The structure of therapeutic agents identified herein by code numbers and pharmaceutical company's initials, and their generic or trademark names, are readily available to those skilled in the art, such as from the standard compendium of drugs (e.g., The Merck Index) or from the applicable pharmaceutical company's web site, as well as dosages applicable for treatment (see also The Physician's Desk Reference). Alternatively, the doses and dosage regimen of a pharmaceutical agent, used in conjunction with a compound of the invention in combination therapy, can be determined by a physician, taking into account the medical literature, the health, age and sex of the patient, the disease or condition or disorder to be treated, the mode of administration and dosing schedule of the pharmaceutical agent, and other relevant considerations. Generally, dosages of such agents can range from about 0.1 mg to 1000 mg per day, with more specific dosages dependent on the aforementioned factors.

Accordingly, provided herein is a pharmaceutical composition or medicament comprising a medically effective amount of a compound of one or more of Formula **I**, in combination with a medically effective amount of one or more allergy medications; and optionally further comprising a pharmaceutically acceptable carrier.

In addition, the compounds having DOT1L inhibition activity in accordance with the present invention, when used to treat cancer, may be used in combination with one or more chemotherapeutic agents, with the potential for synergistically enhancing apoptosis and/or growth inhibition of cancer cells by the combination. Such chemotherapeutic agents include, but are not limited to, LSD1 blockers PPAR (peroxisome proliferating-activator receptor) ligands (e.g., rosiglitazone); alkylating agents (e.g., nitrogen mustards, such as mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, and melphalan; nitrosoureas, such as streptozocin, carmustine, and lomustine; alkyl sulfonates, such as busulfan; triazines, such as dacarbazine and temozolomide; ethylenimines, such as thiotepa and altretamine; and platinum-based drugs, such as cisplatin, carboplatin, and oxalaplatin); antimetabolites (e.g., 5-fluorouracil, 6-mercaptopurine, capecitabine, cladribine, clofarabine, cytarabine, floxuridine, fludarabine, gemcitabine, hydroxyurea, methotrexate, pemetrexed, pentostatin, and thioguanine); anti-tumor antibiotics (e.g., anthracyclines, such as daunorubicin, doxorubicin, epirubicin, and idarubicin; and actinomycin-D, bleomycin, mitomycin-C, and mitoxantrone); topoisomerase inhibitors (e.g.,

topoisomerase I inhibitors such as topotecan and irinotecan; and topoisomerase II inhibitors, such as etoposide, teniposide, and mitoxantrone); mitotic inhibitors (e.g., taxanes, such as paclitaxel and docetaxel; epothilones such as ixabepilone; Vinca alkaloids, such as vinblastine, vincristine, and vinorelbine; and estramustine); corticosteroids (e.g., prednisone, methylprednisolone, and dexamethasone); proteosome inhibitors (e.g., bortezomib); targeted therapies (e.g., imatinib, gefitinib, sunitinib, rituximab, alemtuzumab, trastuzumab, and bortezomib); differentiating agents (e.g., retinoids, tretinoin, and bexarotene); and hormonal agents (e.g., anti-estrogens, such as fulvestrant, tamoxifen, and toremifene; aromatase inhibitors, such as anastrozole, exemestane, and letrozole; progestins, such as megestrol acetate; estrogens; anti-androgens, such as bicalutamide, flutamide, and nilutamde; gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH) agonists or analogs, such as leuprolide and goserelin).

Furthermore, the present invention provides a method for preventing or treating precancerous transformation or cancer in a mammal, which comprises administering the compound of formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof to the mammal. The method includes treating a disease, disorder, or condition by administering to an individual (a mammal, such as a human) in need of inhibiting DOT1L activity; and inhibiting DOT1L activity by administering to an individual (a mammal, such as a human) in need thereof a compound of Formula **I**. The disease, disorder, or condition modulated by inhibiting DOT1L is selected from the group consisting of precancerous transformation, and cancer (e.g., lymphoma; leukemia; and solid, non-lymphoid tumors).

In these methods, one or more compounds of the invention may be administered in a medically effective amount as the sole pharmaceutical agent, or may be administered in combination therapy wherein a medically effective amount of a compound of the invention is administered with a medically effective amount of at least one additional pharmaceutical agent. Such combination therapy may comprise (a) a single pharmaceutical composition comprised of a compound of the invention, at least one additional pharmaceutical agent, and a pharmaceutically acceptable carrier; or (b) two separate pharmaceutical compositions, which can be administered simultaneously or sequentially, comprising a first composition comprising a compound

of the invention and a pharmaceutically acceptable carrier; and a second composition comprising at least one additional pharmaceutical agent and a pharmaceutically acceptable carrier.

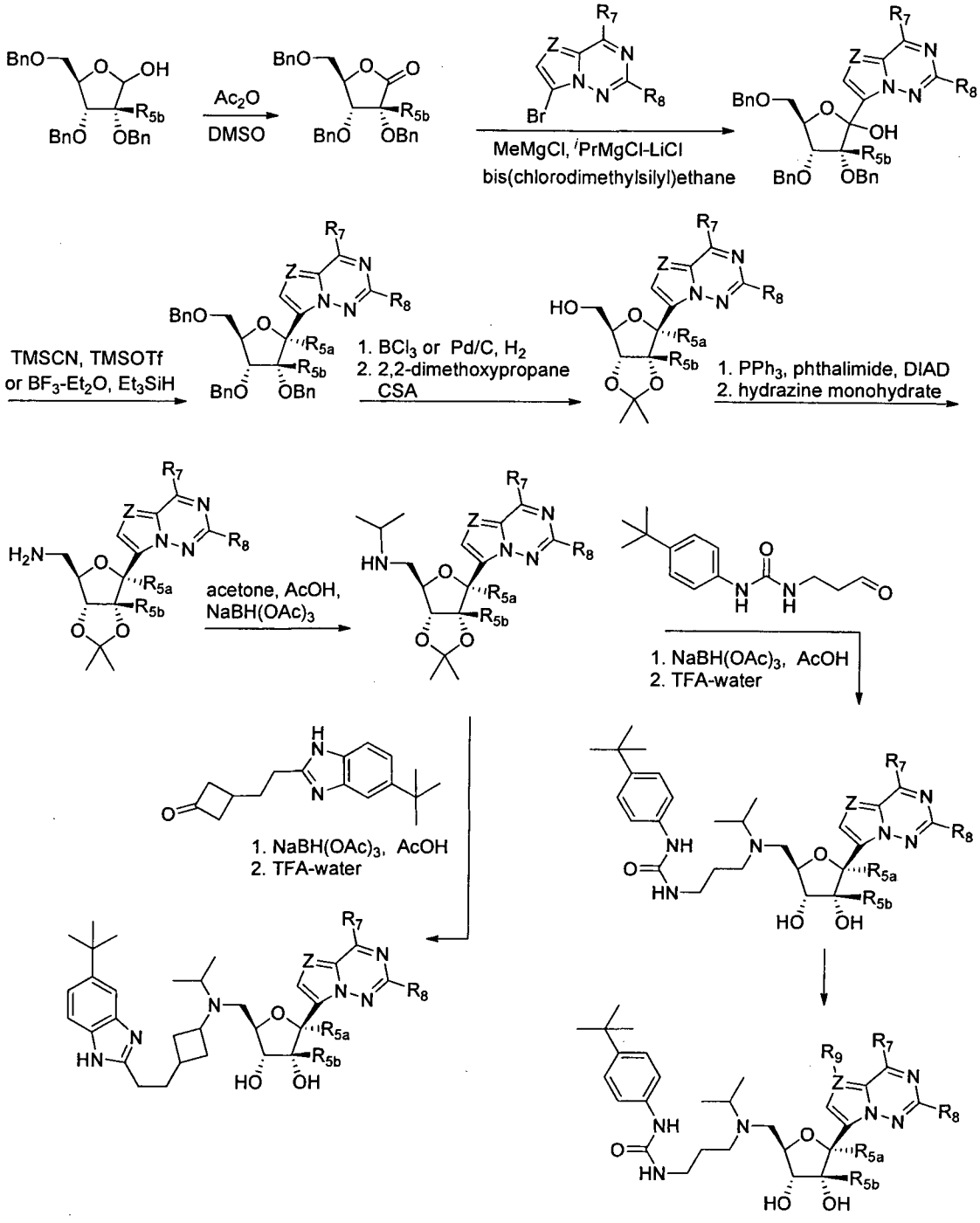
In addition, the present invention provides a use of the compound of formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof for the manufacture of a medicament for preventing or treating precancerous transformation or cancer.

General Synthetic Methods

The general methods for preparing the compounds of this invention are illustrated in the following Schemes. Such compounds can then be evaluated for their ability to inhibit DOT1L activity in standard, commercially available histone methyltransferase assays, and *in vitro* transcription assays.

In this Schemes illustrated are structures and schemes for synthesis of inhibitors of DOT1L, in forming a compound of the invention of Formula **I**. Schematics below are provided as examples.

<Scheme I>



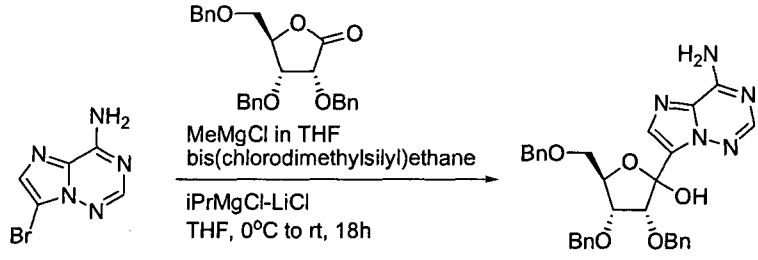
EXAMPLES

Hereinafter, the present invention is described in more detail. The following Examples are given for the purpose of illustration only, and are not intended to limit

the scope of the invention.

Example 1: Preparation of 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea

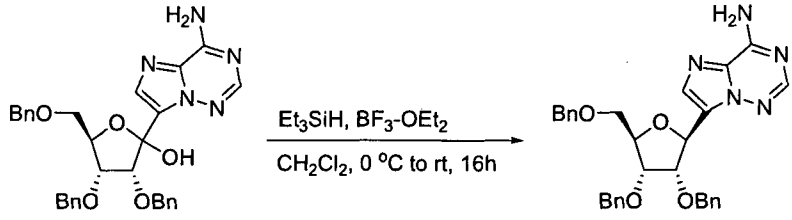
<1-1> Preparation of (3*R*,4*R*,5*R*)-2-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (2)



1 2

To a stirred suspension of 7-bromoimidazo[2,1-*f*][1,2,4]triazin-4-amine (856 mg, 4.00 mmol) in THF (20 mL) was successively added 1.35 mL of MeMgCl solution (3 M in THF) dropwise, 1,2-bis(chloro-dimethylsilyl)ethane (861 mg, 4.00 mmol), and 1.35 mL of MeMgCl (3M in THF). After stirring for 0.5 h, the reaction mixture was treated with the super Grignard (3.4 mL, 1.3 M in TF) slowly. The resulting dark solution was allowed to warm to room temperature, and conversion was checked by TLC. Once the conversion of 7-bromoimidazo[2,1-*f*][1,2,4]triazin-4-amine was >95% complete (3 h), the solution was cooled to 0°C and treated slowly with a solution of (3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)dihydrofuran-2(3*H*)-one (2.51 g, 6.00 mmol) in 10 mL of THF. The resulting orange solution was allowed to room temperature and stirred for overnight. The reaction was cooled to 0°C, carefully quenched with aqueous NH_4Cl solution, stirred vigorously for 30 min, and extracted with EtOAc (50 mL). The separated aqueous layer was extracted with ethyl acetate (50 ml). The combined organic layer was washed with 0.5 N HCl (100 mL*2), dried with anhydrous Na_2SO_4, concentrated under the reduced pressure, and the residue was purified by flash silica gel chromatography to give inseparable isomeric mixture of compound **2** (952 mg, 43%) as a colorless oil: MS (EI) for $C_{34}H_{31}N_5O_5$ $(M + H)^+$ calculated, 554.2; found, 554.3.

<1-2> Preparation of 7-((2*S*,3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine (3)

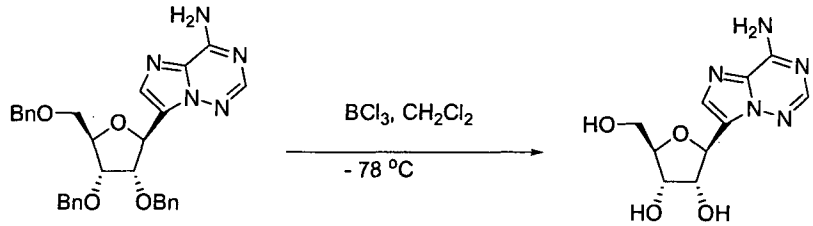


2 3

To a stirred solution of the compound **2** (580 mg, 1.05 mmol) in dichloromethane (30 ml) was added triethylsilane (1.34 mL, 8.40 mmol) followed by dropwise addition of boron trifluoride etherate (0.778 mL, 6.30 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was saturated sodium bicarbonate and the separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash column chromatography to afford stereospecially compound **3** (437 mg, 77%) as an off white solid.

^{1}H NMR (400 MHz, methanol-d_4): δ 7.98 (s, 1H), 7.46 (s, 1H), 7.36 - 7.26 (m, 11H), 7.21 - 7.19 (m, 4H), 5.45 (d, J = 5.2 Hz, 1H), 4.68 - 4.44 (m, 7H), 4.44 (t, J = 5.0 Hz, 1H), 4.29 - 4.27 (m, 1H), 4.20 (t, J = 5.2 Hz, 1H), 3.71 (dd, J = 10.8, 4.0 Hz, 1H)), 3.62 (dd, J = 10.8, 4.4 Hz, 1H).

<1-3> Preparation of (2*S*,3*R*,4*S*,5*R*)-2-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (4)



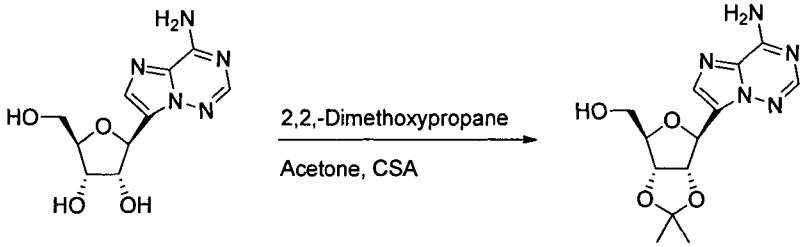
3 4

To a stirred solution of the compound **3** (430 mg, 0.80 mmol) in CH_2Cl_2 (30 mL) at -78°C was slowly added BCl_3 (5.6 mL, 1.0 M in CH_2Cl_2), and the reaction

mixture was stirred at -78°C for 3 h. The reaction mixture was treated with MeOH (5 mL) to destroy excess BCl_3 and slowly allowed to warm up to room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was taken in MeOH (10 mL) and concentrated under reduced pressure. The residue was diluted with 3 mL of H_2O, directly purified by flash chromatography to afford compound **4** (214 mg, 100%) as a white solid.

^{1}H NMR (400 MHz, methanol-d_4): δ 8.05 (s, 1H), 7.66 (s, 1H), 5.21 (d, J = 6.8 Hz, 1H), 4.54 (t, J = 5.6 Hz, 1H), 4.21 (dd, J = 9.2, 4.8 Hz, 1H), 4.04 (dd, J = 7.6, 4.0 Hz, 1H), 3.80 (dd, J = 12.0, 3.2 Hz, 1H)), 3.69 (dd, J = 12.0, 4.0 Hz, 1H).

<1-4> Preparation of ((*3aR,4R,6S,6aS*)-6-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (5)



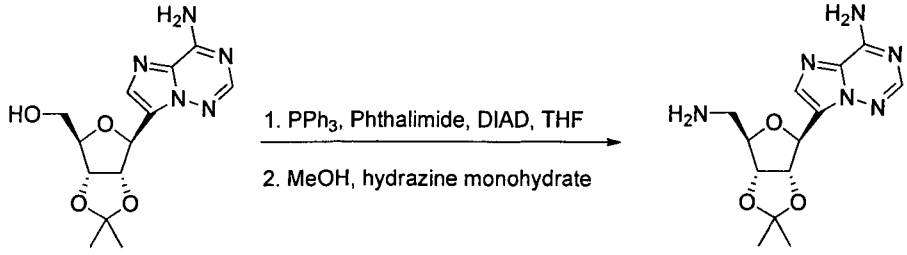
4 **5**

To a stirred suspension of the compound **4** (214 mg, 0.80 mmol) in acetone (30 mL) was added 2,2-dimethoxypropane (4.92 mL, 40.0 mmol) and camphor-10-sulfonic acid (186 mg, 0.80 mmol). The resulting mixture was stirred at room temperature for overnight. The reaction mixture was diluted with aqueous sodium bicarbonate (20 mL) and most of organic solvents were removed under reduced pressure. The remaining aqueous layer was extracted with 5% MeOH in CH_2/Cl_2 (20 mLx5), the combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford compound **5** (229 mg, 93%) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.66 (s, 1H), 5.21 (d, J = 6.0 Hz, 1H), 5.12 (t, J = 6.0 Hz, 1H), 5.02 (dd, J = 10.8, 2.4 Hz, 1H), 4.41 (q, J = 2.0 Hz, 1H), 3.92 (dd, J = 12.0, 2.0 Hz, 1H)), 3.69 (dd, J = 12.0, 2.0 Hz, 1H), 1.63 (s, 3H), 1.37 (s, 3H).

<1-5> Preparation of ((*3aR,4R,6S,6aS*)-6-(aminomethyl)-

2,2,dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine (6)

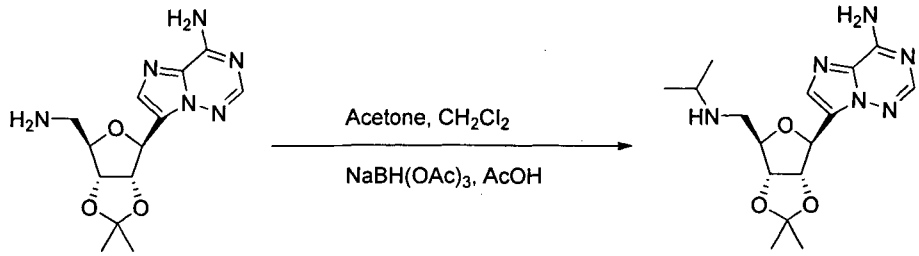


5 **6**

To a stirred solution of the compound **5** (65 mg, 0.21 mmol), triphenylphosphine (67 mg, 0.26 mmol), and phthalimide (37 mg, 0.25 mmol) in THF (4 mL) was added DIAD (51 mg, 0.25 mmol) and the resulting mixture was stirred at room temperature for 1 h. Additional amount of triphenylphosphine (28 mg, 0.11 mmol), phthalimide (16 mg, 0.11 mmol), and DIAD (22 mg, 0.11 mmol) was added to the reaction mixture and the reaction mixture was stirred for additional 1 h. The reaction mixture was concentrated under reduced pressure and the residue was directly purified by flash chromatography to give 2-substituted phthalimide (49 mg) along with inseparable impurity (49 mg). The solution of 2-substituted phthalimide (49 mg) in MeOH (5 mL) was treated with hydrazine monohydrate (0.5 mL, excess) and the resulting mixture was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure and the residue was directly purified by flash chromatography to afford compound **6** (20 mg, 31% in 2 steps) as a white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 8.06 (s, 1H), 7.65 (s, 1H), 5.28 (d, J = 4.4 Hz, 1H), 5.19 (dd, J = 6.8, 4.8 Hz, 1H), 4.81 (dd, J = 6.8, 4.4 Hz, 1H), 4.12-4.08 (m, 1H), 2.94-2.81 (m, 2H)), 1.57 (s, 3H), 1.36 (s, 3H).

<1-6> Preparation of 7-((*3aR,4R,6S,6aS*)-6-((isopropylamino)methyl)-2,2,dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine (7)

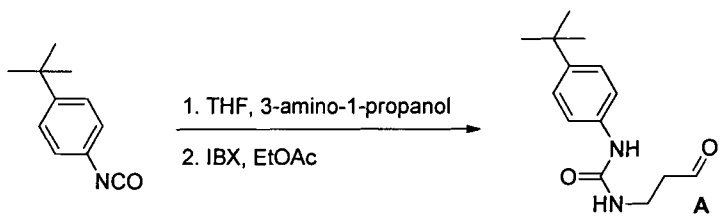


6 7

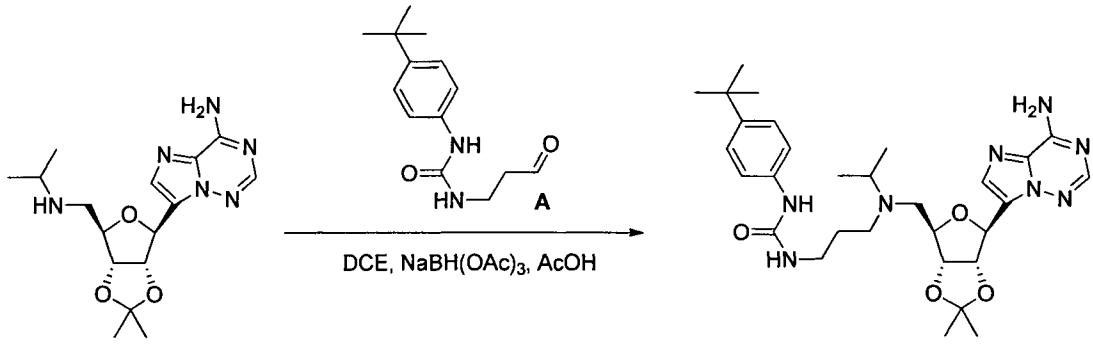
To a stirred solution of the compound **6** (20 mg, 0.065 mmol), acetone (11 mg, 0.189 mmol), and two drops of AcOH in CH_2Cl_2 (5 mL) was added sodium triacetoxyborohydride (55 mg, 0.26 mmol) and the resulting mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with aqueous sodium bicarbonate (10 mL), extracted with 5% MeOH in CH_2Cl_2 (20 mLx5), the combined extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to give compound **7** (23 mg, 100%)

^{1}H NMR (400 MHz, methanol-d_4): δ 8.07 (s, 1H), 7.65 (s, 1H), 5.31 (d, J = 4.0 Hz, 1H), 5.24 (dd, J = 6.4, 4.4 Hz, 1H), 4.80 (dd, J = 6.8, 4.0 Hz, 1H), 4.22-4.16 (m, 1H), 2.86 (dd, J = 12.4, 4.0 Hz, 1H), 2.78-2.72 (m, 2H)), 1.57 (s, 3H), 1.36 (s, 3H), 1.02 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.4Hz, 3H).

<1-7> Preparation of 1-(3-((((*3aR,4R,6S,6aS*)-6-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-2,2,-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(isopropyl)amino)propyl)-3-(4-*tert*-butyl)phenyl)urea (8)



Firstly, compound **A** (1-(4-(*tert*-butyl)phenyl)-3-(3-oxopropyl)urea) was prepared from 4-*tert*-butylphenylisocyanate through coupling with 3-amino-1-propanol followed by IBX oxidation (*see* WO2012/075500 A2).

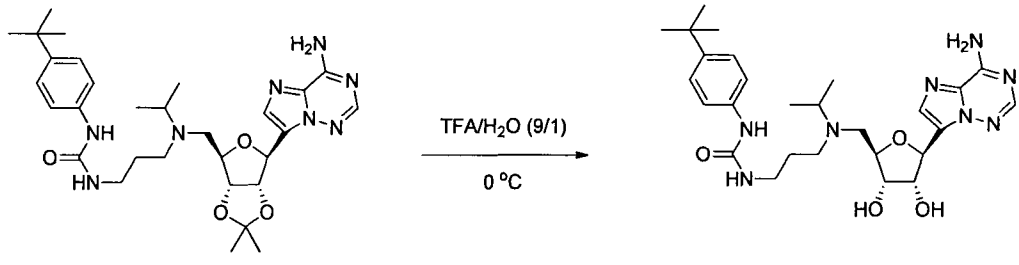


7 A 8

Next, a mixture of **7** (23 mg, 0.066 mmol) and aldehyde **A** (41 mg, 0.165 mmol) in 1,2-dichloroethane (6 mL) was treated with 2 drops of AcOH and $NaBH(OAc)_3$ (70 mg, 0.33 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with aqueous sodium bicarbonate (10 mL), extracted with 5% MeOH in CH_2Cl_2 (20 mLx5), the combined extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to give compound **8** (31 mg, 81%).

^1H NMR (400 MHz, methanol-d_4): δ 8.04 (s, 1H), 7.62 (s, 1H), 7.27-7.20 (m, 4H), 5.33 (d, J = 4.0 Hz, 1H), 5.19 (dd, J = 6.8, 4.0 Hz, 1H), 4.79 (dd, J = 6.8, 4.4 Hz, 1H), 4.25-4.21 (m, 1H), 3.21 (t, J = 6.4 Hz, 2H), 3.16-3.13 (m, 1H), 2.89-2.70 (m, 4H), 1.70-1.65 (m, 2H)), 1.55 (s, 3H), 1.35 (s, 3H), 1.28 (s, 9H), 1.06 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.8Hz, 3H).

<1-8> Preparation of 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea (9)



8 9

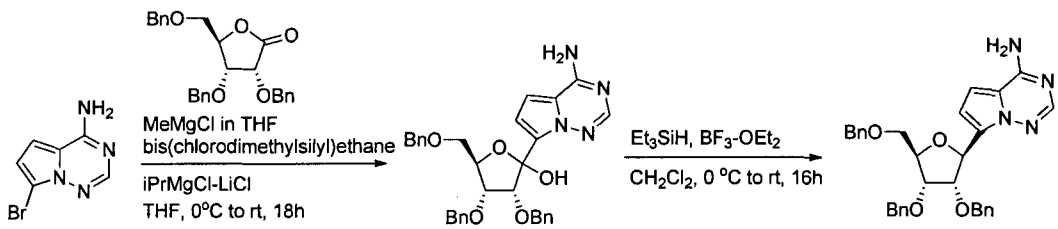
The compound **8** (31 mg, 0.053 mmol) was treated with TFA/H_2O (4 mL, 9/1) and stirred at ice bath for 1.5 h. The reaction mixture was concentrated under

reduced pressure, diluted with 10% MeOH in CH_2Cl_2 (20 mL), basified to pH 8-9 with aqueous sodium bicarbonate, and the separated aqueous layer was extracted with 10% MeOH in CH_2Cl_2 (20 mLx3). The combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford compound **9** (24 mg, 83%), which was then lyophilized with acetonitrile and water to form compound **9** as a white solid.

^{1}H NMR (400 MHz, methanol-d_4): δ 8.00 (s, 1H), 7.58 (s, 1H), 7.23-7.14 (m, 4H), 5.23 (d, J = 4.8 Hz, 1H), 4.48 (t, J = 5.2 Hz, 1H), 4.12-4.05 (m, 2H), 3.28-3.11 (m, 3H), 2.87-2.61 (m, 4H), 1.74-1.65 (m, 2H), 1.26 (s, 9H), 1.05 (d, J = 6.4 Hz, 3H), 1.02 (d, J = 6.8Hz, 3H). MS (EI) for $C_{27}H_{40}N_8O_4$, found 541.3 (MH^+)

Example 2: Preparation of 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea

<2-1> Preparation of 7-((2S,3S,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (11)



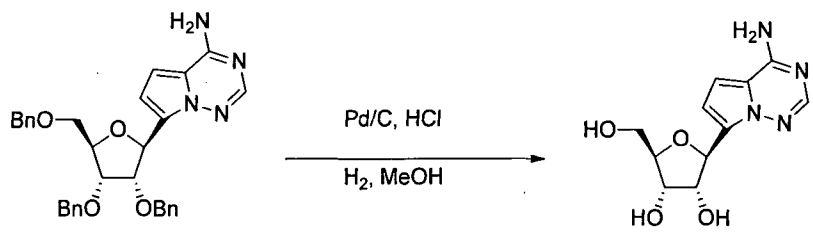
To a stirred suspension of 7-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-amine (639 mg, 3.00 mmol) in THF (15 mL) was successively added 1.00 mL of MeMgCl solution (3 M in THF) dropwise, 1,2-bis(chlorodimethylsilyl)ethane (646 mg, 3.00 mmol), and 1.00 mL of MeMgCl (3 M in THF). After stirring for 0.5 h, the reaction mixture was treated with the super Grignard (2.6 mL, 1.3 M in TF) slowly. The resulting dark solution was allowed to warm to room temperature, and conversion was checked by TLC. Once the conversion of 7-bromoimidazo[2,1-*f*][1,2,4]triazin-4-amine was >95% complete (5 h), the solution was cooled to 0°C and treated slowly with a solution

of (3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)dihydrofuran-2(3*H*)-one (2.51 g, 6.00 mmol) in 10 mL of THF. The resulting orange solution was allowed to room temperature and stirred for overnight. The reaction was cooled to 0°C, carefully quenched with aqueous NH_4Cl solution, stirred vigorously for 0.5 h, and extracted with EtOAc (50 mL). The separated aqueous layer was extracted with ethyl acetate (50 mLx2). The combined organic layer was washed with 0.5 N HCl (100 mLx2), dried with anhydrous Na_2SO_4, concentrated under the reduced pressure, and the residue was purified by flash silica gel chromatography to give compound **10** (651 mg, 39%) as a colorless oil.

To a stirred solution of the compound **10** (651 mg, 1.18 mmol) in dichloromethane (30 mL) was added triethylsilane (1.13 mL, 7.10 mmol) followed by dropwise addition of boron trifluoride etherate (0.728 mL, 5.90 mmol) at -78°C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was saturated sodium bicarbonate and the separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried with sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash column chromatography to afford stereospecially compound **11** (548 mg, 87%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.33-7.19 (m, 15H), 6.69 (d, *J* = 4.8 Hz, 1H), 6.49 (d, *J* = 4.8 Hz, 1H), 5.67 (d, *J* = 4.0 Hz, 1H), 5.24 (br s, 2H), 4.72 (s, 2H), 4.61-4.09 (m, 7H), 3.77 (dd, *J* = 10.8, 3.6 Hz, 1H)), 3.64 (dd, *J* = 10.8, 4.0 Hz, 1H).

<2-2> Preparation of (2*S*,3*R*,4*S*,5*R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (12)



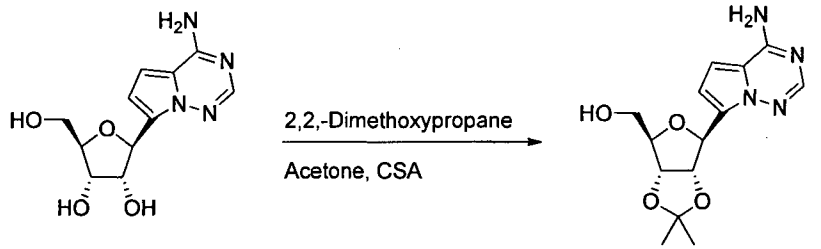
11 **12**

A mixture of the compound **11** (2.2 g, 4.1 mmol), Pd/C (700 mg, 10% on carbon), HCl (2 mL, 3N in MeOH) in MeOH (60 mL) were stirred under H_2 balloon

for 4 h. The resulting reaction mixture was filtered through Celite, washed with MeOH, the filtrates were concentrated under reduced pressure, and purified by silica gel plug to give compound **12** (957 mg, 88%) as an off white solid.

^{1}H NMR (400 MHz, methanol-d_4): δ 7.75 (s, 1H), 6.84 (d, J = 4.8 Hz, 1H), 6.72 (d, J = 4.8 Hz, 1H), 5.22 (d, J = 7.2 Hz, 1H), 4.50 (dd, J = 6.8, 5.2 Hz, 1H), 4.16 (dd, J = 5.2, 3.6 Hz, 1H), 4.02 (dd, J = 7.2, 4.0 Hz, 1H), 3.77 (dd, J = 12.0, 3.2 Hz, 1H)), 3.67 (dd, J = 12.0, 4.0 Hz, 1H).

<2-3> Preparation of ((*3aR,4R,6S,6aS*)-6-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (13)

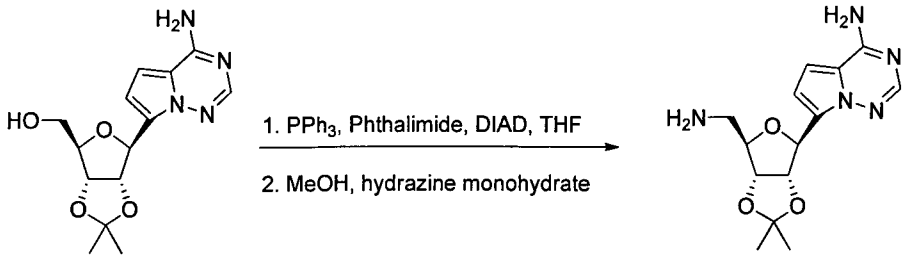


12 **13**

To a stirred suspension of the compound **12** (957 mg, 3.59 mmol) in acetone (100 mL) was added 2,2,-dimethoxypropane (1.0 mL, 8.13 mmol) and camphor-10-sulfonic acid (834 mg, 3.59 mmol). The resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with aqueous sodium bicarbonate (50 mL) and most of organic solvents were removed under reduced pressure. The aqueous layer was extracted with 5% MeOH in CH_2/Cl_2 (50 mLx5), the combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford compound **12** (1.03 g, 94%) as an off white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 7.79 (s, 1H), 6.85 (d, J = 4.8 Hz, 1H), 6.74 (d, J = 4.4 Hz, 1H), 5.31 (d, J = 4.8 Hz, 1H), 5.09 (dd, J = 6.4, 5.2 Hz, 1H), 4.84 (dd, J = 6.8, 4.0 Hz, 1H), 4.15 (dd, J = 8.0, 4.4 Hz, 1H), 3.68 (dd, J = 8.4, 4.4 Hz, 2H), 1.58 (s, 3H), 1.36 (s, 3H).

<2-4> Preparation of 7-((*3aR,4S,6R,6aR*)-6-(aminomethyl)-2,2,dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (14)



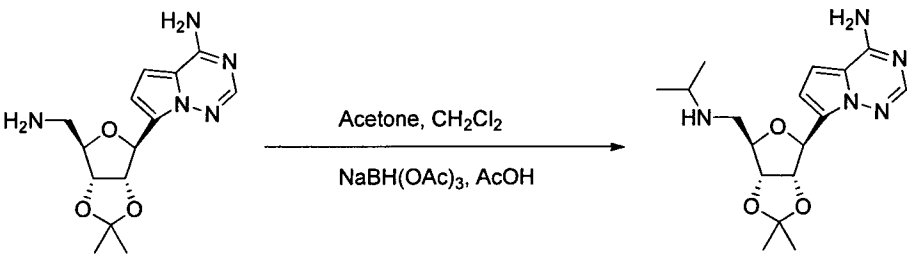
13 **14**

To a stirred solution of the compound **13** (459 mg, 1.50 mmol), triphenylphosphine (590 mg, 2.25 mmol), and phthalimide (331 mg, 2.25 mmol) in THF (30 mL) was added DIAD (455 mg, 2.25 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was directly purified by flash chromatography to give 2-substituted phthalimide (1.1 g) along with inseparable triphenylphosphine oxide.

The solution of crude 2-substituted phthalimide (1.1 g) in MeOH (20 mL) was treated with hydrazine monohydrate (2.0 mL, excess) and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was directly purified by flash chromatography to afford compound **14** (396 mg, 86% in 2 steps) as an off white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 7.79 (s, 1H), 6.85 (d, J = 4.4 Hz, 1H), 6.73 (d, J = 4.4 Hz, 1H), 5.31 (d, J = 4.8 Hz, 1H), 5.15 (dd, J = 6.8, 4.8 Hz, 1H), 4.78 (dd, J = 6.4, 4.0 Hz, 1H), 4.07 (q, J = 6.4 Hz, 1H), 2.88-2.79 (m, 2H)), 1.56 (s, 3H), 1.35 (s, 3H).

<2-5> Preparation of 7-((*3aS,4S,6R,6aR*)-6-((isopropylamino)methyl)-2,2,dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (15)



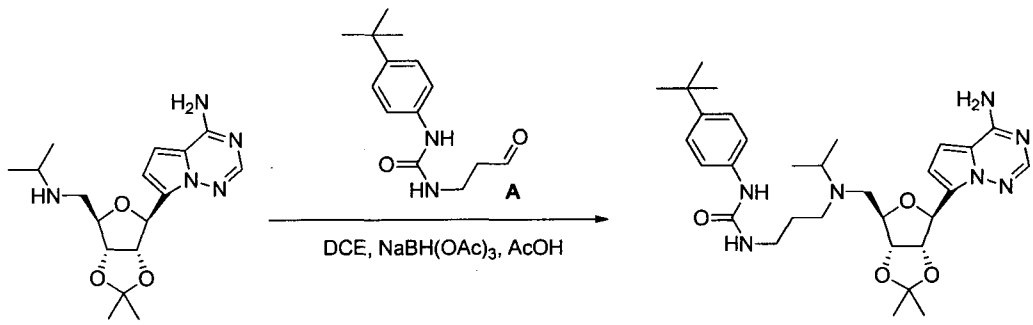
14 **15**

To a stirred solution of the compound **14** (396 mg, 1.30 mmol), acetone (113 mg, 1.9 mmol), and two drops of AcOH in CH_2Cl_2 (5 mL) was added sodium

triacetoxyborohydride (551 mg, 2.60 mmol) and the resulting mixture was stirred at room temperature for 5 hrs. The reaction mixture was diluted with aqueous saturated sodium bicarbonate (30 mL), extracted with 5% MeOH in CH_2Cl_2 (30 mLx5), the combined extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to give compound **15** (421 mg, 93%).

^{1}H NMR (400 MHz, methanol-d_4): δ 7.82 (s, 1H), 6.85 (d, J = 4.4 Hz, 1H), 6.75 (d, J = 4.4 Hz, 1H), 5.39 (d, J = 4.0 Hz, 1H), 5.22 (dd, J = 6.8, 4.0 Hz, 1H), 4.87 (dd, J = 6.8, 4.8 Hz, 1H), 4.29-4.25 (m, 1H), 3.34-3.24 (m, 3H)), 1.57 (s, 3H), 1.26 (s, 3H), 1.21 (d, J = 5.6 Hz, 6H).

<2-6> Preparation of 1-(3-((((*3aR,4R,6S,6aS*)-6-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-2,2,-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(isopropyl)amino)propyl)-3-(4-*tert*-butyl)phenyl)urea (16)



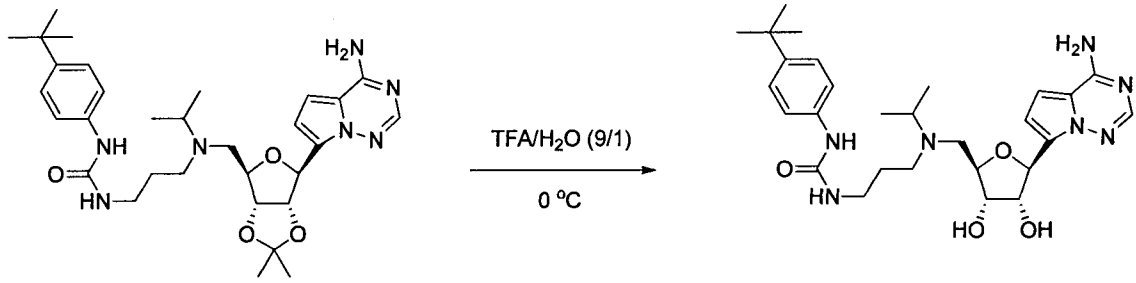
15 **16**

A mixture of the compound **15** (200 mg, 0.576 mmol) and aldehyde **A** (286 mg, 1.15 mmol) in 1,2-dichloroethane (30 mL) was treated with 10 drops of AcOH and $NaBH(OAc)_3$ (366 mg, 1.73 mmol) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with aqueous saturated sodium bicarbonate (30 mL), extracted with 5% MeOH in CH_2Cl_2 (40 mLx5), the combined extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to give compound **16** (291 mg, 87%).

^{1}H NMR (400 MHz, methanol-d_4): δ 7.77 (s, 1H), 7.28-7.23 (m, 4H), 6.85 (d, J = 4.8 Hz, 1H), 6.71 (d, J = 4.4 Hz, 1H), 5.40 (d, J = 3.6 Hz, 1H), 5.18 (dd, J = 6.8, 3.6

Hz, 1H), 4.80 (dd, J = 6.4, 4.4 Hz, 1H), 4.26-4.22 (m, 1H), 3.22 (t, J = 6.0 Hz, 2H), 2.95-2.73 (m, 5H), 1.73-1.65 (m, 2H)), 1.54 (s, 3H), 1.33 (s, 3H), 1.28 (s, 9H), 1.07 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.4Hz, 3H).

<2-7> Preparation of 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea (17)

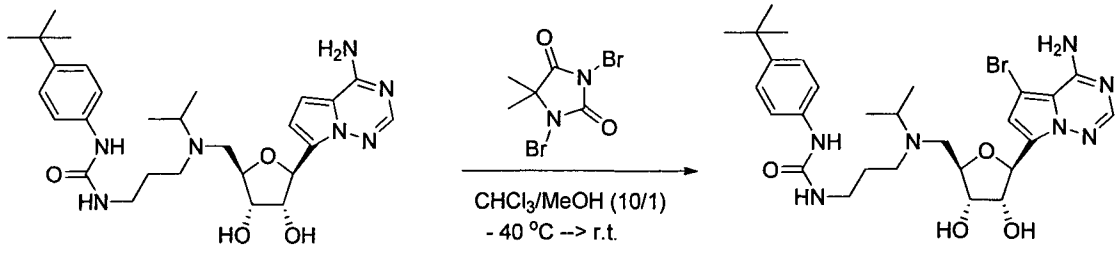


16 17

The compound **16** (291 mg, 0.502 mmol) was treated with TFA/H_2O (10 mL, 9/1) and stirred at ice bath for 1.5 h. The reaction mixture was concentrated under reduced pressure, diluted with 10% MeOH in CH_2Cl_2 (40 mL), basified to pH 8-9 with aqueous sodium bicarbonate, and the separated aqueous layer was extracted with 10% MeOH in CH_2Cl_2 (40 mLx3). The combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford compound **17** (221 mg, 82%), which was then lyophilized to provide compound **17** as a white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 7.72 (s, 1H), 7.22-7.12 (m, 4H), 6.84 (d, J = 4.4 Hz, 1H), 6.68 (d, J = 4.4 Hz, 1H), 5.34 (d, J = 4.8 Hz, 1H), 4.39 (t, J = 5.2 Hz, 1H), 4.10-4.06 (m, 1H), 4.03 (t, J =5.6 Hz, 1H), 3.27-3.16 (m, 2H), 3.10-3.07 (m, 1H), 2.80-2.77 (m, 1H), 2.69-2.61 (m, 3H), 1.72-1.64 (m, 2H), 1.27 (s, 9H), 1.02 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8Hz, 3H). MS (EI) for $C_{28}H_{41}N_7O_4$, found 540.3 (MH^+)

Example 3: Preparation of 1-(3-((((*2R,3S,4R,5S*)-5-(4-amino-5-bromopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea



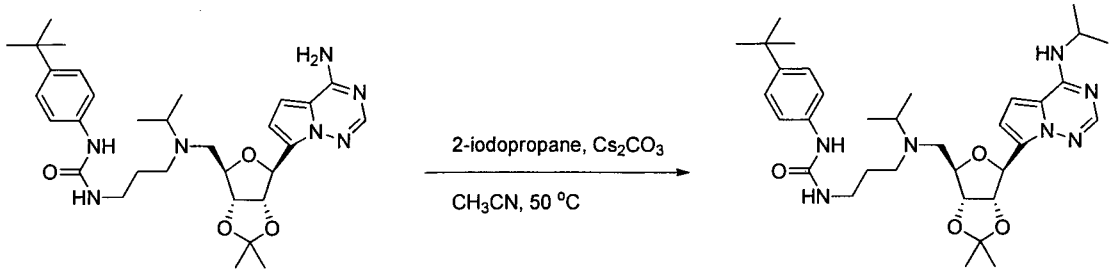
17 18

To a stirred solution of the compound **17** (36 mg, 0.067 mmol) in $CHCl_3$/MeOH (4 mL/0.4 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (9.5 mg, 0.033 mmol) at -40°C and the reaction mixture was slowly allowed to warm up to room temperature. The reaction mixture was diluted with aqueous sodium bicarbonate, extracted with 5% MeOH in CH_2Cl_2 (10 mLx5), the combined extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by prep. HPLC to afford compound **18** (31 mg, 75%) as formic acid salt, which was then lyophilized to give as a white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 8.52 (br s, 1H), 7.75 (s, 1H), 7.26-7.16 (m, 4H), 6.74 (s, 1H), 5.27 (d, J = 4.0 Hz, 1H), 4.34 (dd, J = 5.2, 4.0 Hz, 1H), 4.21-4.16 (m, 1H), 4.03 (dd, J = 6.8, 5.6 Hz, 1H), 3.68-3.64 (m, 1H), 3.46-3.11 (m, 7H), 1.93-1.86 (m, 2H), 1.30 (d, J = 7.2 Hz, 3H), 1.27 (d, J = 7.6 Hz, 3H), 1.26 (s, 9H). MS (EI) for $C_{28}H_{40}BrN_7O_4$, found 618.2, 620.2 (MH^+)

Example 4: Preparation of 1-(4-(tert-butyl)phenyl)-3-(3-((((*2R,3S,4R,5S*)-3,4-dihydroxy-5-(4-(isopropylamino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)tetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)urea

<4-1> Preparation of 1-(4-(*tert*-butyl)phenyl)-3-(3-isopropyl(((*3aR,4R,6S,6aS*)-6-(4-isopropylamino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-2,2,-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)amino)propyl)urea (19)

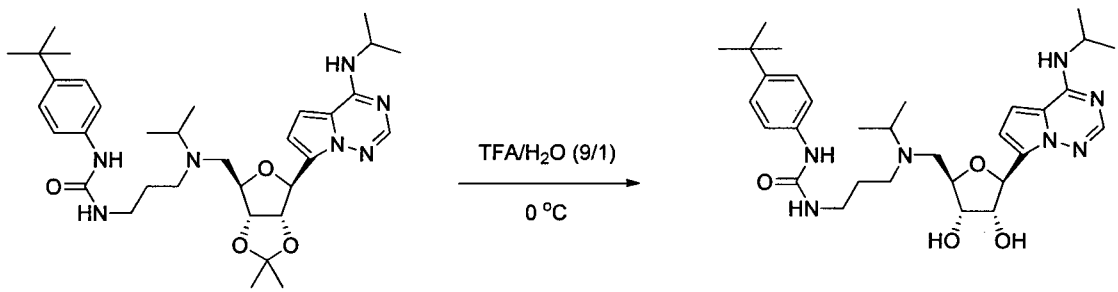


16 19

A mixture of the compound **16** (41 mg, 0.071 mmol), 2-iodopropane (121 mg, 0.71 mmol), and Cs_2CO_3 (92 mg, 0.282 mmol) in CH_3CN, 4 mL) were stirred at 50 °C for 48 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to afford compound **19** (34 mg, 77%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (s, 1H),7.95 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 4.4 Hz, 1H), 6.69 (d, *J* = 4.4 Hz, 1H), 6.01 (t, *J* = 5.2 Hz, 1H), 5.21 (d, *J* = 4.0 Hz, 1H), 5.04 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.69 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.44-4.35 (m, 1H), 3.97-3.93 (m, 1H), 3.10-3.02 (m, 2H), 2.90-2.85 (m, 1H), 2.53-2.31 (m, 4H), 1.51-1.46 (m, 5H)), 1.28 (s, 3H), 1.21 (s, 9H), 1.21 (d, *J* = 5.2 Hz, 6H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H).

<4-2> Preparation of 1-(4-(tert-butyl)phenyl)-3-(3-((((*2R,3S,4R,5S*)-3,4-dihydroxy-5-(4-(isopropylamino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)tetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)urea(20)



19 20

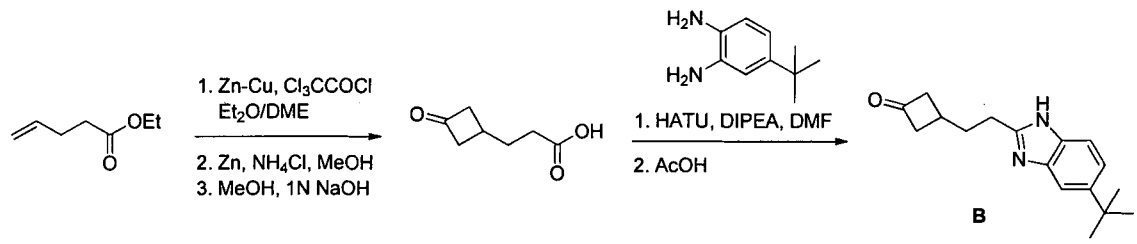
The compound **19** (34 mg, 0.055 mmol) was treated with TFA/H_2O (10 mL, 9/1) at 0°C and allowed to warm up to room temperature. After stirred for 1 h, the reaction mixture was concentrated under reduced pressure, diluted with 10% MeOH in CH_2Cl_2 (10 mL), basified to pH 8-9 with aqueous sodium bicarbonate, and the

separated aqueous layer was extracted with 10% MeOH in CH_2Cl_2 (10 mLx3). The combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford compound **20** (27 mg, 85%), which was then lyophilized to convert compound **20** as a white powder.

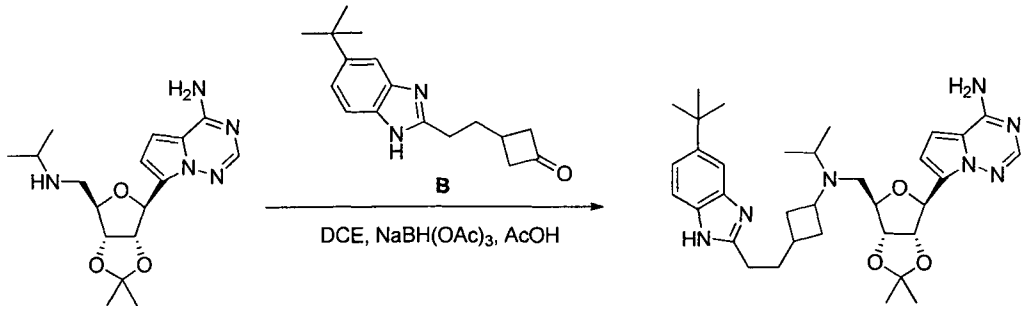
^{1}H NMR (400 MHz, methanol-d_4): δ 7.76 (s, 1H), 7.21-7.12 (m, 4H), 6.86 (d, *J* = 4.0 Hz, 1H), 6.63 (d, *J* = 4.4 Hz, 1H), 5.33 (d, *J* = 5.2 Hz, 1H), 4.42-4.36 (m, 2H), 4.10-4.01 (m, 2H), 3.28-3.17 (m, 2H), 3.11-3.06 (m, 1H), 2.79-2.76 (m, 1H), 2.68-2.61 (m, 3H), 1.71-1.64 (m, 2H), 1.28 (d, *J* = 5.2 Hz, 6H), 1.26 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). MS (EI) for $C_{31}H_{47}N_7O_4$, found 582.3 (MH^+)

Example 5: Preparation of (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol

<5-1> Preparation of 7-((*3aS,4S,6R,6aR*)-6-(((3-(2-(5-*tert*-butyl)-1H-benzo[*d*]imidazole-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)-2,2,-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (21)



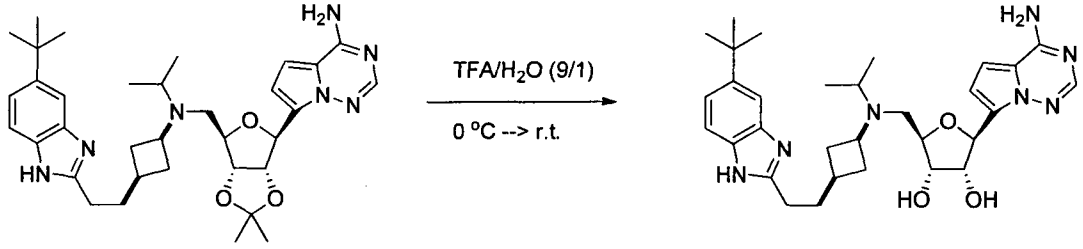
Firstly, Compound **B** was prepared from ethyl 4-pentenoate by using literature methods (see WO2012/075381 A1).



15 21

Next, to a stirred solution of the compound **15** (70 mg, 0.20 mmol) and a ketone **B** (108 mg, 0.40 mmol) in 1,2-dichloroethane (10 mL) was treated with 5 drops of AcOH and $NaBH(OAc)_3$ (212mg, 1.00 mmol) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with aqueous saturated sodium bicarbonate (30 mL), extracted with 5% MeOH in CH_2Cl_2 (40 mLx5), the combined extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to give compound **21** (106 mg, 88%) as a mixture of cis and trans isomer. Only cis isomer was protected with Boc group under CH_2Cl_2, DIPEA, and Boc_2O.

<5-2> Preparation of (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol (22)



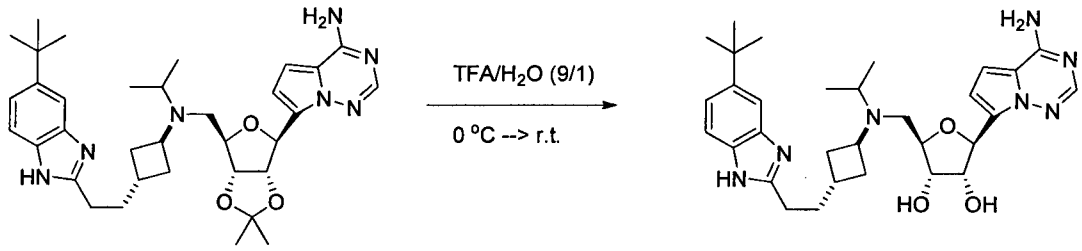
cis-21 22

The compound **cis-21** (76 mg, 0.108 mmol) was treated with TFA/H_2O (5 mL, 9/1) at 0°C and allowed to warm up to room temperature. After stirred for 3 h, the reaction mixture was concentrated under reduced pressure, diluted with 10% MeOH in CH_2Cl_2 (10 mL), basified to pH 8-9 with aqueous sodium bicarbonate, and the separated aqueous layer was extracted with 10% MeOH in CH_2Cl_2 (10 mLx3). The combined organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure, and the residue was purified by flash chromatography to afford

compound **22** (47 mg, 77%), which was then lyophilized give compound **22** as a white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 7.78 and 7.77 (2 s, 1H), 7.47 (br s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.29-7.26 (m, 1H), 6.85 (d, J = 4.4 Hz, 1H), 6.66 (d, J = 4.4 Hz, 1H), 5.29 (d, J = 4.4 Hz, 1H), 4.39 (t, J = 4.8 Hz, 1H), 4.03-3.96 (m, 2H), 3.68-3.64 and 3.30-3.26 (m, 1H), 3.18-3.12 (m, 1H), 2.95-2.90 (m, 1H), 2.83-2.76 (m, 3H), 2.28-2.23 (m, 2H), 2.15-1.65 (m, 5H), 1.35 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H). MS (EI) for $C_{31}H_{43}N_7O_4$, found 562.4 (MH^+)

Example 6: Preparation of (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*s*,3*R*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol



trans-21 **23**

The compound **trans-21** (28 mg, 0.047 mmol) was treated with TFA/H_2O (5 mL, 9/1) at 0°C and allowed to warm up to room temperature. After stirred for 3 h, the reaction mixture was concentrated under reduced pressure, diluted with 10% MeOH in CH_2Cl_2 (10 mL), basified to pH 8-9 with aqueous sodium bicarbonate, and the separated aqueous layer was extracted with 10% MeOH in CH_2Cl_2 (10 mLx3). The combined organic layer was dried with anhydrous sodium sulfate , concentrated under reduced pressure, and the residue was purified by flash chromatography followed by prep HPLC to afford compound **23** (14 mg, 54%), which was then lyophilized give compound **23** (formic acid salt) as a white powder.

^{1}H NMR (400 MHz, methanol-d_4): δ 8.44 (br s, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 9.2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 4.4 Hz, 1H), 6.68 (d, J = 4.4 Hz, 1H), 5.31 (d, J = 3.6 Hz, 1H), 4.48 (t, J = 4.8 Hz, 1H), 4.12-4.08 (m, 2H), 3.75-3.62 (m, 2H), 2.81-2.78 (m, 2H), 2.52-2.36 (m, 2H), 2.04-1.84 (m, 5H), 1.35 (s, 9H), 1.26 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H). MS (EI) for $C_{31}H_{43}N_7O_4$, found

562.3 (MH^+)

Test Example 1: Measurement of DOT1L enzyme activity

The DOT1L enzyme activity was measured using recombinant human DOT1L in the Reaction Biology Corporation (Malvern, Pennsilvanis). The reaction includes 0.05 mg/ml oligo nucleosomes and 1 uM of SAM (*S*-adenosyl-L-methionine), and tritium labeled *S*-adenosyl-L-[methyl-3H]methionine. After incubation, the labeled product of the nucleosome was isolated and measured the radioactivity. The test compounds were serially diluted 3 folds and duplicate experiments for the inhibition were done 10 dose with curve fitting for IC_{50} profiling. The assay was validated using SAH (IC_{50} = 450 nM) as a reference compound.

Other histone methyltransferase assays such as EZH1, EZH2, G9a, PRMT4, and SET7 were done identical ways except using different substrates. The results are shown in Table 1.

<Table 1>

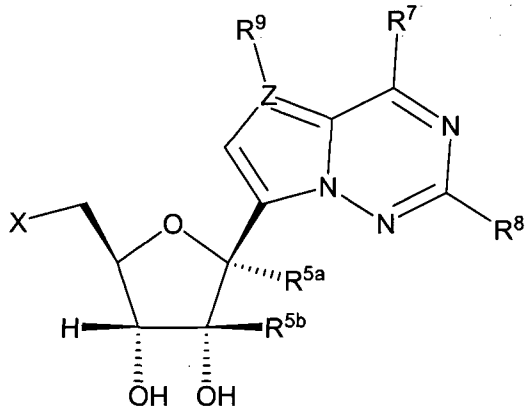
Compounds	DOT1L IC_{50} (nM)	EZH2/G9a/PRMT4/SET7
Example 1	5.9	Above 10 μM
Example 2	2.6	Above 10 μM
Example 3	3.4	Above 10 μM
Example 4	94.8	Above 10 μM
Example 5	0.4	Above 10 μM
Example 6	0.5	Above 10 μM

As shown in Table 1, the compounds of the present invention were found to effectively inhibit DOT1L activity. In contrast, the inventive compounds did not inhibit other histone methyltranferases, e.g., EZH1, EZH2, G9a, PRMT4, and SET7, at all.

The results indicate that the compounds of the present invention selectively inhibit DOT1L activity.

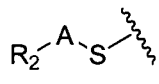
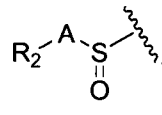
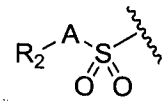
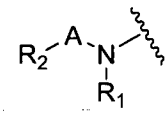
What is claimed is:

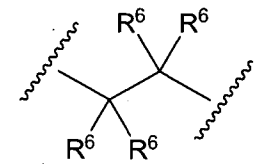
1. A compound of Formula **I**, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof:

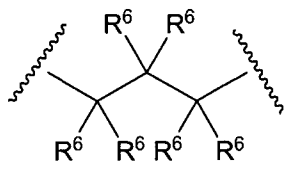
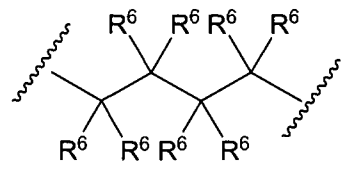
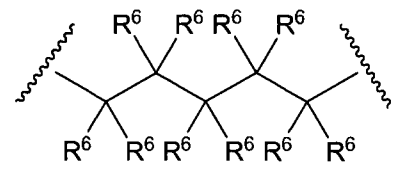


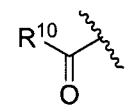
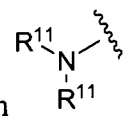
I

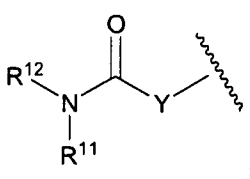
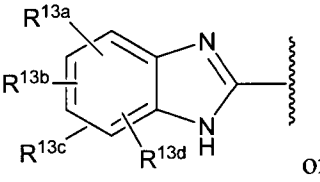
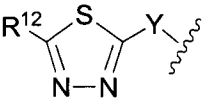
wherein,

X is  ,  ,  or  ;

A being alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl,  ,

 ,  or  ,

R_1 being hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, alkylaryl, haloalkyl, formyl, heterocyclyl, heterocyclylalkyl,  or C_{2-4} alkyl substituted with  , and

R_2 being  ,  or 

R^6 being hydrogen, alkyl or halogen, or two geminal R^6 taken together are ethyl, propyl or butyl,

R^{10} being alkyl, cycloalkyl, cycloalkylalkyl or haloalkyl,

R^{11} being hydrogen, alkyl or cycloalkyl,

R^{12} being alkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heteroarylaryl, fused bicyclyl, biaryl, aryloxyaryl, heteroaryloxyaryl, aryloxyheteroaryl or heteroaryloxyheteroaryl,

R^{13a}, R^{13b}, R^{13c} and R^{13d} being each independently $-M_2-T_2$ or $-T_2$, in which M_2 is a bond, SO_2, SO, S, CO, CO_2, O, O-C_{1-4} alkyl linker, C_{1-4} alkyl linker, NH, or $N(R_t)$, R_t being C_1-C_6 alkyl, and T_2 is H, halogen, alkyl, heterocycloalkyl, heteroaryl or haloalkyl, and

Y being –NH, -N(alkyl) or –N(haloalkyl);

Z is nitrogen or carbon;

R^{5a} is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl or CN;

R^{5b} is hydrogen, halogen or hydroxyl;

R^7 is halogen, NR^3R^4, $N(R^3)OR^3$, NO, NO_2, CHO, CN, -CH(=NR^3), -CH=NNHR^3, -CH=N(OR^3), -$CH(OR^3)_2$, -C(=O)NR^3R^3, -C(=S)NR^3R^3, -C(=O)OR^3, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl, heteroaryl, -C(=O)-C_{1-8} alkyl, -$S(O)_n$-C_{1-8} alkyl, aryl-C_{1-8} alkyl, OR^3 or SR^3; and

R^8 and R^9 are each independently H, halogen, alkyl, haloalkyl, NR^3R^4, $N(R^3)OR^3$, NO, NO_2, CHO, CN, -CH(=NR^3), -CH=NNHR^3, -CH=N(OR^3), -$CH(OR^3)_2$, -C(=O)NR^3R^3, -C(=S)NR^3R^3, -C(=O)OR^3, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl, heteroaryl, -$S(O)_n$-C_{1-8} alkyl, aryl-C_{1-8} alkyl, OR^3 or SR^3;

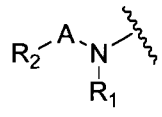
R^3 being hydrogen, alkyl, alkyloxy, aryl, aralkyloxy, alkylcarbonyloxy or silyloxy,

R^4 being hydrogen, alkyloxy or alkyl, and

n being an integer of 0 to 2.

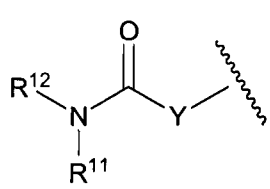
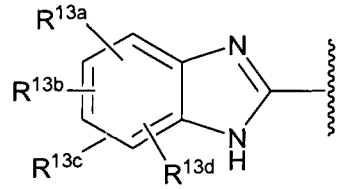
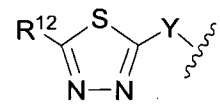
2. The compound of claim 1,

wherein

X is  ;

A being alkyl, cycloalkyl, cycloalkylalkyl or heterocyclyl,

R_1 being hydrogen, alkyl, cycloalkyl or alkylcycloalkyl, and

R_2 being  ,  or 

R^{11} being hydrogen, alkyl or cycloalkyl,

R^{12} being alkyl, aryl, heteroaryl, aralkyl or heteroarylalkyl,

R^{13a}, R^{13b}, R^{13c} and R^{13d} being each independently H, halogen, alkyl, heterocycloalkyl, heteroaryl or haloalkyl, and

Y being –NH;

Z is nitrogen or carbon;

R^{5a} is hydrogen, C_{1-8} alkyl or CN;

R^{5b} is hydrogen, halogen or hydroxyl;

R^7 is halogen, NR^3R^4, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl or heteroaryl; and

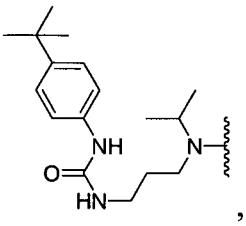
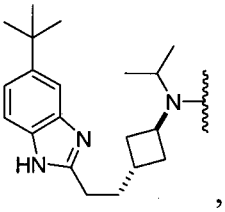
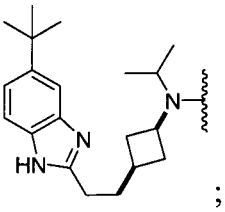
R^8 and R^9 are each independently H, halogen, alkyl, haloalkyl, NR^3R^4, CN, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} carbocyclylalkyl, C_{6-20} aryl, heterocyclyl, heteroaryl, OR^3 or SR^3;

R^3 being hydrogen, alkyl, alkyloxy, aryl, aralkyloxy, alkylcarbonyloxy or silyloxy, and

R^4 being hydrogen, alkyloxy or alkyl.

3. The compound of claim 1,

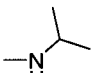
wherein,

X is  ,  , or  ;

Z is nitrogen or carbon;

R^{5a} is hydrogen;

R^{5b} is hydrogen;

R^7 is $-NH_2$ or  ;

R^8 is hydrogen; and

R^9 is hydrogen or bromo.

4. The compound of claim 1, which is selected from the group consisting of:

(1) 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea;

(2) 1-(3-((((*2R,3S,4R,5S*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea;

(3) 1-(3-((((*2R,3S,4R,5S*)-5-(4-amino-5-bromopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(*tert*-butyl)phenyl)urea;

(4) 1-(4-(tert-butyl)phenyl)-3-(3-((((*2R,3S,4R,5S*)-3,4-dihydroxy-5-(4-(isopropylamino)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl)tetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)urea;

(5) (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol; and

(6) (*2S,3R,4S,5R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-((((1*s*,3*R*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol.

5. A pharmaceutical composition for preventing or treating precancerous transformation or cancer, comprising as an active ingredient the compound of formula **I** of claim 1, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof, and a pharmaceutically acceptable carrier.

6. The pharmaceutical composition of claim 5, which further comprises at least one additional pharmaceutical agent.

7. The pharmaceutical composition of claim 6, wherein the pharmaceutical agent is selected from the group consisting of a binder, a filler, an excipient, a disintegrating agent, a lubricant and a flavoring agent.

8. A method for preventing or treating precancerous transformation or cancer in a mammal, which comprises administering the compound of formula **I** of claim 1, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof to the mammal.

9. A method for preventing or treating precancerous transformation or cancer in a mammal, comprising the steps of:

(i) administering to the mammal in need thereof a first composition comprising a compound of Formula **I** of claim 1, and a pharmaceutically acceptable carrier; and

(ii) administering to the mammal in need thereof a second composition comprising at least one additional pharmaceutical agent comprising a chemotherapeutic agent.

10. The method of claim 9, wherein the first composition and second composition are administered simultaneously.

11. The method of claim 9, wherein the first composition and second composition are administered sequentially and in any order.

12. A use of the compound of formula **I** of claim 1, or a pharmaceutically acceptable salt, a prodrug, a hydrate, a solvate, or an isomer thereof for the manufacture

of a medicament for preventing or treating precancerous transformation or cancer.