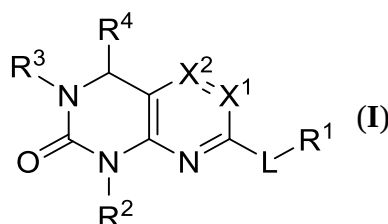


encoding p16. For example, deletion of the MTAP gene, but not p16INK4A was reported to be indicative of a cancer at an early stage of development, whereas deletion of the genes encoding for p16 and MTAP was reported to be indicative of a cancer at a more advanced stage of tumor development. In some osteosarcoma patients, the MTAP gene was present at diagnosis but was deleted at a later time point (Garcia-Castellano *et al.*, *Clin. Cancer Res.* 8(3) 2002 782-787).

## SUMMARY

**[0009]** The present disclosure provides compounds that inhibit MAT2A. The compounds and their pharmaceutical compositions are useful in methods for treating various cancers, including those that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy, and hormonal therapy.

**[0010]** Thus, in accordance with some example, the present disclosure provides a compound according to Formula I or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof:



**[0011]** In Formula I,  $X^1$  is N or  $CR^5$ , and  $X^2$  is N or  $CR^6$ , wherein  $X^1$  and  $X^2$  are not simultaneously N.

**[0012]** L is O, S, NR, or a bond. Substituent R is H or  $C_1$ - $C_6$ -alkyl.

**[0013]**  $R^1$  is selected from the group consisting of  $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_3$ - $C_6$ -carbocyclyl,  $-(C_1$ - $C_6$ -alkyl)( $C_3$ - $C_6$ -carbocyclyl), and  $-(C_1$ - $C_6$ -alkyl)( $C_3$ - $C_6$ -cycloalkenyl) wherein any alkyl in  $R^1$  is straight or branched.

**[0014]** Further,  $R^1$  is optionally substituted by 1 - 6 halo. When  $X^1$  is N,  $X^2$  is  $CR^6$ , L is NR or S, R is H, and  $R^1$  is  $C_1$ - $C_6$ -alkyl, then  $R^1$  is substituted by 1 - 6 halo.

**[0015]** Alternatively, in an example when L is NR, then R and  $R^1$  can be taken together in combination with L to form a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring

members are independently selected from N, O, and S) optionally substituted by one or more R<sup>A</sup>.

**[0016]** R<sup>2</sup> and R<sup>3</sup> are independently selected from the group consisting of optionally substituted C<sub>6</sub>-C<sub>10</sub>-aryl, optionally substituted C<sub>3</sub>-C<sub>6</sub>-carbocyclyl, optionally substituted 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), and optionally substituted 3- to 14-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S).

**[0017]** R<sup>2</sup> and R<sup>3</sup> are independently and optionally substituted by one or more substituents that are selected from the group consisting of R<sup>A</sup>, OR<sup>A</sup>, halo, -N=N-R<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, -C(O)OR<sup>A</sup>, -C(O)NR<sup>A</sup>R<sup>B</sup>, -OC(O)R<sup>A</sup>, and -CN.

**[0018]** In other examples, R<sup>2</sup> and R<sup>3</sup> are independently and optionally substituted by one or more substituents that are selected from the group consisting of R<sup>A</sup>, OR<sup>A</sup>, halo, -N=N-R<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, -C(O)OR<sup>A</sup>, -C(O)NR<sup>A</sup>R<sup>B</sup>, -OC(O)R<sup>A</sup>, -NR<sup>A</sup>C(O)NR<sup>A</sup>R<sup>B</sup>, and -CN. In further examples, R<sup>2</sup> and/or R<sup>3</sup> are -NR<sup>A</sup>C(O)NR<sup>A</sup>R<sup>B</sup>.

**[0019]** R<sup>4</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, halo, oxo, -CN, and -NR<sup>C</sup>R<sup>D</sup>.

**[0020]** R<sup>5</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, halo, -CN, and -NR<sup>C</sup>R<sup>D</sup>.

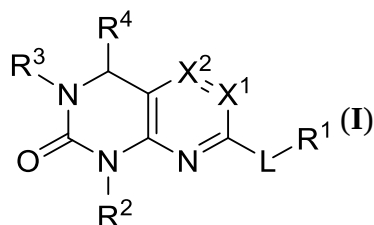
**[0021]** R<sup>6</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl (optionally substituted by one or more halo), -O(C<sub>1</sub>-C<sub>6</sub>-alkyl) (optionally substituted by one or more halo), -OH, halo, -CN, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, and -NR<sup>A</sup>R<sup>B</sup>.

**[0022]** R<sup>A</sup> and R<sup>B</sup> are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, -NH<sub>2</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), -S(O)<sub>0-2</sub>-(C<sub>6</sub>-C<sub>10</sub>-aryl), -C(O)(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C(O)(C<sub>3</sub>-C<sub>14</sub>-carbocyclyl), -C<sub>3</sub>-C<sub>14</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>14</sub>-carbocyclyl), C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S).

**[0023]** In R<sup>A</sup> and R<sup>B</sup>, each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety is optionally substituted with one or more substituents selected from the group consisting of deuterium, hydroxy, halo, -NR'<sup>2</sup> (wherein each R' is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S)), -NHC(O)(OC<sub>1</sub>-C<sub>6</sub>-alkyl), -NO<sub>2</sub>, -CN, oxo, -C(O)OH, -C(O)O(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C<sub>1</sub>-C<sub>6</sub>-alkyl(C<sub>1</sub>-C<sub>6</sub>-alkoxy), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl, -C(O)C<sub>1</sub>-C<sub>6</sub>-alkyl, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, -Si(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>3</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), C<sub>6</sub>-C<sub>10</sub>-aryl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>6</sub>-C<sub>10</sub>-aryl), 3- to 14-membered heterocycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C<sub>6</sub>-C<sub>14</sub>-aryl). Each alkyl, alkenyl, aryl, and heterocycloalkyl substituent is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, halo, -NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NH<sub>2</sub>, -C(O)OH, CN, and oxo.

**[0024]** R<sup>C</sup> and R<sup>D</sup> are each independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl.

**[0025]** In some examples, the disclosure is directed to compounds of Formula



**[0026]** wherein

**[0027]** X<sup>1</sup> is N or CR<sup>5</sup>;

**[0028]** X<sup>2</sup> is N or CR<sup>6</sup>, wherein X<sup>1</sup> and X<sup>2</sup> are not simultaneously N;

**[0029]** L is O, S, NR, or a bond;

**[0030]** R is H or C<sub>1</sub>-C<sub>6</sub>-alkyl;

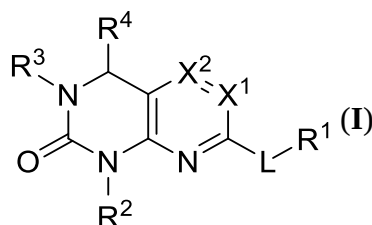
**[0031]** R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-carbocyclyl), and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkenyl)

group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S)), -NHC(O)(OC<sub>1</sub>-C<sub>6</sub>-alkyl), -NO<sub>2</sub>, -CN, oxo, -C(O)OH, -C(O)O(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C<sub>1</sub>-C<sub>6</sub>-alkyl(C<sub>1</sub>-C<sub>6</sub>-alkoxy), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl-C(O)C<sub>1</sub>-C<sub>6</sub>-alkyl, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, -Si(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>3</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), C<sub>6</sub>-C<sub>10</sub>-aryl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>6</sub>-C<sub>10</sub>-aryl), 3- to 14-membered heterocycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C<sub>6</sub>-C<sub>14</sub>-aryl), wherein each alkyl, alkenyl, aryl, and heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, halo, -NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NH<sub>2</sub>, -C(O)OH, CN, and oxo;

**[0038]** R<sup>C</sup> and R<sup>D</sup> are each independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl;

**[0039]** or a pharmaceutically acceptable salt thereof.

**[0040]** In some examples, the disclosure is directed to compounds of Formula I:



**[0041]** wherein

**[0042]** X<sup>1</sup> is N or CR<sup>5</sup>;

**[0043]** X<sup>2</sup> is N or CR<sup>6</sup>, wherein X<sup>1</sup> and X<sup>2</sup> are not simultaneously N;

**[0044]** L is O, S, NR, or a bond;

**[0045]** R is H or C<sub>1</sub>-C<sub>6</sub>-alkyl;

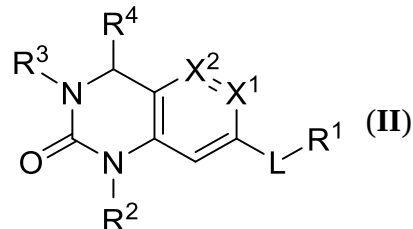
**[0046]** R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-carbocyclyl), and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkenyl) wherein any alkyl in R<sup>1</sup> is straight or branched, R<sup>1</sup> is optionally substituted by 1 - 6 halo; and

membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S)), -NHC(O)(OC<sub>1</sub>-C<sub>6</sub>-alkyl), -NO<sub>2</sub>, -CN, oxo, -C(O)OH, -C(O)O(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C<sub>1</sub>-C<sub>6</sub>-alkyl(C<sub>1</sub>-C<sub>6</sub>-alkoxy), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl-C(O)C<sub>1</sub>-C<sub>6</sub>-alkyl, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, -Si(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>3</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), C<sub>6</sub>-C<sub>10</sub>-aryl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>6</sub>-C<sub>10</sub>-aryl), 3- to 14-membered heterocycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C<sub>6</sub>-C<sub>14</sub>-aryl), wherein each alkyl, alkenyl, aryl, and heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, halo, -NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NH<sub>2</sub>, -C(O)OH, CN, and oxo;

**[0053]** R<sup>C</sup> and R<sup>D</sup> are each independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl;

**[0054]** or a pharmaceutically acceptable salt thereof.

**[0055]** Another example of the disclosure is a compound according to Formula II, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof:



**[0056]** In Formula II, X<sup>1</sup> is N and X<sup>2</sup> is CR<sup>6</sup>, X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>, X<sup>1</sup> and X<sup>2</sup> are both N, or X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>.

**[0057]** L is O, S, NR, or a bond. Substituent R is H or C<sub>1</sub>-C<sub>6</sub>-alkyl.

**[0058]** R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-carbocyclyl), and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkenyl), wherein any alkyl in R<sup>1</sup> is straight or branched. R<sup>1</sup> is optionally substituted by 1 – 6 halo.

**[0059]** In an example when L is NR, then R and R<sup>1</sup> can be taken together in combination with L to form a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S) optionally substituted by one or more R<sup>A</sup>.

aryl), 3- to 14-membered heterocycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C<sub>6</sub>-C<sub>14</sub>-aryl). Each alkyl, alkenyl, aryl, and heterocycloalkyl substituent is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, halo, -NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NH<sub>2</sub>, -C(O)OH, CN, and oxo.

**[0066]** R<sup>C</sup> and R<sup>D</sup> are each independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl.

**[0067]** The disclosure provides in another example a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, and a pharmaceutically acceptable carrier.

**[0068]** In accordance with an additional example, the disclosure provides a method for treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a MAT2A inhibitor that is a compound, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue as described herein.

**[0069]** The disclosure also provides in a further example a method for inhibiting the synthesis of S-adenosyl methionine (SAM) in a cell, comprising introducing into the cell an effective amount of a compound, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein.

**[0070]** The disclosure also provides in a further example a method for inhibiting the synthesis of S-adenosyl methionine (SAM) in a subject, comprising administering to the subject an effective amount of a compound, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein.

**[0071]** In another example, the disclosure provides a method for treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a compound or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein.

**[0072]** In accordance with still another example, the disclosure provides a method for treating a cancer in a subject suffering therefrom, wherein the cancer is characterized by a reduction or absence of methylthioadenosine phosphorylase (MTAP) gene expression, the

absence of the MTAP gene, or reduced function of MTAP protein, as compared to cancers where the MTAP gene or protein is present and/or fully functioning. The method comprises administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein.

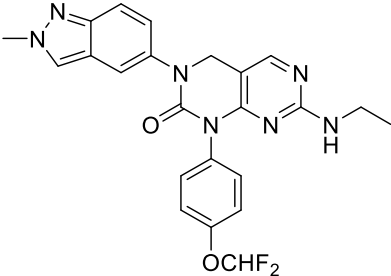
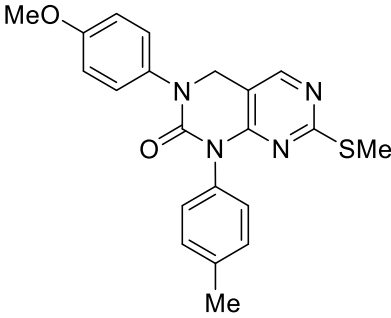
**[0073]** The disclosure provides in an example a compound as described herein, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, for inhibiting the synthesis of S-adenosyl methionine (SAM).

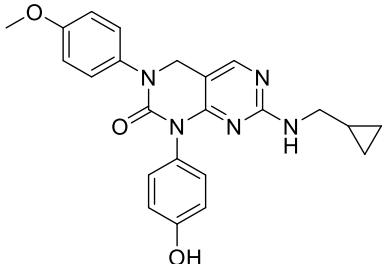
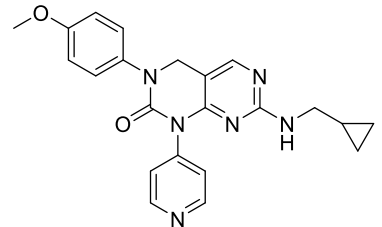
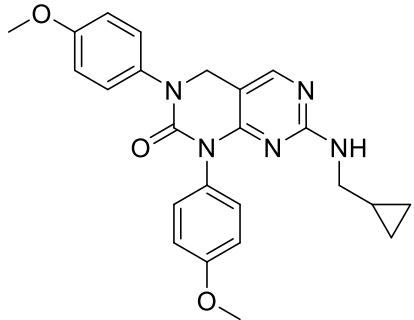
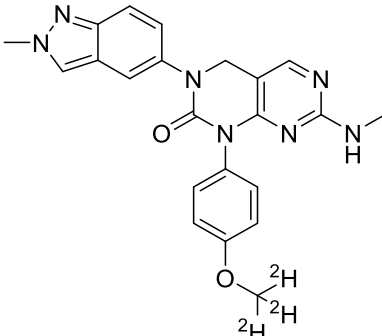
**[0074]** Another example is a compound as described herein, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, for treating a cancer in a subject suffering therefrom.

**[0075]** A further example is a compound as described herein, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, for use in treating a cancer in a subject suffering therefrom.

**[0076]** The disclosure also provides the use of a compound as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.

**[0076a]** In one aspect, the present disclosure refers to a compound that is:

|                   |                                                                                      |
|-------------------|--------------------------------------------------------------------------------------|
| <p><b>190</b></p> |  |
| <p><b>244</b></p> |  |

|     |                                                                                      |
|-----|--------------------------------------------------------------------------------------|
| 265 |    |
| 266 |    |
| 267 |   |
| 419 |  |

or a pharmaceutically acceptable salt thereof.

**[0076b]** In another aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

**[0076c]** In another aspect, the present disclosure refers to a use of compound, or a pharmaceutically acceptable salt thereof, as described herein in the preparation of a medicament for treating a cancer, wherein the cancer is characterized by a reduction or absence of methylthioadenosine phosphorylase (MTAP) gene expression, the absence of the

MTAP gene, or reduced function of MTAP protein, as compared to cancers where the MTAP gene or protein is present and/or fully functioning.

**[0076d]** In another aspect, the present disclosure refers to a compound as described herein or a pharmaceutically acceptable salt thereof, for use in therapy.

#### DETAILED DESCRIPTION

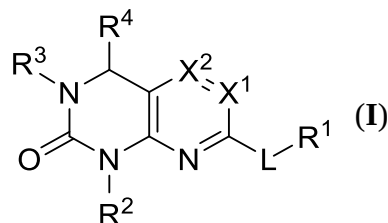
**[0077]** The compounds described herein are inhibitors of MAT2A. The present disclosure thus relates not only to such compounds in conformity with Formula I or II, but also to their pharmaceutical compositions, tautomers, and/or isotopologues. The compounds and compositions are useful in treating cancers. Some cancers include various MTAP-deleted cancers, i.e., those cancers characterized by the absence or deletion of the MTAP gene or reduced function of the MTAP protein.

#### Definitions

**[0078]** "Alkyl" refers to straight or branched chain hydrocarbyl including from 1 to about 20 carbon atoms. For instance, an alkyl can have from 1 to 10 carbon atoms or 1 to 6 carbon atoms. Exemplary alkyl includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and the like, and also includes branched chain isomers of straight chain alkyl groups, for example without limitation,  $-\text{CH}(\text{CH}_3)_2$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$ ,  $-\text{CH}(\text{CH}_2\text{CH}_3)_2$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $\text{C}(\text{CH}_2\text{CH}_3)_3$ , -

**WE CLAIM:**

1. A compound according to Formula I:



wherein

$X^1$  is N or  $CR^5$ ;

$X^2$  is N or  $CR^6$ , wherein  $X^1$  and  $X^2$  are not simultaneously N;

L is O, S, NR, or a bond;

R is H or  $C_1$ - $C_6$ -alkyl;

$R^1$  is selected from the group consisting of  $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl,  $C_3$ - $C_6$ -carbocyclyl,  $-(C_1$ - $C_6$ -alkyl)( $C_3$ - $C_6$ -carbocyclyl), and  $-(C_1$ - $C_6$ -alkyl)( $C_3$ - $C_6$ -cycloalkenyl) wherein

any alkyl in  $R^1$  is straight or branched,

$R^1$  is optionally substituted by 1 - 6 halo; and

when  $X^1$  is N,  $X^2$  is  $CR^6$ , L is NR or S, R is H, and  $R^1$  is  $C_1$ - $C_6$ -alkyl, then

$R^1$  is substituted by 1 - 6 halo;

or when L is NR, then R and  $R^1$  can be taken together in combination with L to form a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S) optionally substituted by one or more  $R^A$ ;

$R^2$  and  $R^3$  are independently selected from the group consisting of  $C_6$ - $C_{10}$ -aryl,  $C_3$ - $C_6$ -carbocyclyl, 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), and 3- to 14-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S),

wherein  $R^2$  and  $R^3$  are independently and optionally substituted by one or more substituents that are selected from the group consisting of  $R^A$ ,  $OR^A$ , halo,  $-N=N-R^A$ ,  $-NR^A R^B$ ,  $-(C_1$ - $C_6$ -alkyl) $NR^A R^B$ ,  $-C(O)OR^A$ ,  $-C(O)NR^A R^B$ ,  $-OC(O)R^A$ , and  $-CN$ ;

R<sup>4</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, halo, oxo, -CN, and -NR<sup>C</sup>R<sup>D</sup>;

R<sup>5</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, halo, -CN, and -NR<sup>C</sup>R<sup>D</sup>;

R<sup>6</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl (optionally substituted by one or more halo), -O(C<sub>1</sub>-C<sub>6</sub>-alkyl) (optionally substituted by one or more halo), -OH, halo, -CN, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, and -NR<sup>A</sup>R<sup>B</sup>;

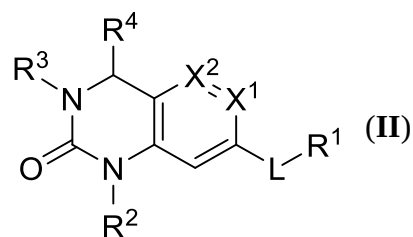
R<sup>A</sup> and R<sup>B</sup> are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, -NH<sub>2</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), -S(O)<sub>0-2</sub>-(C<sub>6</sub>-C<sub>10</sub>-aryl), -C(O)(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C(O)(C<sub>3</sub>-C<sub>14</sub>-carbocyclyl), -C<sub>3</sub>-C<sub>14</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>14</sub>-carbocyclyl), C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S);

wherein each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety of R<sup>A</sup> and R<sup>B</sup> is optionally substituted with one or more substituents selected from the group consisting of deuterium, hydroxy, halo, -NR'<sub>2</sub> (wherein each R' is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S)), -NHC(O)(OC<sub>1</sub>-C<sub>6</sub>-alkyl), -NO<sub>2</sub>, -CN, oxo, -C(O)OH, -C(O)O(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C<sub>1</sub>-C<sub>6</sub>-alkyl(C<sub>1</sub>-C<sub>6</sub>-alkoxy), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl-C(O)C<sub>1</sub>-C<sub>6</sub>-alkyl, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, -Si(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>3</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), C<sub>6</sub>-C<sub>10</sub>-aryl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>6</sub>-C<sub>10</sub>-aryl), 3- to 14-membered heterocycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C<sub>6</sub>-C<sub>14</sub>-aryl),

wherein each alkyl, alkenyl, aryl, and heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, halo, -NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NH<sub>2</sub>, -C(O)OH, CN, and oxo;

R<sup>C</sup> and R<sup>D</sup> are each independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl; or a pharmaceutically acceptable salt thereof.

2. A compound according to Formula II:



wherein

X<sup>1</sup> is N and X<sup>2</sup> is CR<sup>6</sup>, or X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>, X<sup>1</sup> and X<sup>2</sup> are both N, or X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>;

L is O, S, NR, or a bond;

R is H or C<sub>1</sub>-C<sub>6</sub>-alkyl;

R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>3</sub>-C<sub>6</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-carbocyclyl), and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkenyl) wherein

any alkyl in R<sup>1</sup> is straight or branched,

R<sup>1</sup> is optionally substituted by 1 - 6 halo;

or when L is NR, then R and R<sup>1</sup> can be taken together in combination with L to form a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S) optionally substituted by one or more R<sup>A</sup>;

R<sup>2</sup> and R<sup>3</sup> are independently selected from the group consisting of C<sub>6</sub>-C<sub>10</sub>-aryl, C<sub>3</sub>-C<sub>6</sub>-carbocyclyl, 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), and 3- to 14-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S),

wherein R<sup>2</sup> and R<sup>3</sup> are independently and optionally substituted by one or more substituents that are selected from the group consisting of R<sup>A</sup>,

OR<sup>A</sup>, halo, -N=N-R<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, -C(O)OR<sup>A</sup>, -C(O)NR<sup>A</sup>R<sup>B</sup>, -OC(O)R<sup>A</sup>, and -CN;

R<sup>4</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, halo, oxo, -CN, and -NR<sup>C</sup>R<sup>D</sup>;

R<sup>5</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, halo, -CN, and -NR<sup>C</sup>R<sup>D</sup>;

R<sup>6</sup> is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl (optionally substituted by one or more halo), -O(C<sub>1</sub>-C<sub>6</sub>-alkyl) (optionally substituted by one or more halo), -OH, halo, -CN, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, and -NR<sup>A</sup>R<sup>B</sup>;

R<sup>A</sup> and R<sup>B</sup> are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, -NH<sub>2</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), -S(O)<sub>0-2</sub>-(C<sub>6</sub>-C<sub>10</sub>-aryl), -C(O)(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C(O)(C<sub>3</sub>-C<sub>14</sub>-carbocyclyl), -C<sub>3</sub>-C<sub>14</sub>-carbocyclyl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>3</sub>-C<sub>14</sub>-carbocyclyl), C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S);

wherein each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety of R<sup>A</sup> and R<sup>B</sup> is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'<sub>2</sub> (wherein each R' is independently selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>6</sub>-C<sub>10</sub>-aryl, 3- to 14-membered heterocycloalkyl and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), -NHC(O)(OC<sub>1</sub>-C<sub>6</sub>-alkyl), -NO<sub>2</sub>, -CN, oxo, -C(O)OH, -C(O)O(C<sub>1</sub>-C<sub>6</sub>-alkyl), -C<sub>1</sub>-C<sub>6</sub>-alkyl(C<sub>1</sub>-C<sub>6</sub>-alkoxy), -C(O)NH<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub>-alkyl, -C(O)C<sub>1</sub>-C<sub>6</sub>-alkyl, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, -Si(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>3</sub>, -S(O)<sub>0-2</sub>-(C<sub>1</sub>-C<sub>6</sub>-alkyl), C<sub>6</sub>-C<sub>10</sub>-aryl, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)(C<sub>6</sub>-C<sub>10</sub>-aryl), 3- to 14-membered heterocycloalkyl, and -(C<sub>1</sub>-C<sub>6</sub>-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle

members are independently selected from N, O, and S), and -O(C<sub>6</sub>-C<sub>14</sub>-aryl),

wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R<sup>A</sup> and R<sup>B</sup> is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC<sub>1</sub>-C<sub>6</sub>-alkyl, halo, -NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NH<sub>2</sub>, -C(O)OH, CN, and oxo,

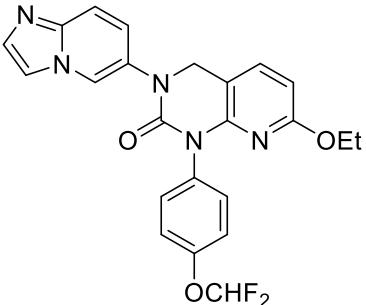
R<sup>C</sup> and R<sup>D</sup> are each independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl; or a pharmaceutically acceptable salt thereof.

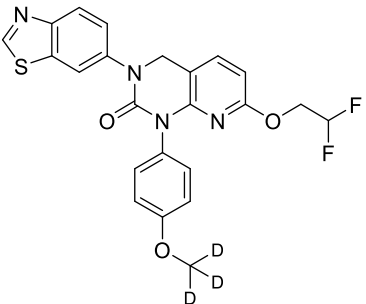
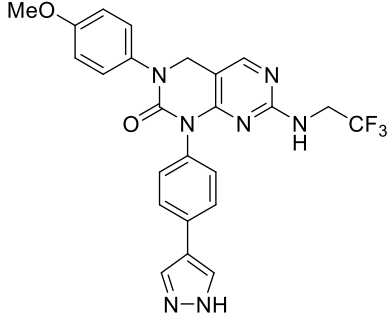
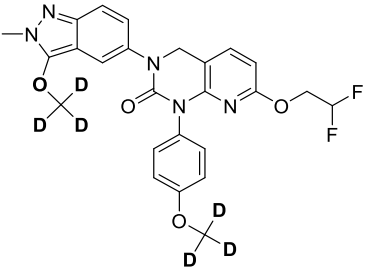
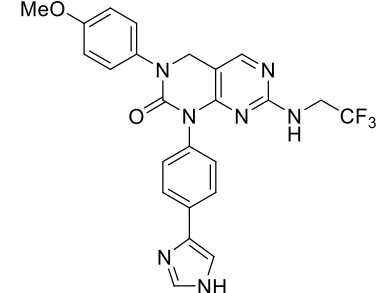
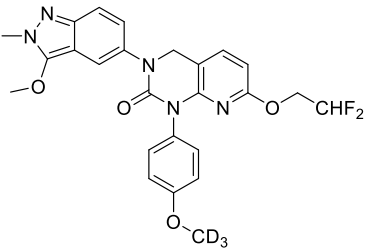
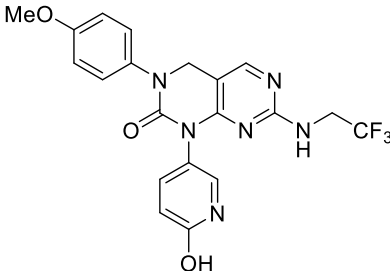
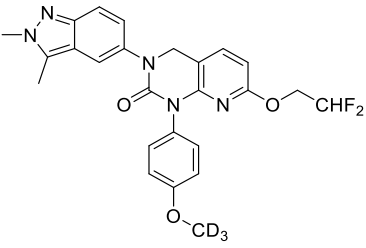
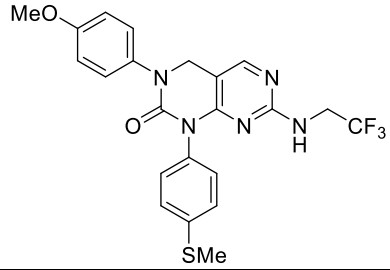
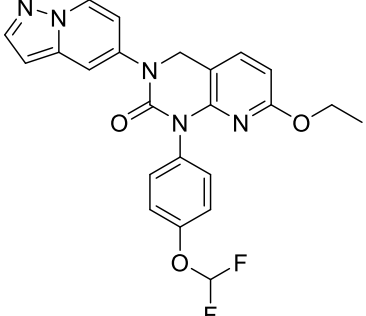
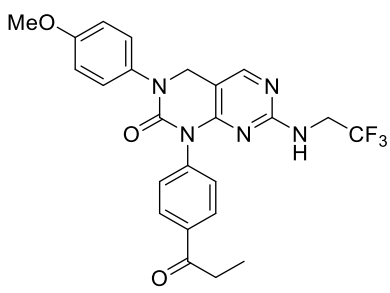
3. The compound according to claim 1, wherein:
  - (i) X<sup>1</sup> is N and X<sup>2</sup> is CR<sup>6</sup>; or
  - (ii) X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>; or
  - (iii) X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is N; or
  - (iv) X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>; or
  - (v) X<sup>1</sup> is N and X<sup>2</sup> is CR<sup>6</sup>; or
  - (vi) X<sup>1</sup> and X<sup>2</sup> are both N; or
  - (vii) X<sup>1</sup> is CR<sup>5</sup> and X<sup>2</sup> is CR<sup>6</sup>.
4. The compound according to any one of claims 1 to 3, wherein each of R<sup>4</sup> and R<sup>5</sup> (when present) is independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl, and R<sup>6</sup> (when present) is selected from the group consisting of H, C<sub>1</sub>-C<sub>6</sub>-alkyl optionally substituted by one or more halo, C<sub>1</sub>-C<sub>6</sub>-alkoxy, -(C<sub>1</sub>-C<sub>6</sub>-alkyl)NR<sup>A</sup>R<sup>B</sup>, and -NR<sup>A</sup>R<sup>B</sup> (wherein R<sup>A</sup> and R<sup>B</sup> are independently selected from H and C<sub>1</sub>-C<sub>6</sub>-alkyl).
5. The compound according to any one of claims 1 to 3, wherein at least one of R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> (when present) is H.
6. The compound according to any one of claims 1 to 5, wherein one or all of R<sup>4</sup>, R<sup>5</sup>, or R<sup>6</sup> is H.
7. The compound according to any one of claims 1 to 6, wherein R<sup>2</sup> is optionally substituted C<sub>6</sub>-C<sub>10</sub>-aryl or optionally substituted 5- to 10-membered heteroaryl.

8. The compound according to claim 7, wherein  $R^2$  is optionally substituted  $C_6$ - $C_{10}$ -aryl such as optionally substituted phenyl.
9. The compound according to claim 7, wherein  $R^2$  is optionally substituted 5- to 10-membered heteroaryl, and wherein 1 ring member is N such as optionally substituted pyridyl.
10. The compound according to any one of claims 1 to 9, wherein  $R^3$  is optionally substituted 3- to 14-membered heterocycloalkyl or optionally substituted 5- to 10-membered heteroaryl such as benzothiazolyl, benzoisothiazolyl, benzoxazolyl, pyridinyl, pyridinonyl, pyridazinyl, benzimidazolyl, benzotriazolyl, indazolyl, quinoxalinyl, quinoliny, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, triazolopyridinyl, cinnoliny, isoxazolyl, pyrazolyl, benzofuranyl, dihydrobenzofuranyl, dihydrobenzodioxinyl, and tetrahydrobenzodioxinyl, any of which may be optionally substituted.
11. The compound according to any one of claims 1 to 10, wherein  $R^3$  is optionally substituted  $C_6$ - $C_{10}$ -aryl such as optionally substituted phenyl.
12. The compound according to any one of claims 1 to 6, wherein  $R^2$  is optionally substituted phenyl and  $R^3$  is optionally substituted 3- to 14-membered heterocycloalkyl or optionally substituted 5- to 10-membered heteroaryl.
13. The compound according to any one of claims 1 to 12, wherein L is O or NR.
14. The compound according to claim 13, wherein  $R^1$  is optionally substituted  $C_1$ - $C_6$ -alkyl or optionally substituted  $C_3$ - $C_6$ -carbocyclyl, wherein when  $R^1$  is  $C_1$ - $C_3$ -alkyl, it is optionally substituted by 1 – 3 F.
15. The compound according to any one of claims 1 to 3, wherein  
L is O or NR and R is H;  
 $R^1$  is  $C_1$ - $C_3$ -alkyl that is optionally substituted by 1 – 3 F;  
 $R^2$  is optionally substituted 3- to 14-membered heterocycloalkyl or optionally substituted 5- to 10-membered heteroaryl (wherein 1 heterocycloalkyl or heteroaryl member is N) or optionally substituted  $C_6$ - $C_{10}$ -aryl;

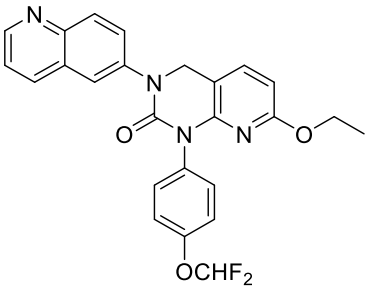
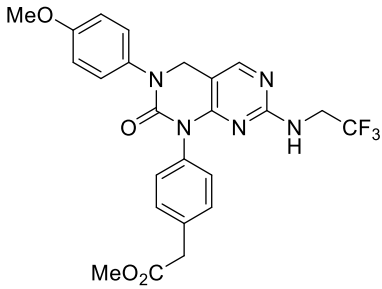
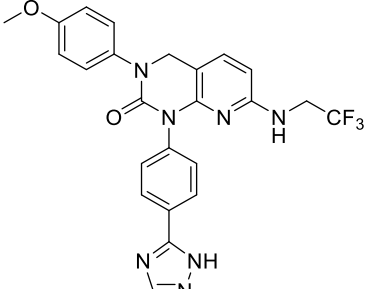
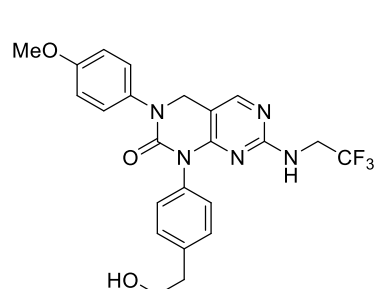
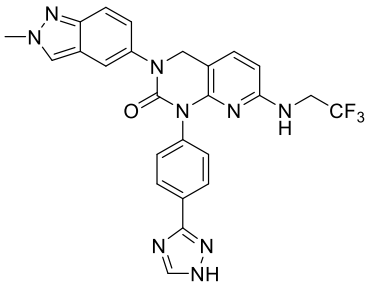
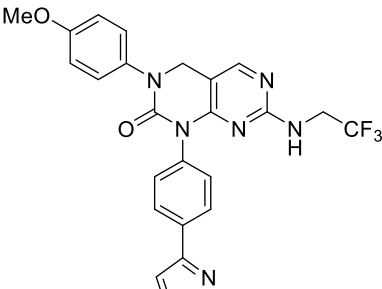
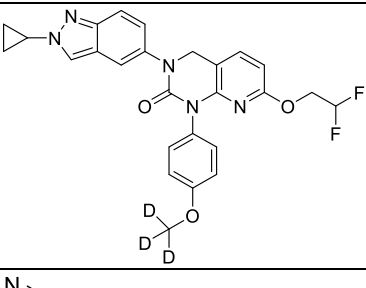
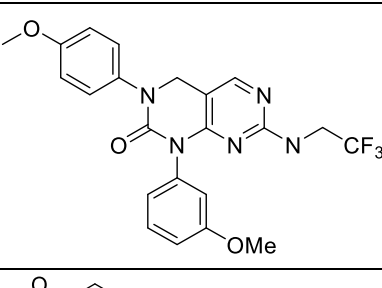
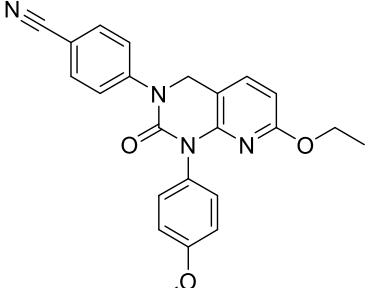
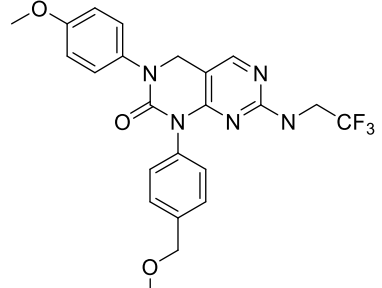
R<sup>3</sup> is optionally substituted 3- to 14-membered heterocycloalkyl, optionally substituted 5- to 10-membered heteroaryl wherein 1 to 3 heterocycloalkyl or heteroaryl members are independently selected from N, O, and S, or optionally substituted C<sub>6</sub>-C<sub>10</sub>-aryl; and  
each of R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> (when present) is H.

16. The compound according to claim 15, wherein L is NR.
17. The compound according to claim 15 or 16, wherein
  - (i) R<sup>2</sup> is optionally substituted phenyl; and R<sup>3</sup> is an optionally substituted 5- to 10-membered heteroaryl wherein 1 to 3 heteroaryl members are independently selected from N, O, and S; or
  - (ii) R<sup>2</sup> is an optionally substituted 5- to 10-membered heteroaryl wherein 1 to 3 heteroaryl members are independently selected from N, O, and S; and R<sup>3</sup> is optionally substituted phenyl.
18. The compound according to claim 17, wherein R<sup>3</sup> is selected from the group consisting of optionally substituted benzothiazolyl, benzoisothiazolyl, benzoxazolyl, pyridinyl, pyridinonyl, pyridazinyl, benzimidazolyl, benzotriazolyl, indazolyl, quinoxalinyl, quinolinyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, triazolopyridinyl, cinnolinyl, isoxazolyl, pyrazolyl, benzofuranyl, dihydrobenzofuranyl, dihydrobenzodioxinyl, and tetrahydrobenzodioxinyl, any of which may be optionally substituted.
19. The compound according to claim 15 or 16, wherein R<sup>2</sup> and R<sup>3</sup> independently are optionally substituted phenyl.
20. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:

|            |                                                                                     |  |  |
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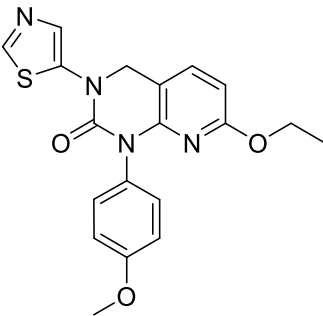
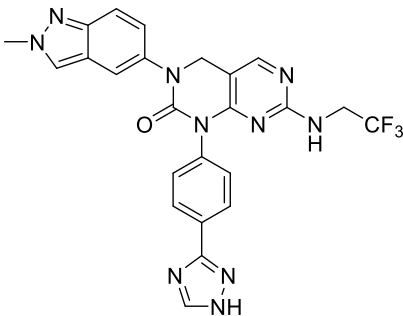
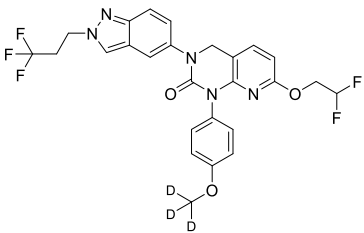
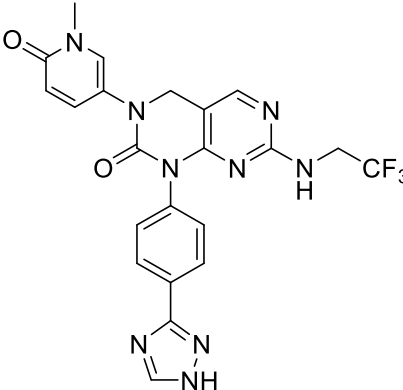
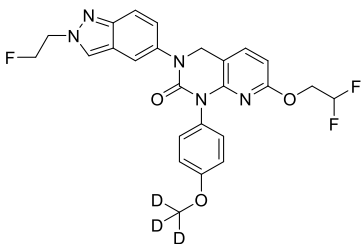
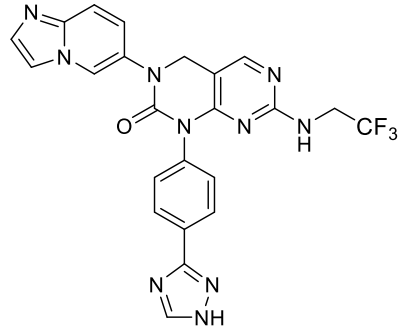
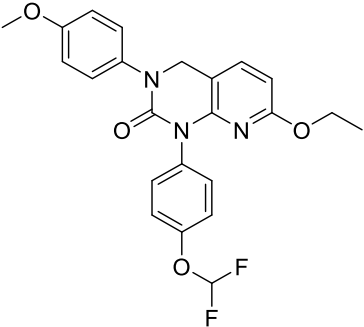
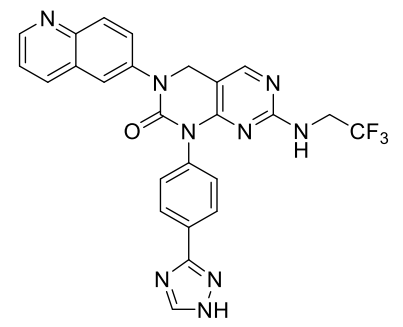
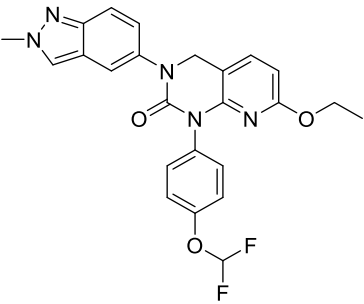
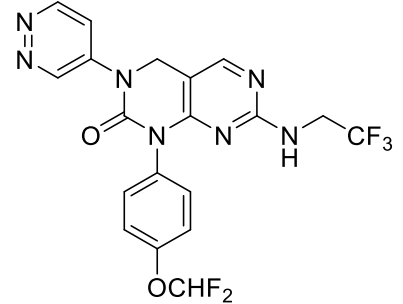
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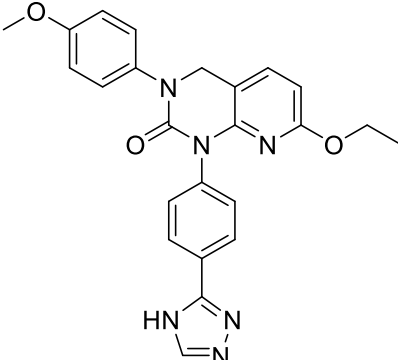
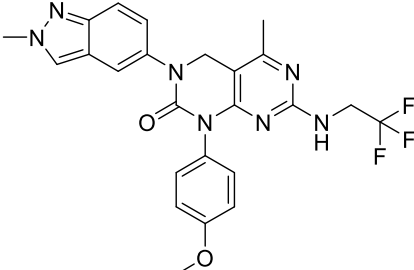
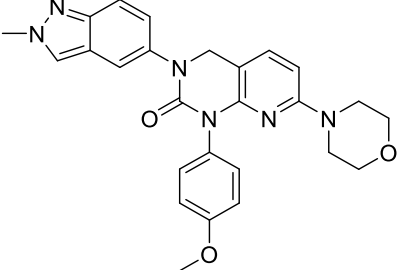
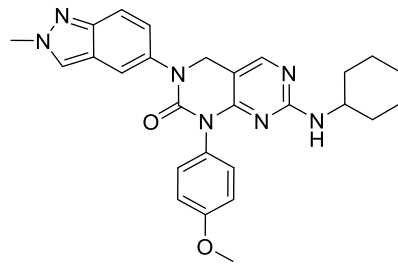
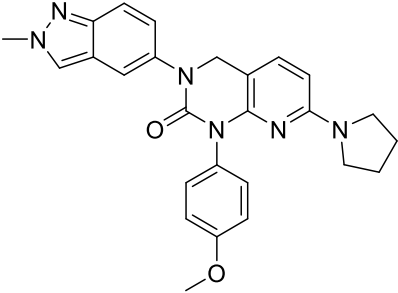
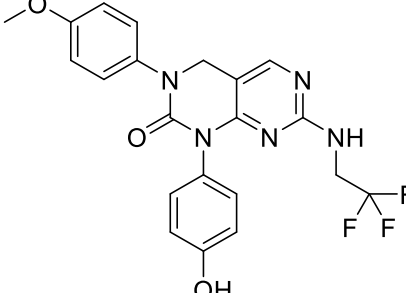
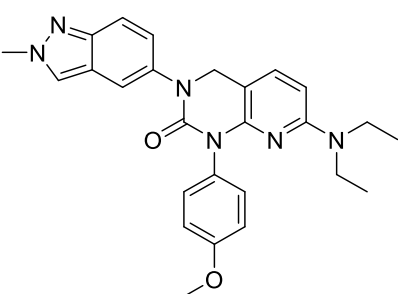
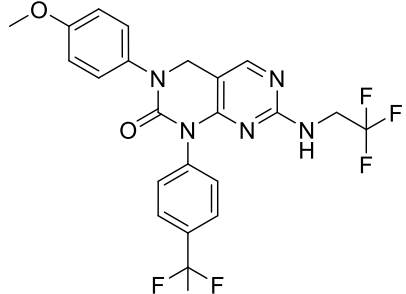
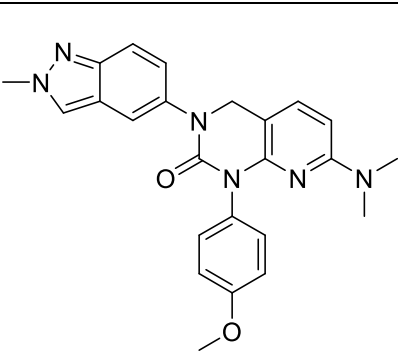
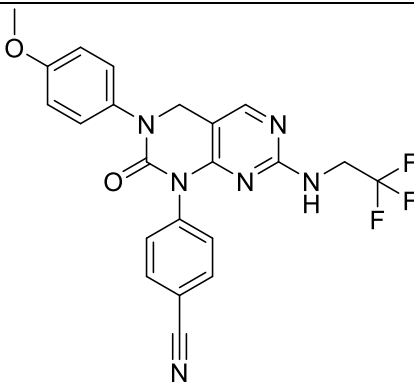
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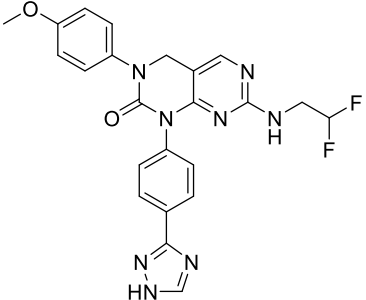
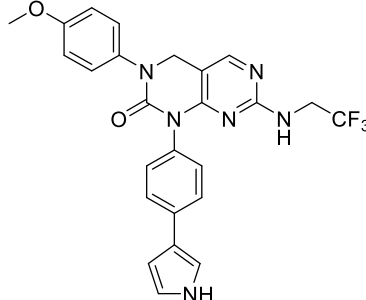
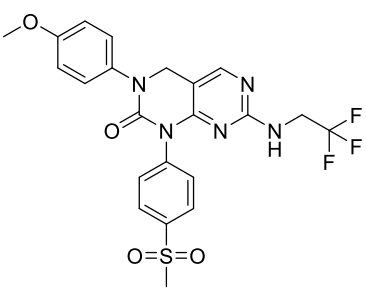
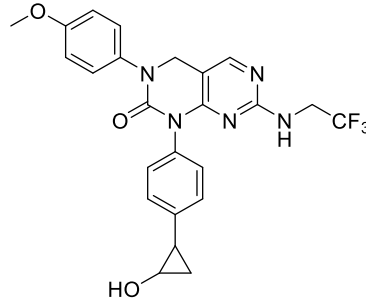
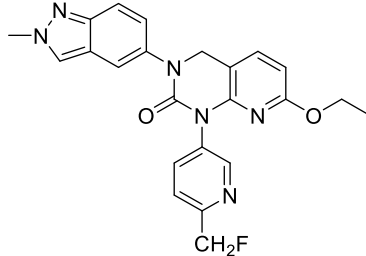
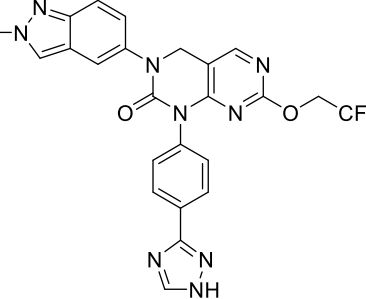
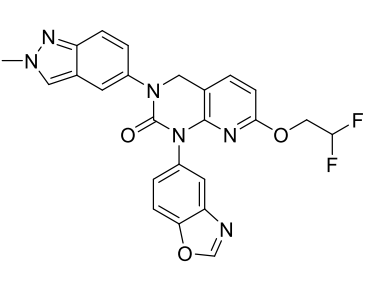
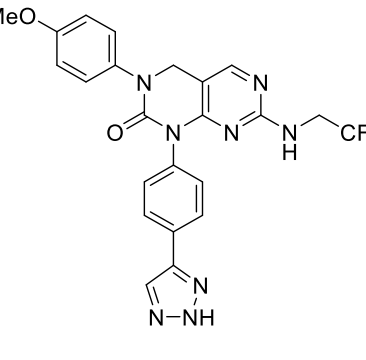
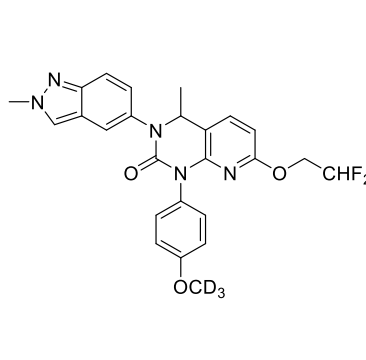
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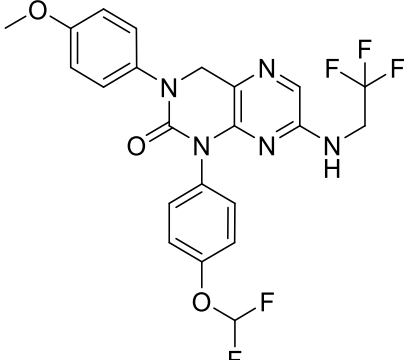
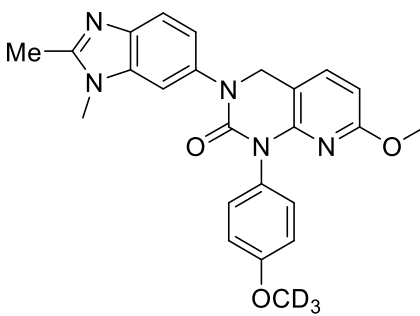
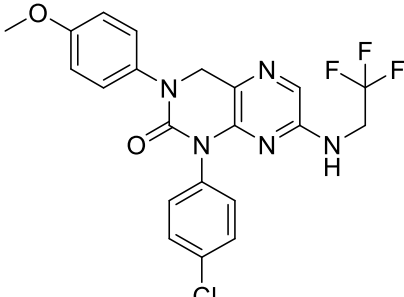
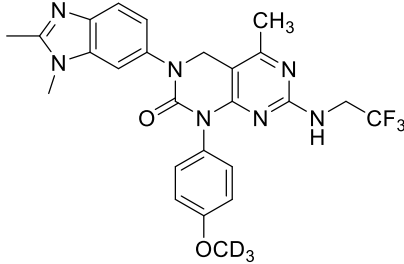
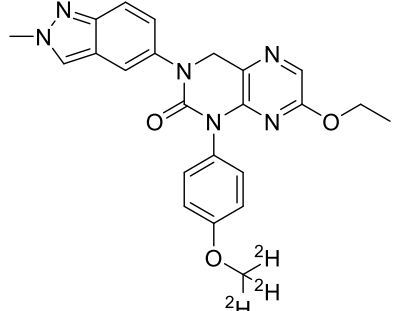
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| 188 |    | 280 |             |
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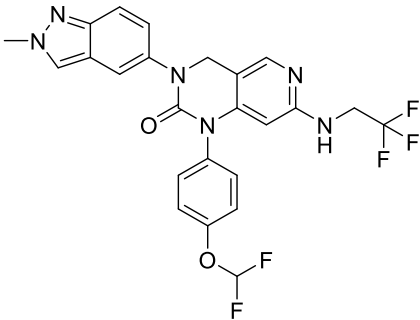
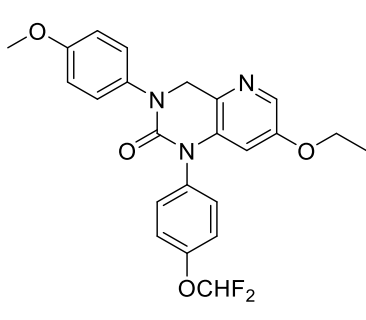
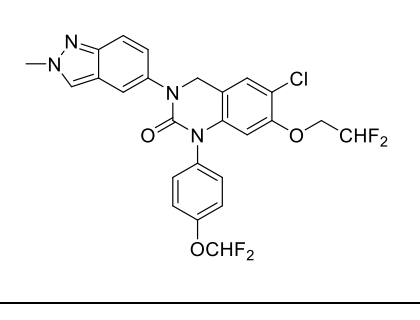
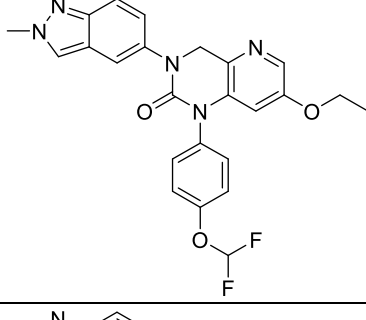
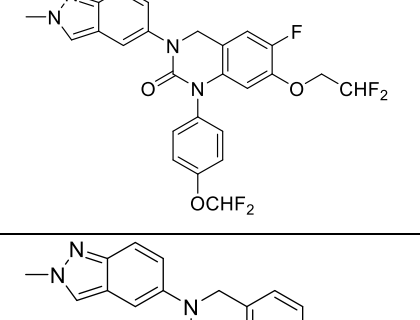
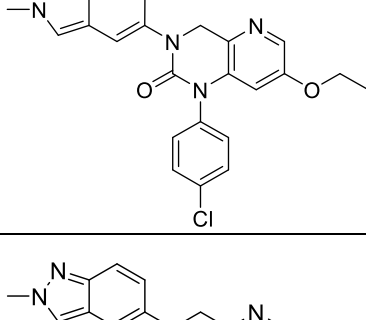
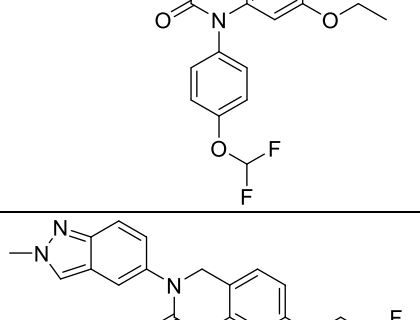
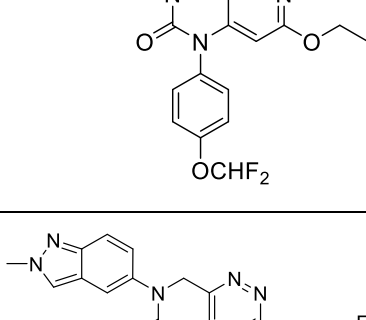
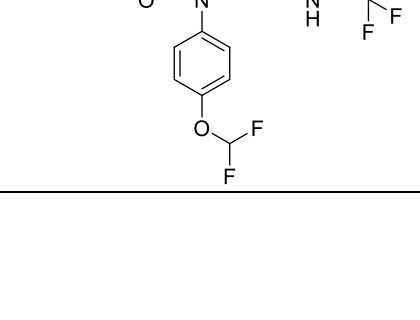
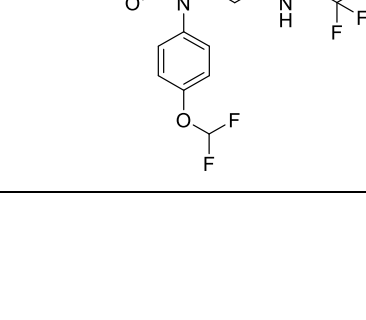
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| 403 |  | 421 |  |

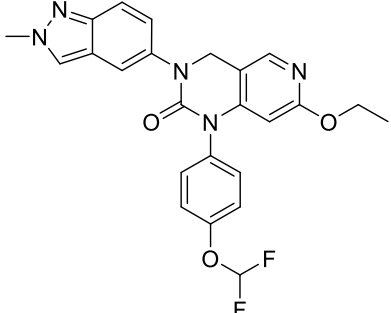
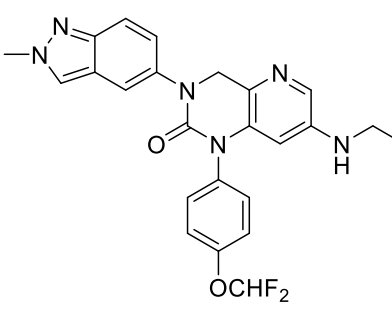
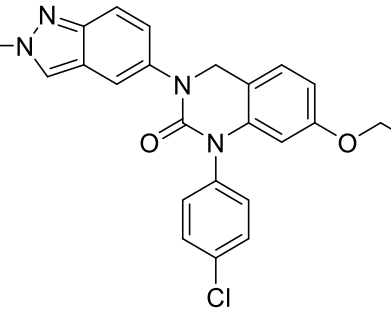
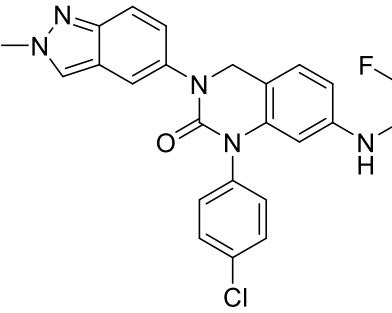
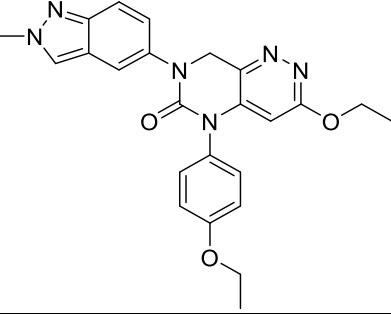
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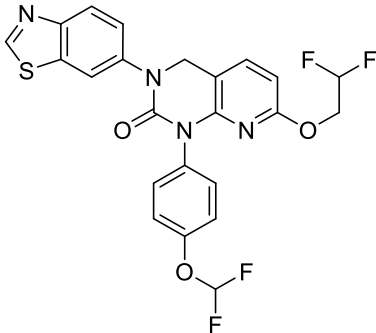
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| 415 |   | 434 |  |
| 416 |   | 435 |  |
| 417 |  |     |                                                                                    |

21. The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:

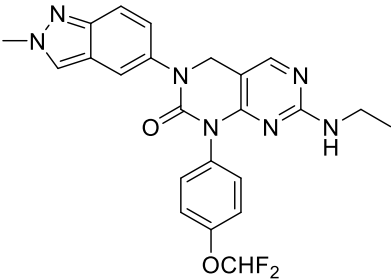
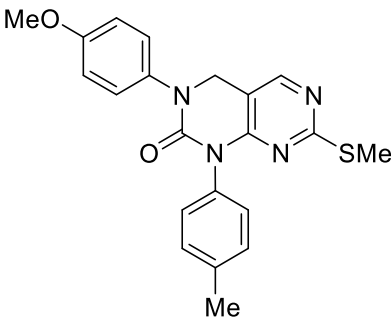
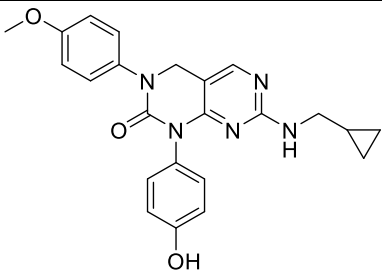
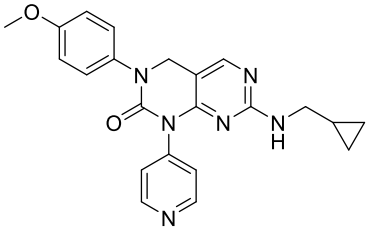
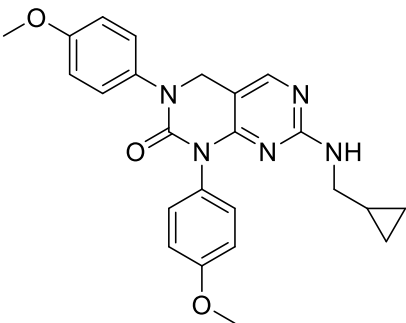
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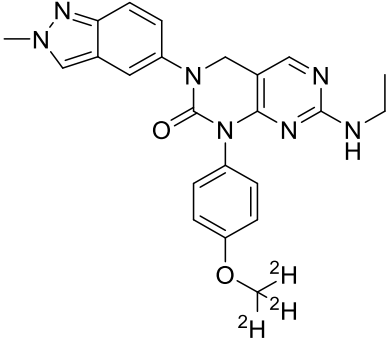
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| 187 |   | 428 |  |
| 436 |   | 437 |  |
| 438 |  |     |                                                                                    |

22. The compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:

| Example | Structure                                                                           | Example | Structure |
|---------|-------------------------------------------------------------------------------------|---------|-----------|
| 408     |  |         |           |

23. A compound that is:

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| 190 |    |
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| 419 |  |
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or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
25. Use of compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 23 in the preparation of a medicament for treating a cancer, wherein the cancer is characterized by a reduction or absence of methylthioadenosine phosphorylase (MTAP) gene expression, the absence of the MTAP gene, or reduced function of MTAP protein, as compared to cancers where the MTAP gene or protein is present and/or fully functioning.
26. A compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, for use in therapy.
27. Use of a compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.
28. The use according to claim 27, or a pharmaceutically acceptable salt thereof, wherein the cancer is an MTAP-deleted cancer.
29. The use according to claim 27 or 28, or a pharmaceutically acceptable salt thereof, wherein the cancer is selected from the group consisting of mesothelioma, neuroblastoma, rectum carcinoma, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma,

hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, renal carcinoma, kidney parenchyma carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, bladder carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors, lymphoma, head and neck cancer, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, chorioidea melanoma, seminoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma, or such as B-cell acute lymphocytic leukemia (B-ALL), mesothelioma, lymphoma, pancreatic carcinoma, lung cancer, gastric cancer, esophageal cancer, bladder carcinoma, brain cancer, head and neck cancer, melanoma, and breast cancer.

30. The use according to claim 29, or a pharmaceutically acceptable salt thereof, wherein the cancer is:
  - (i) a lung cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, adenocarcinoma of the lung, and squamous cell carcinoma of the lung; or
  - (ii) triple negative breast cancer (TNBC); or
  - (iii) a brain tumor selected from the group consisting of glioma, glioblastoma, astrocytoma, meningioma, medulloblastoma, peripheral neuroectodermal tumors, and craniopharyngioma; or
  - (iv) a lymphoma selected from the group consisting of mantle cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and adult T-cell leukemia/lymphoma.