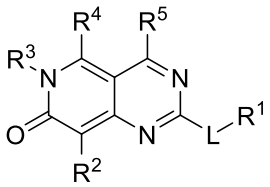
-(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 ring members are independently selected from N, O, and S), -NHC(O)(OC_1-C_6-alkyl), -NO_2, -CN, oxo, -C(O)OH, -C(O)O(C_1-C_6-alkyl), -C_1-C_6-alkyl(C_1-C_6-alkoxy), -C(O)NH_2, C_1-C_6-alkyl, -C(O)C_1-C_6-alkyl, -OC_1-C_6-alkyl, -Si(C_1-C_6-alkyl)$_3$, -S(O)$_{0\text{-}2}$-(C_1-C_6-alkyl), C_6-C_{10}-aryl, -(C_1-C_6-alkyl)(C_6-C_{10}-aryl), 3- to 14-membered heterocycloalkyl, and -(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and -O(C_6-C_{14}-aryl), wherein each alkyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC_1-C_6-alkyl, halo, -NH_2, -(C_1-C_6-alkyl)NH_2, -C(O)OH, CN, and oxo.

[0018a] In one aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof according to claim 2, wherein the compound has a structure according to Formula (IA):

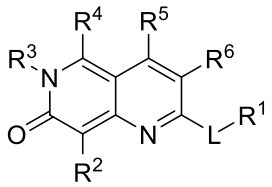


(IA)

wherein 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, and R^1 is optionally substituted by 1 – 6 halo; or when L is NR, then R and R^1 in combination with L represent 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, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A,

and -CN; R^4 and R^5 are independently selected from the group consisting of R^A, OR^A, halo, NR^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, and -OC(O)R^A; R^A and R^B are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, NH_2, -$S(O)_{0-2}$-(C_1-C_6-alkyl), -$S(O)_{0-2}$-(C_6-C_{10}-aryl), -C(O)(C_1-C_6-alkyl), -C(O)(C_3-C_{14}-carbocyclyl), -C_3-C_{14}-carbocyclyl, -(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl), C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'_2 (wherein each R' is independently selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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_1-C_6-alkyl), -NO_2, -CN, oxo, -C(O)OH, -C(O)O(C_1-C_6-alkyl), -C_1-C_6-alkyl(C_1-C_6-alkoxy), -C(O)NH_2, C_1-C_6-alkyl, -C(O)C_1-C_6-alkyl, -OC_1-C_6-alkyl, -Si(C_1-C_6-alkyl)$_3$, -$S(O)_{0-2}$-(C_1-C_6-alkyl), C_6-C_{10}-aryl, -(C_1-C_6-alkyl)(C_6-C_{10}-aryl), 3- to 14-membered heterocycloalkyl, and -(C_1-C_6-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C_6-C_{14}-aryl); wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC_1-C_6-alkyl, halo, -NH_2, -(C_1-C_6-alkyl)NH_2, -C(O)OH, CN, and oxo.

[0018b] In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof, wherein the compound has a structure according to Formula (IB):

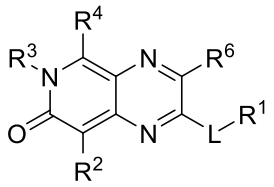


(**IB**)

wherein 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, and R^1 is optionally substituted by 1 – 6 halo; or when L is NR, then R and R^1 in combination with L represent 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, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A, and -CN; R^4, R^5, and R^6 are independently selected from the group consisting of R^A, OR^A, halo, NR^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, and -OC(O)R^A; R^A and R^B are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, NH_2, -$S(O)_{0\text{-}2}$-(C_1-C_6-alkyl), -$S(O)_{0\text{-}2}$-(C_6-C_{10}-aryl), -C(O)(C_1-C_6-alkyl), -C(O)(C_3-C_{14}-carbocyclyl), -C_3-C_{14}-carbocyclyl, -(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl), C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'_2 (wherein each R' is independently selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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_1-C_6-alkyl), -NO_2, -CN, oxo, -C(O)OH, -C(O)O(C_1-C_6-alkyl), -C_1-C_6-alkyl(C_1-C_6-alkoxy), -C(O)NH_2, C_1-C_6-alkyl, -C(O)C_1-C_6-alkyl, -OC_1-C_6-alkyl, -Si(C_1-C_6-alkyl)$_3$, -S(O)$_{0\text{-}2}$-(C_1-C_6-alkyl), C_6-C_{10}-aryl, -(C_1-C_6-alkyl)(C_6-C_{10}-aryl), 3- to 14-membered heterocycloalkyl, and -(C_1-C_6-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C_6-C_{14}-aryl), wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC_1-C_6-alkyl, halo, -NH_2, -(C_1-C_6-alkyl)NH_2, -C(O)OH, CN, and oxo.

[0019] The present disclosure also provides, in accordance with additional embodiments, compounds according to Formula II or pharmaceutically acceptable salts thereof:



(**II**)

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[0020] In Formula II, L is O, S, NR, or a bond; and R is H or C_1-C_6-alkyl.

[0021] 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, and R^1 is optionally substituted by 1 – 6 halo.

[0022] Alternatively, in some embodiments when L is NR, then R and R^1 in combination with L represent 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.

[0023] R^2 and R^3 are independently selected from the group consisting of C_6-C_{10}-aryl, 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

[0027] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0028] In yet another embodiment, the present disclosure provides a method for inhibiting the synthesis of SAM in a cell, comprising contacting the cell with an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[0028a] In another aspect, there is provided an *in vitro* 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 thereof as described herein.

[0029] In yet another embodiment, the present disclosure provides a method for inhibiting the synthesis of SAM in a subject, comprising administering to the subject an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[0030] Yet another embodiment is a method of treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof. In some embodiments, the cancer is an MTAP-deleted cancer.

[0030a] In a further aspect, there is provided a use of a compound as described herein in the manufacture of a medicament for treating a cancer in a subject suffering therefrom, wherein an effective amount of the compound is to be administered to the subject.

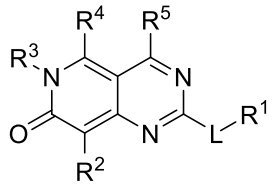
[0031] Also provided in an embodiment is a method for treating a cancer in a subject suffering therefrom, wherein the cancer is characterized by a reduction or absence of MTAP gene expression, or reduced or absent function of MTAP protein, as compared to cancers where the MTAP gene or protein is present and/or fully functioning, or as compared to cancers with wild type MTAP gene, comprising administering to the subject a therapeutically effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[0031a] In another aspect, there is provided a use of a compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament 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, wherein a therapeutically effective amount of a compound is to be administed to the subject.

[0032] In another embodiment, optionally in combination with any other embodiment described herein, the present disclosure provides a compound of Formula I or Formula II I or a pharmaceutically acceptable salt thereof, for use in inhibiting the synthesis of SAM in a cell. Alternatively, in accordance with some embodiments, optionally in combination with any other embodiment described herein, the compound is useful for inhibiting the synthesis of SAM in a subject. Another embodiment, optionally in combination with any other embodiment described herein, provides the use of a compound of Formula I or

WE CLAIM:

1. A compound or pharmaceutically acceptable salt thereof, wherein the compound has a structure according to Formula (IA):



(IA)

wherein

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, and

R^1 is optionally substituted by 1 – 6 halo;

or when L is NR, then R and R^1 in combination with L represent 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, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A, and -CN;

R^4 and R^5 are independently selected from the group consisting of R^A, OR^A, halo, NR^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, and -OC(O)R^A;

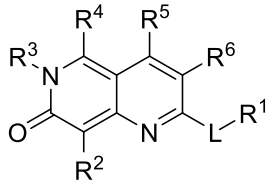
R^A and R^B are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, NH_2, -$S(O)_{0-2}$-(C_1-C_6-alkyl), -$S(O)_{0-2}$-(C_6-C_{10}-aryl), -C(O)(C_1-C_6-alkyl), -

C(O)(C_3-C_{14}-carbocyclyl), -C_3-C_{14}-carbocyclyl, -(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl), C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'$_2$ (wherein each R' is independently selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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_1-C_6-alkyl), -NO_2, -CN, oxo, -C(O)OH, -C(O)O(C_1-C_6-alkyl), -C_1-C_6-alkyl(C_1-C_6-alkoxy), -C(O)NH_2, C_1-C_6-alkyl, -C(O)C_1-C_6-alkyl, -OC_1-C_6-alkyl, -Si(C_1-C_6-alkyl)$_3$, -S(O)$_{0\text{-}2}$-(C_1-C_6-alkyl), C_6-C_{10}-aryl, -(C_1-C_6-alkyl)(C_6-C_{10}-aryl), 3- to 14-membered heterocycloalkyl, and -(C_1-C_6-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C_6-C_{14}-aryl),

wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC_1-C_6-alkyl, halo, -NH_2, -(C_1-C_6-alkyl)NH_2, -C(O)OH, CN, and oxo.

2. A compound or pharmaceutically acceptable salt thereof, wherein the compound has a structure according to Formula (IB):



(**IB**)

wherein

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, and

R^1 is optionally substituted by 1 – 6 halo;

or when L is NR, then R and R^1 in combination with L represent 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, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A, and -CN;

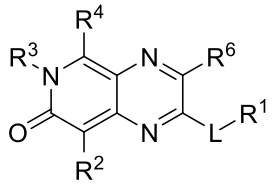
R^4, R^5, and R^6 are independently selected from the group consisting of R^A, OR^A, halo, NR^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, and -OC(O)R^A;

R^A and R^B are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, NH_2, -$S(O)_{0-2}$-(C_1-C_6-alkyl), -$S(O)_{0-2}$-(C_6-C_{10}-aryl), -C(O)(C_1-C_6-alkyl), -C(O)(C_3-C_{14}-carbocyclyl), -C_3-C_{14}-carbocyclyl, -(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl), C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'$_2$ (wherein each R' is independently selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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_1-C_6-alkyl), -NO_2, -CN, oxo, -C(O)OH, -C(O)O(C_1-C_6-alkyl), -C_1-C_6-alkyl(C_1-C_6-alkoxy), -C(O)NH_2, C_1-C_6-alkyl, -C(O)C_1-C_6-alkyl, -OC_1-C_6-alkyl, -Si(C_1-C_6-alkyl)$_3$, -S(O)$_{0-2}$-(C_1-C_6-alkyl), C_6-C_{10}-aryl, -(C_1-C_6-alkyl)(C_6-C_{10}-aryl), 3- to 14-membered heterocycloalkyl, and -(C_1-C_6-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C_6-C_{14}-aryl),

wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC_1-C_6-alkyl, halo, -NH_2, -(C_1-C_6-alkyl)NH_2, -C(O)OH, CN, and oxo.

3. A compound or pharmaceutically acceptable salt thereof according to Formula II:



(**II**)

,

wherein

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, and

R^1 is optionally substituted by 1 – 6 halo;

or when L is NR, then R and R^1 in combination with L represent 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, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A, and -CN;

R^4 and R^6 are independently selected from the group consisting of R^A, OR^A, halo, NR^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, and -OC(O)R^A;

R^A and R^B are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, NH_2, -$S(O)_{0-2}$-(C_1-C_6-alkyl), -$S(O)_{0-2}$-(C_6-C_{10}-aryl), -C(O)(C_1-C_6-alkyl), -C(O)(C_3-C_{14}-carbocyclyl), -C_3-C_{14}-carbocyclyl, -(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl), C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'$_2$ (wherein each R' is independently selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_6-C_{10}-aryl, 3- to 14-membered heterocycloalkyl and -(C_1-C_6-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_1-C_6-alkyl), -NO_2, -CN, oxo, -C(O)OH, -C(O)O(C_1-C_6-alkyl), -C_1-C_6-alkyl(C_1-C_6-alkoxy), -C(O)NH_2, C_1-C_6-alkyl, -C(O)C_1-C_6-alkyl, -OC_1-C_6-alkyl, -Si(C_1-C_6-alkyl)$_3$, -S(O)$_{0\text{-}2}$-(C_1-C_6-alkyl), C_6-C_{10}-aryl, -(C_1-C_6-alkyl)(C_6-C_{10}-aryl), 3- to 14-membered heterocycloalkyl, and -(C_1-C_6-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C_6-C_{14}-aryl),

wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC_1-C_6-alkyl, halo, -NH_2, -(C_1-C_6-alkyl)NH_2, -C(O)OH, CN, and oxo,

or a pharmaceutically acceptable salt thereof.

4. The compound or pharmaceutically acceptable salt thereof according to any one of claims **Error! Reference source not found.** – 3, wherein each of R^4, R^5, and R^6 (if present) is independently selected from the group consisting of H, C_1-C_6-alkyl, and C_1-C_6-alkoxy.
5. The compound or pharmaceutically acceptable salt thereof according to any one of claims **Error! Reference source not found.** to 4, wherein at least one of R^4, R^5, and R^6 (if present) is H.
6. The compound or pharmaceutically acceptable salt thereof according to any one of claims **Error! Reference source not found.** to 5, wherein each of R^4, R^5, and R^6 (if present) is H.
7. The compound according to any one of claims **Error! Reference source not found.** to 5, wherein R^2 is C_6-C_{10}-aryl or 5- to 10-membered heteroaryl.
8. The compound or pharmaceutically acceptable salt thereof according to claim 7, wherein R^2 is C_6-C_{10}-aryl.
9. The compound or pharmaceutically acceptable salt thereof according to claim 8, wherein R^2 is phenyl.

10. The compound or pharmaceutically acceptable salt thereof according to claim 7, wherein R^2 is 5- to 10-membered heteroaryl, and wherein 1 ring member is N.
11. The compound or pharmaceutically acceptable salt thereof according to claim 10, wherein R^2 is pyridyl.
12. The compound or pharmaceutically acceptable salt thereof according to any one of claims **Error! Reference source not found.** to 11, wherein R^3 is 3- to 14-membered heterocycloalkyl or 5- to 10-membered heteroaryl.
13. The compound or pharmaceutically acceptable salt thereof according to claim 12, wherein R^3 is selected from the group consisting of benzothiazolyl, benzoisothiazolyl, benzoxazolyl, pyridinyl, pyridinonyl, benzimidazolyl, benzotriazolyl, indazolyl, quinoxalinyl, quinolinyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, cinnolinyl, isoxazolyl, pyrazolyl, benzofuranyl, dihydrobenzofuranyl, and tetrahydrobenzodioxinyl.
14. The compound or pharmaceutically acceptable salt thereof according to any one of claims **Error! Reference source not found.** to 11, wherein R^3 is C_6-C_{10}-aryl.
15. The compound or pharmaceutically acceptable salt thereof according to any one of claims **Error! Reference source not found.** to 14, wherein L is O or NR.
16. The compound or pharmaceutically acceptable salt thereof according to claim 15, wherein R^1 is C_1-C_6-alkyl or C_3-C_6-carbocyclyl.
17. The compound or pharmaceutically acceptable salt thereof according to claim 15 or 16, wherein R^1 is C_1-C_3-alkyl that is optionally substituted by 1 – 3 F.
18. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1 – 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;

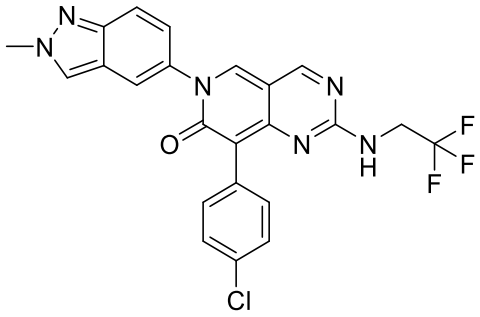
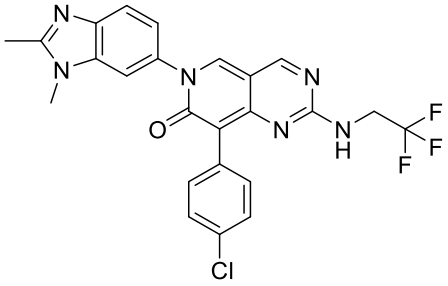
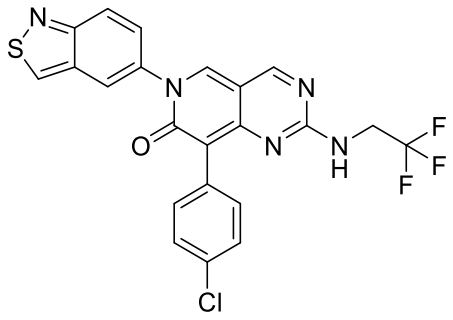
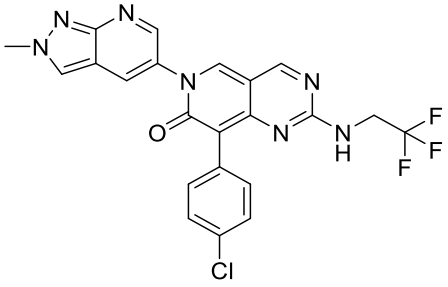
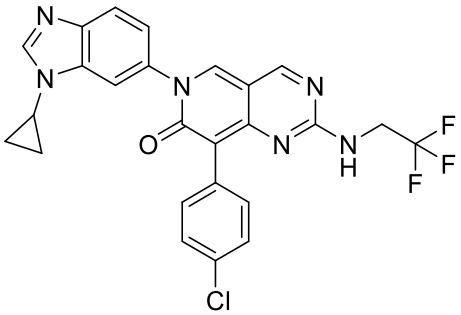
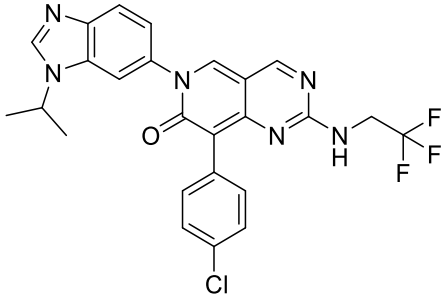
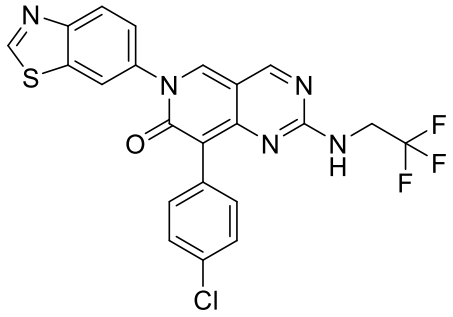
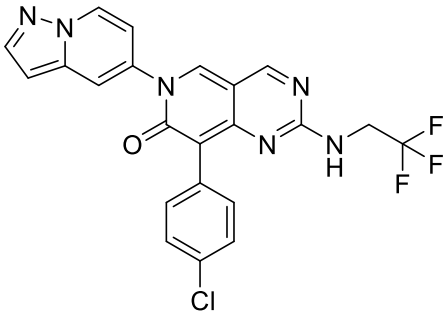
    R^2 is 3- to 14-membered heterocycloalkyl or 5- to 10-membered heteroaryl (wherein 1 heterocycloalkyl or heteroaryl member is N) or C_6-C_{10}-aryl;

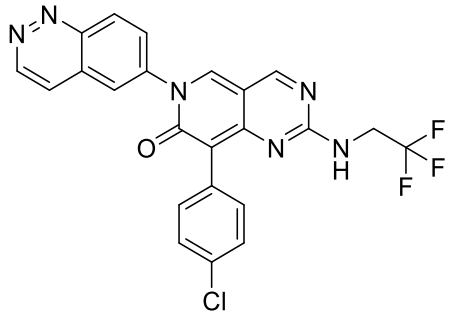
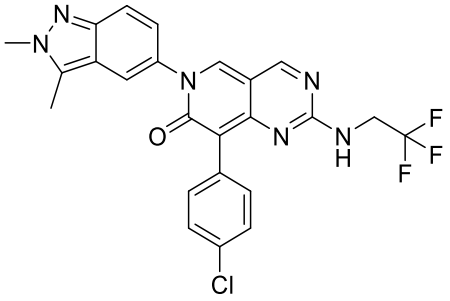
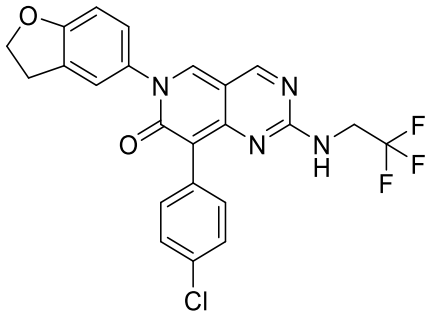
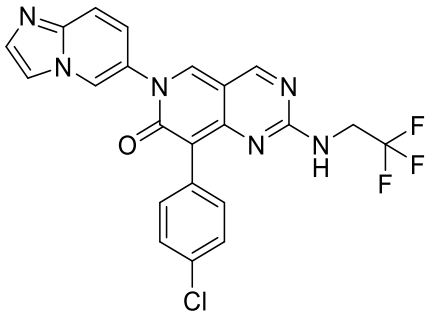
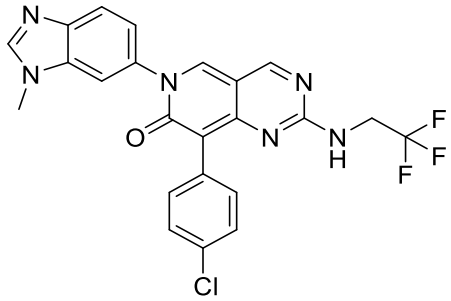
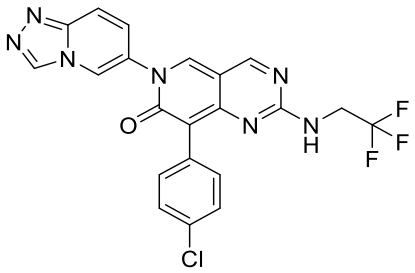
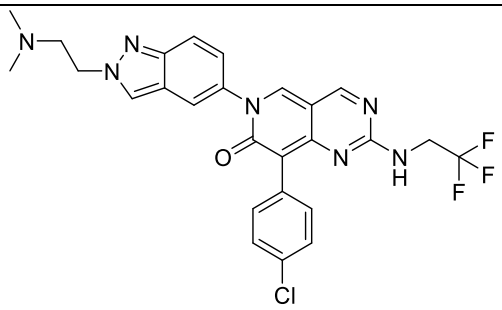
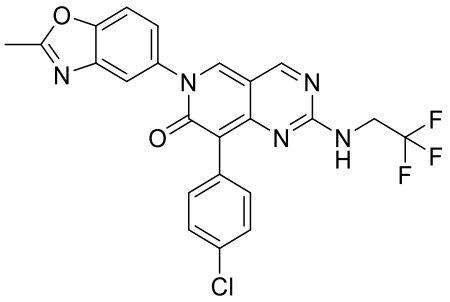
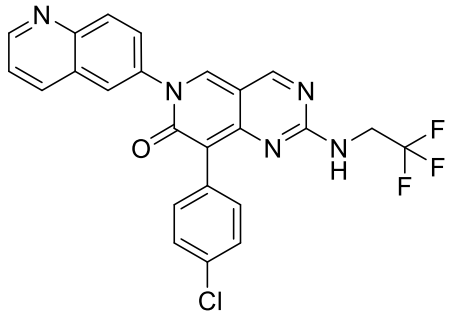
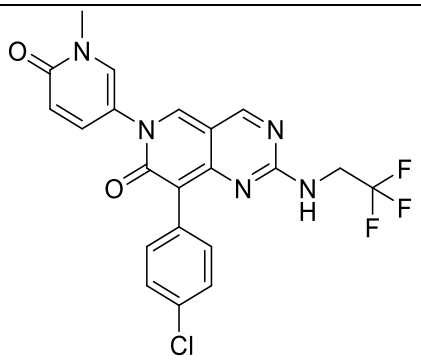
R^3 is 3- to 14-membered heterocycloalkyl or 5- to 10-membered heteroaryl wherein 1 to 3 heterocycloalkyl or heteroaryl members are independently selected from N, O, and S; and

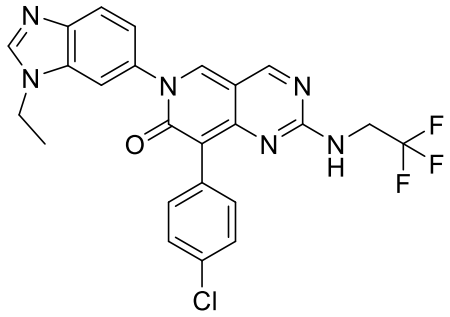
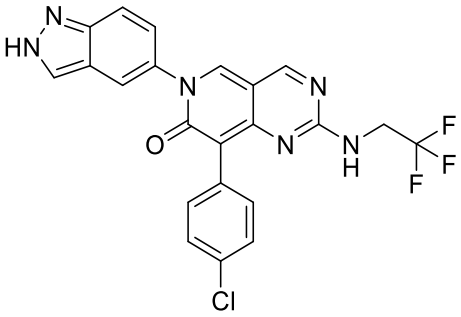
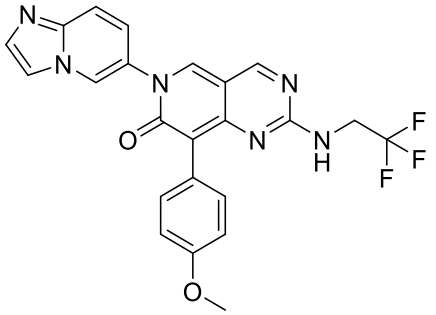
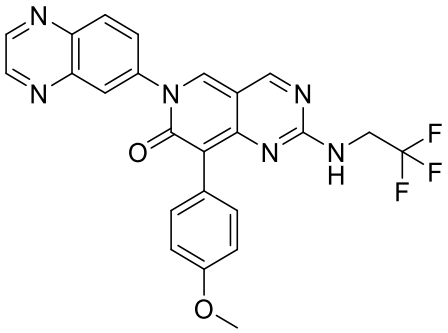
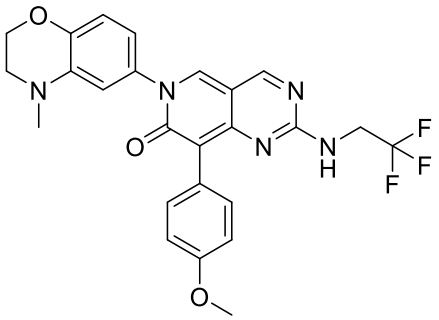
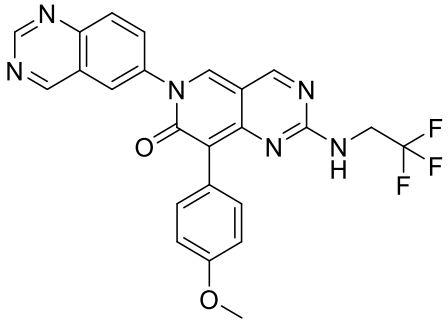
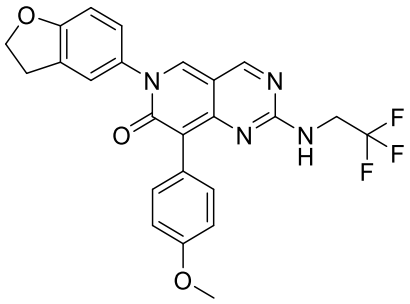
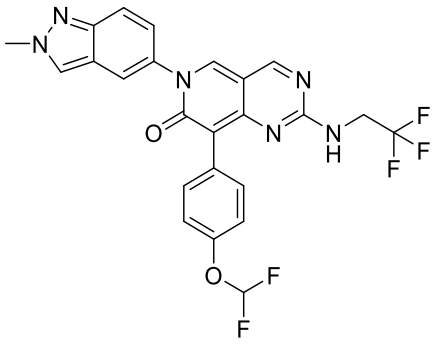
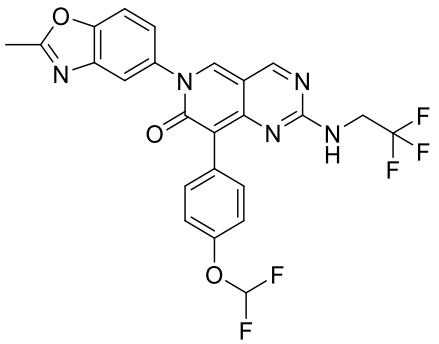
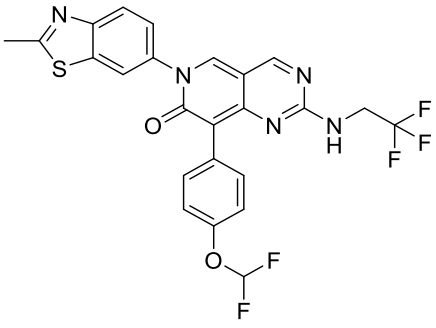
each of R^4, R^5, and R^6 (if present) is H.

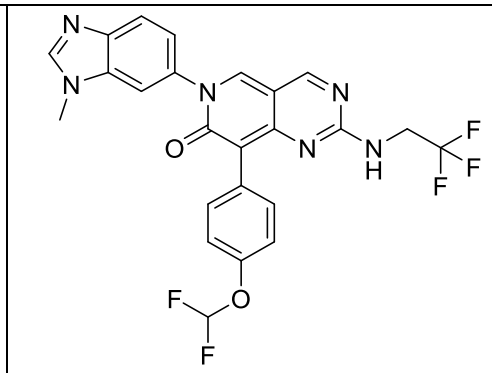
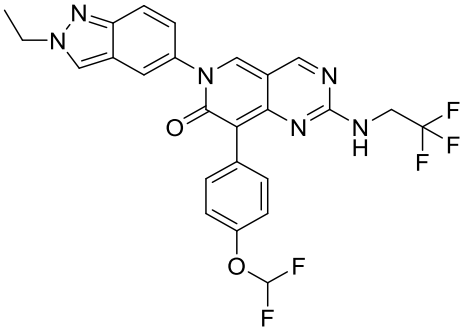
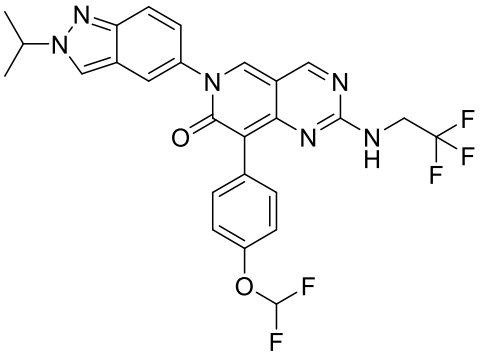
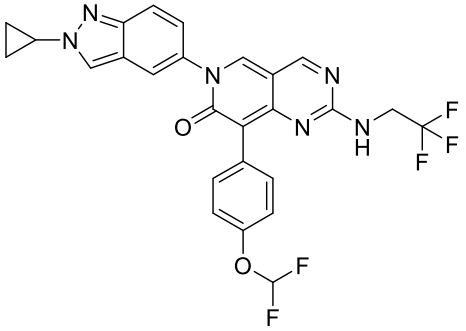
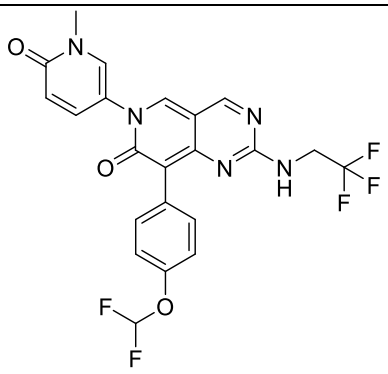
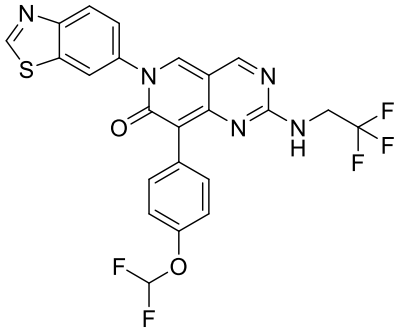
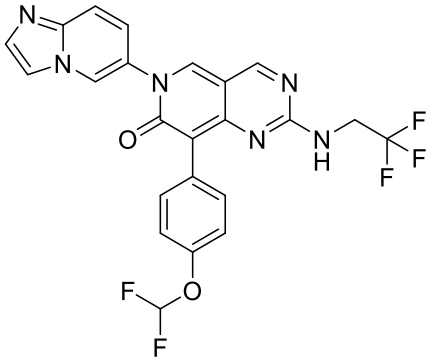
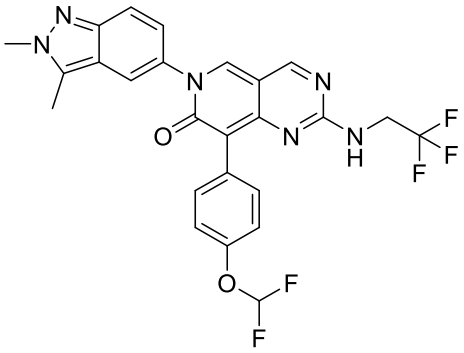
19. The compound or pharmaceutically acceptable salt thereof according to claim 18, wherein L is NR.

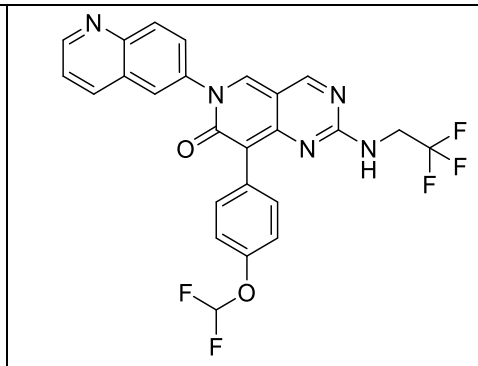
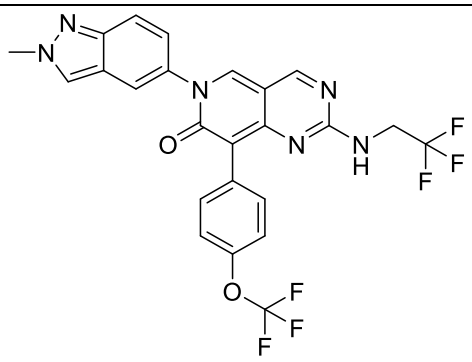
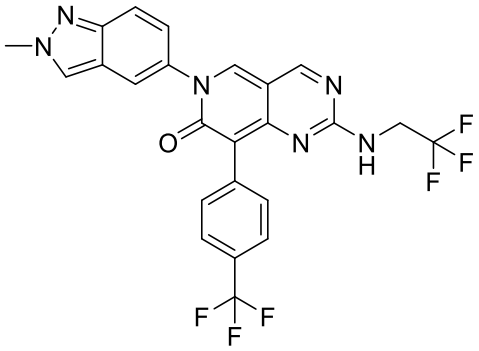
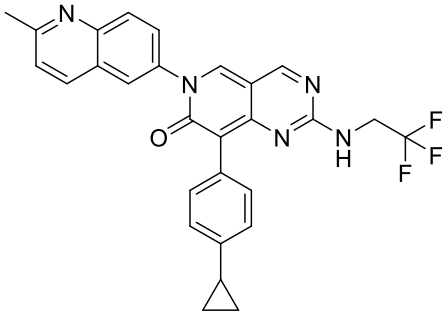
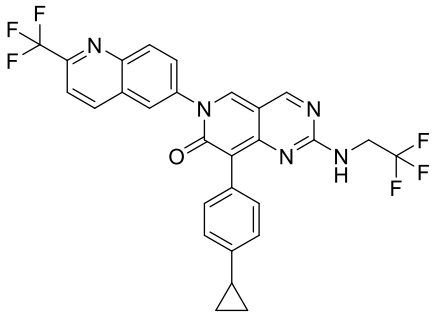
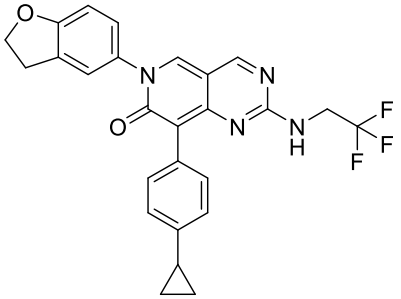
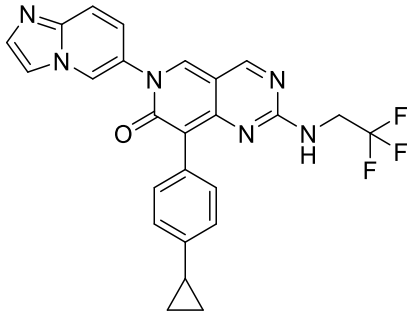
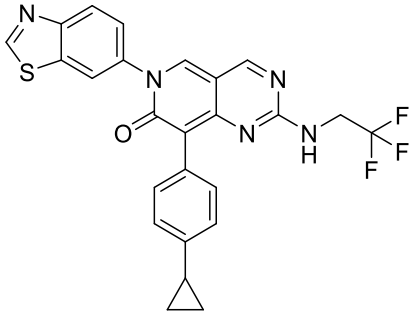
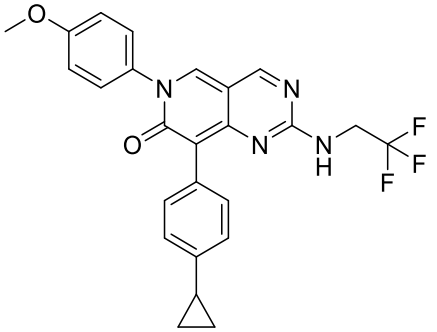
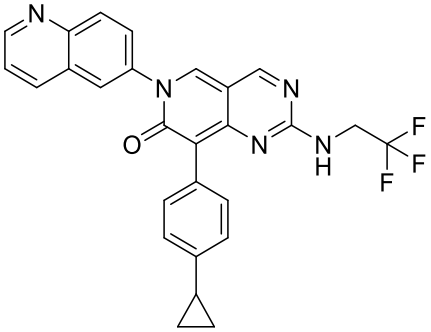
20. The compound according to claim **Error! Reference source not found.**, wherein the compound is selected from the following table:

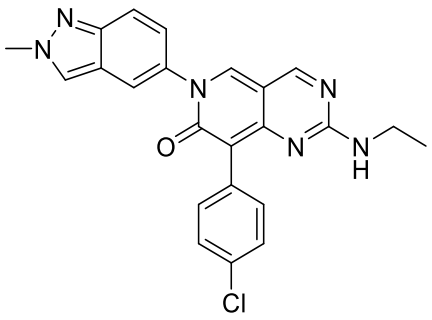
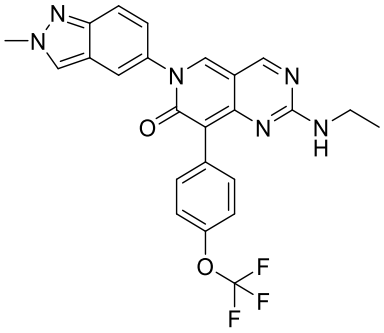
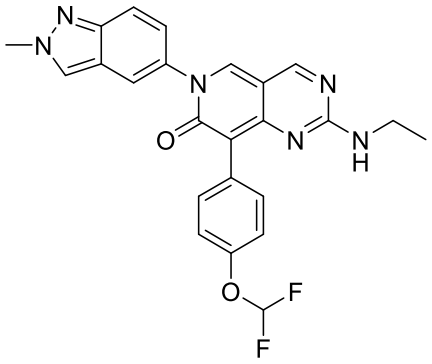
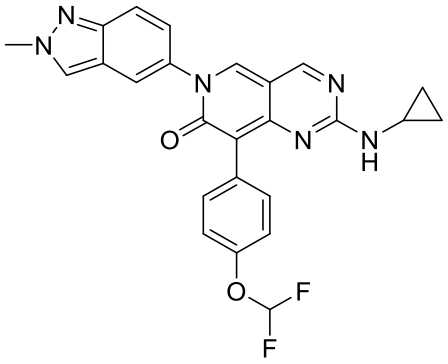
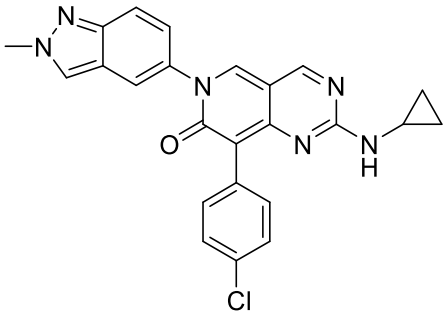
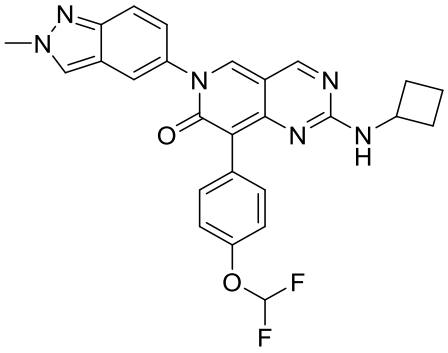
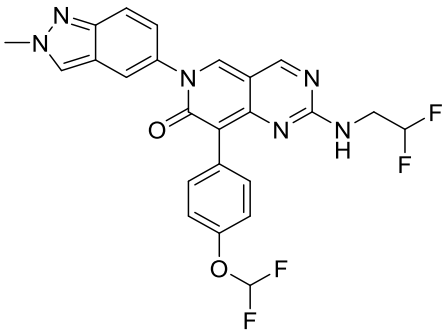
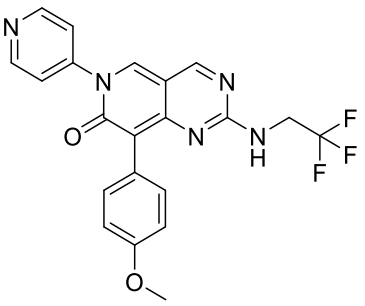
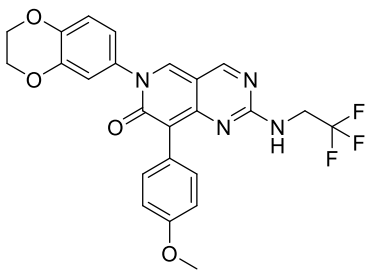
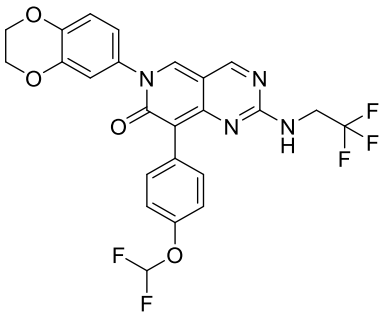
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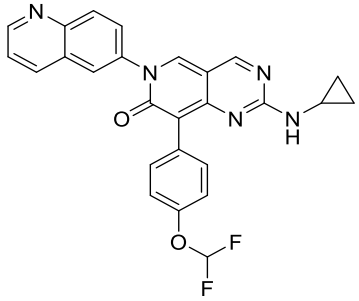
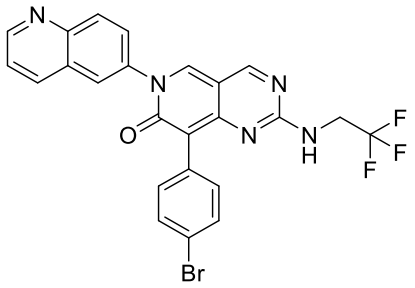
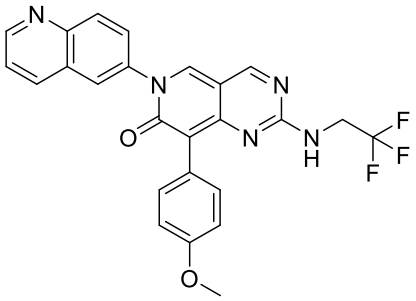
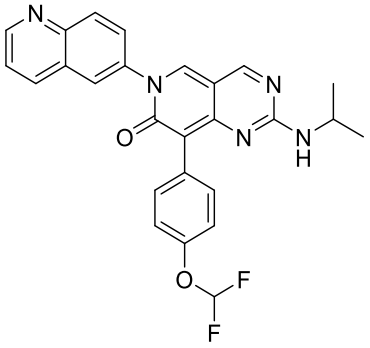
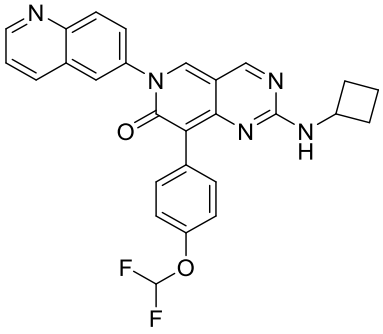
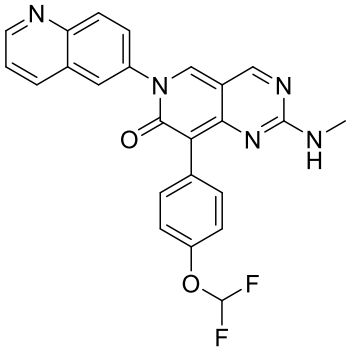
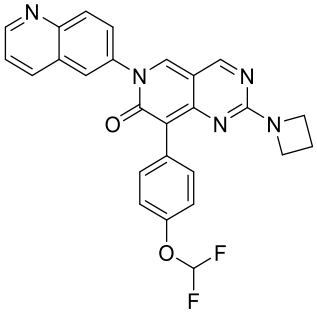
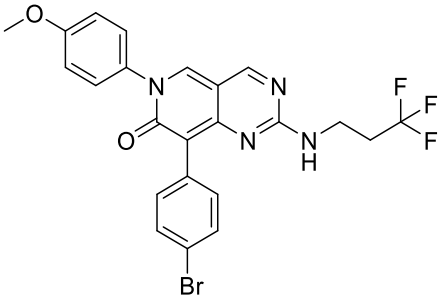
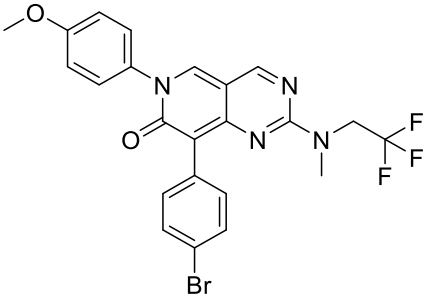
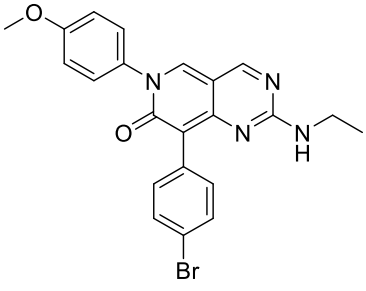
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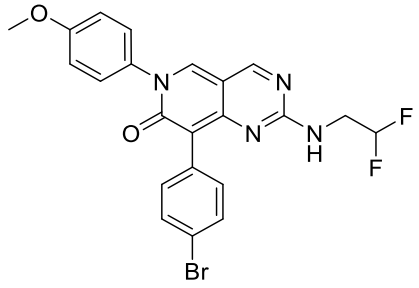
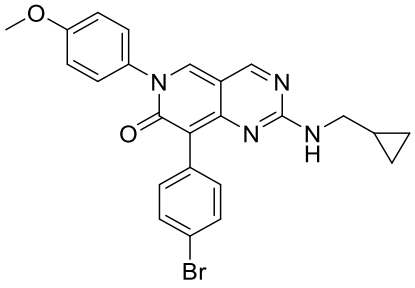
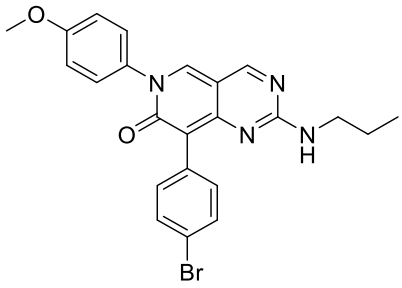
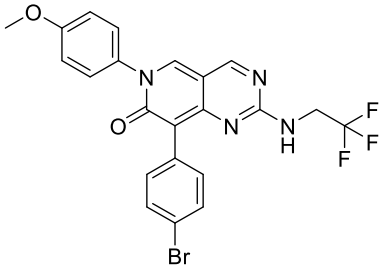
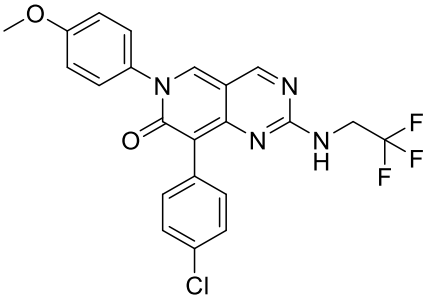
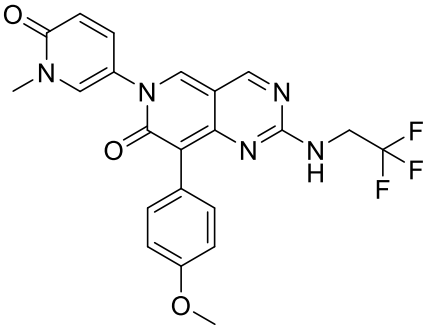
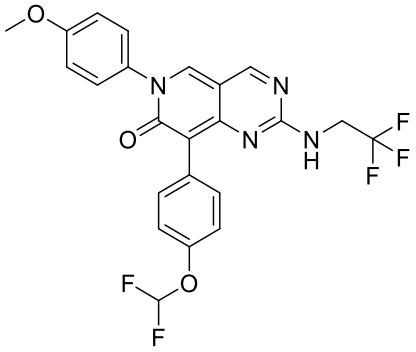
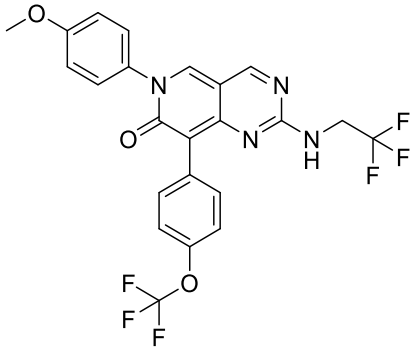
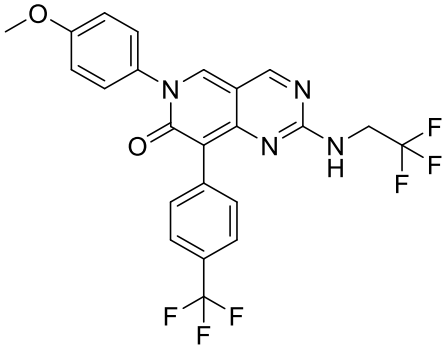
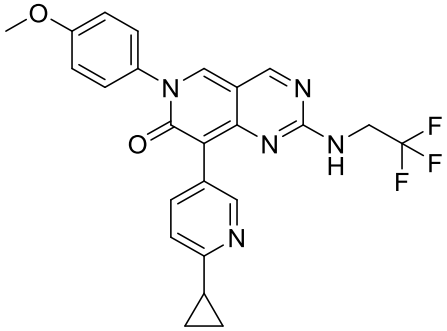
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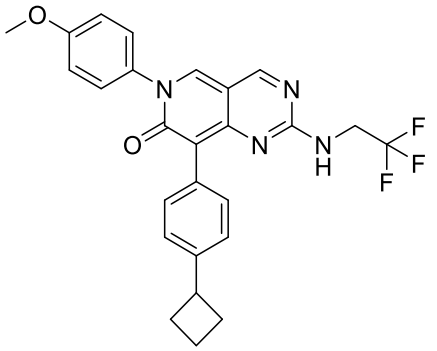
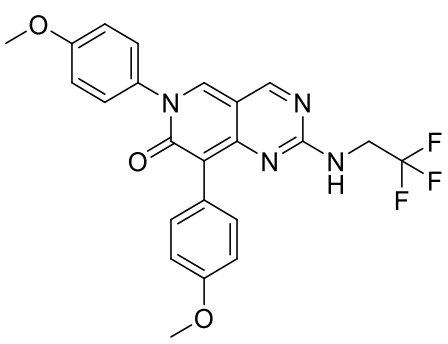
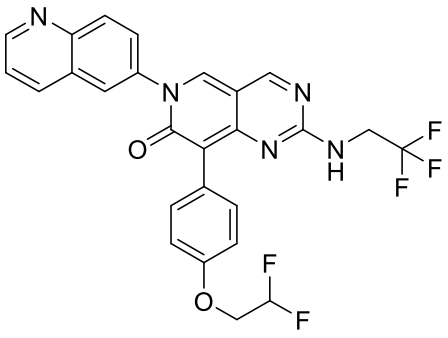
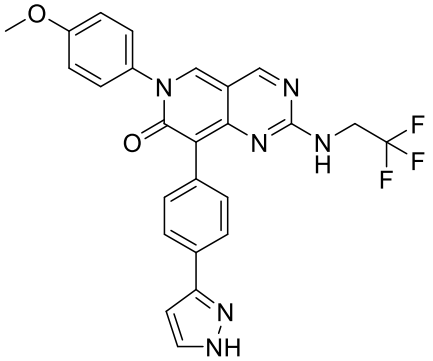
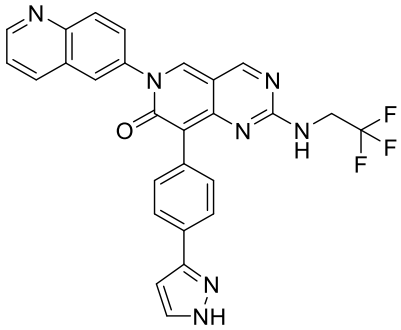
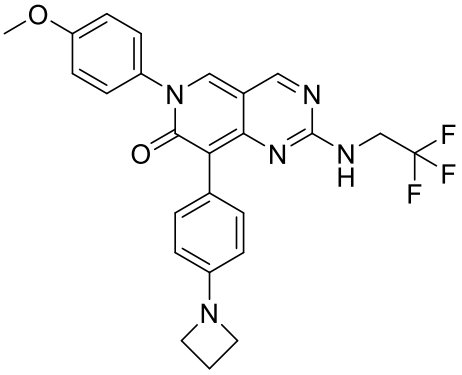
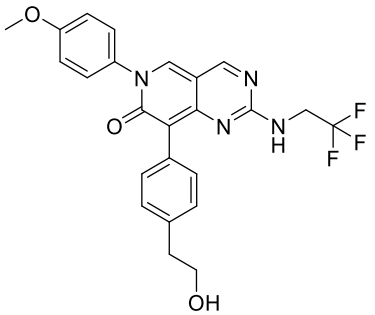
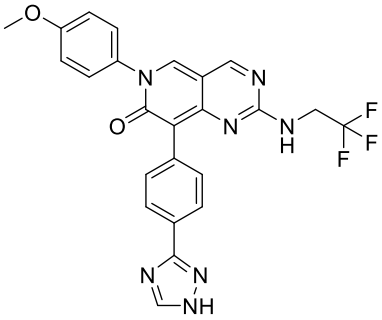
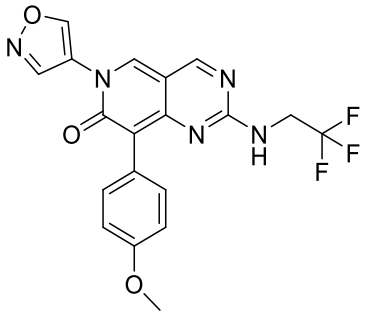
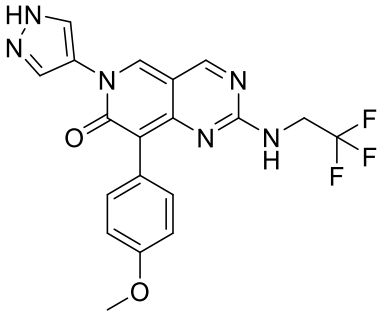
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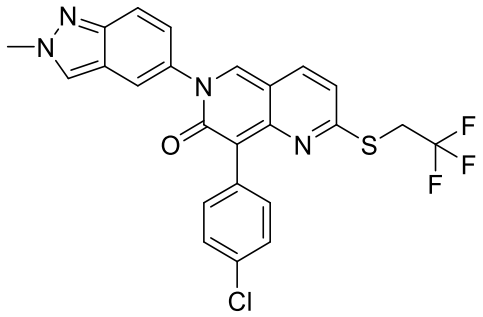
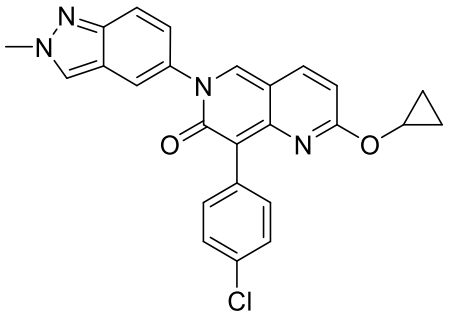
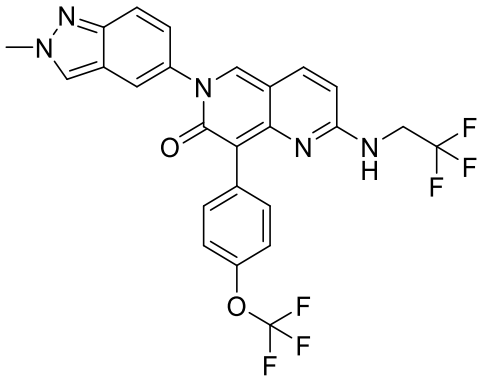
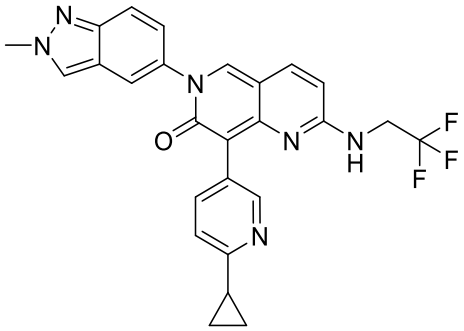
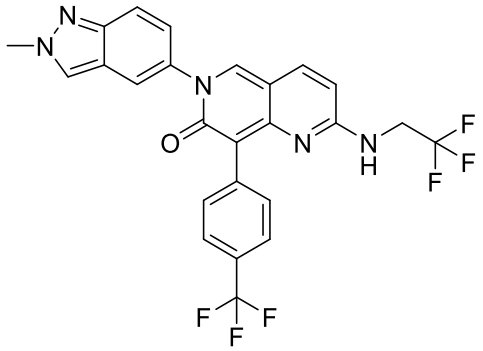
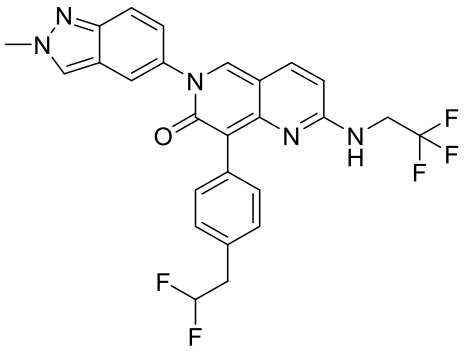
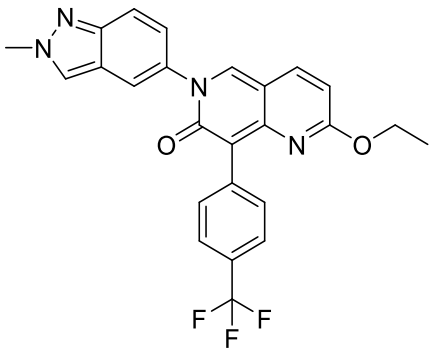
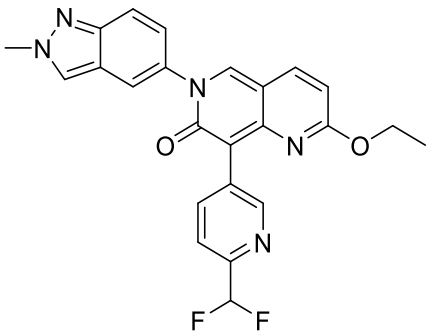
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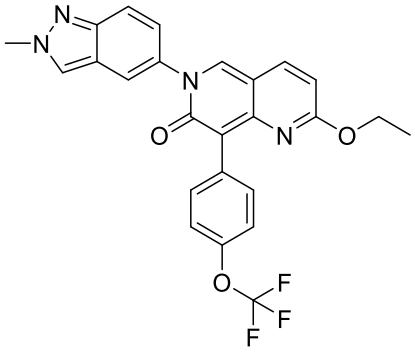
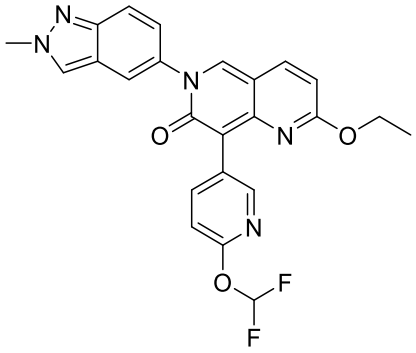
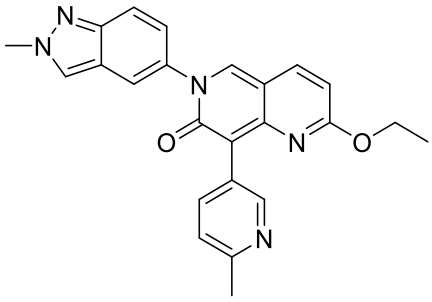
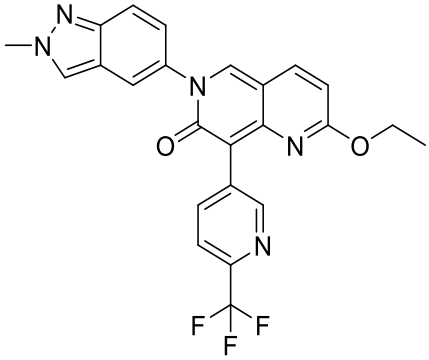
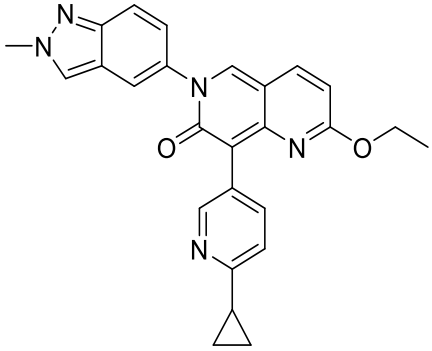
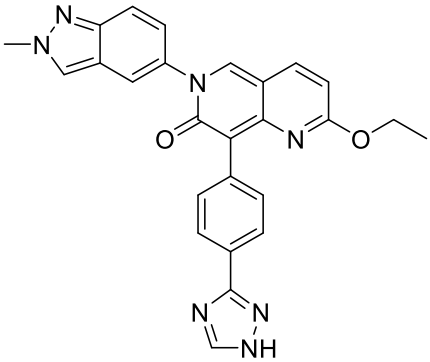
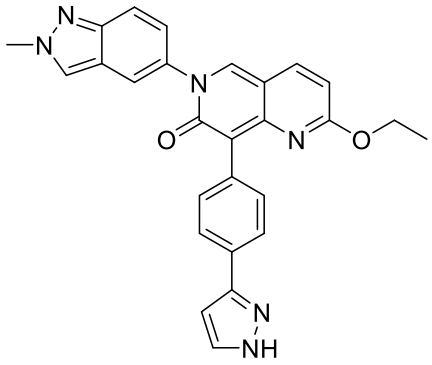
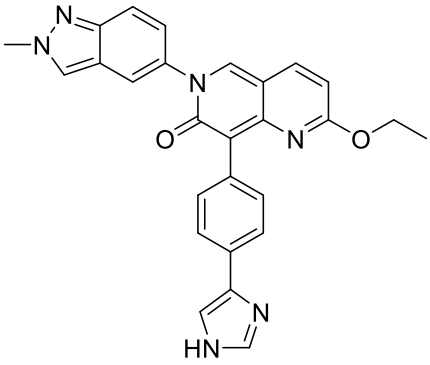
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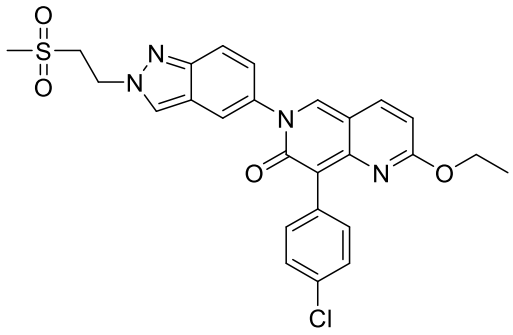
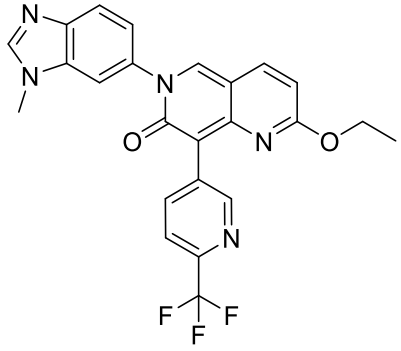
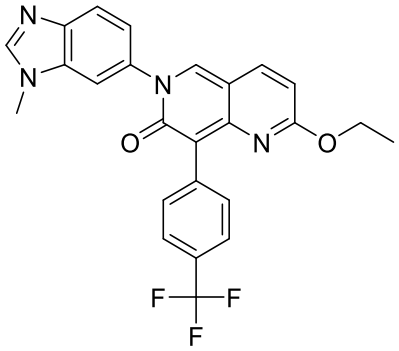
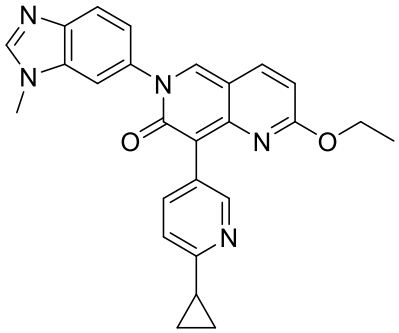
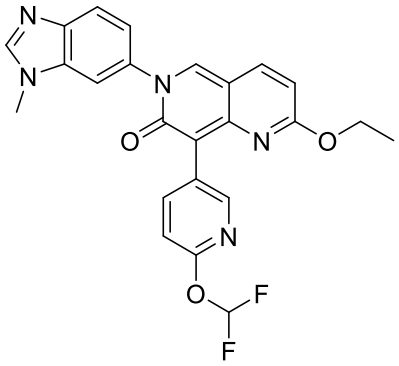
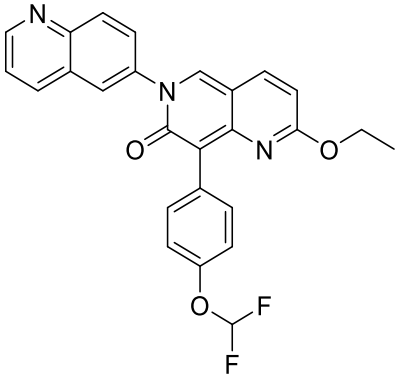
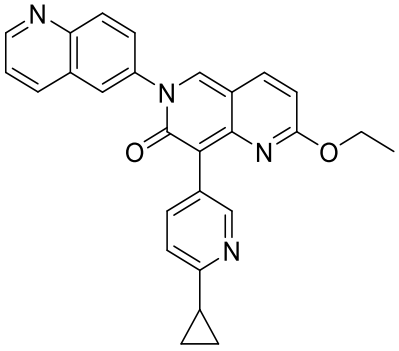
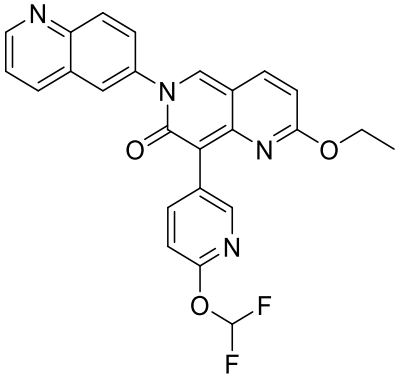
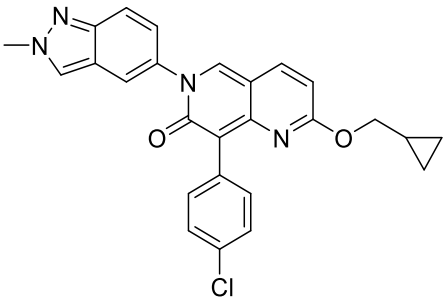
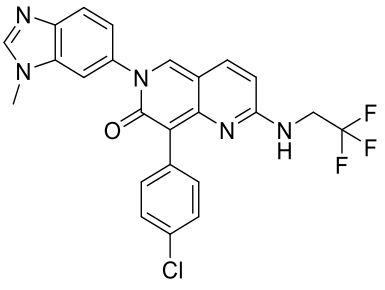
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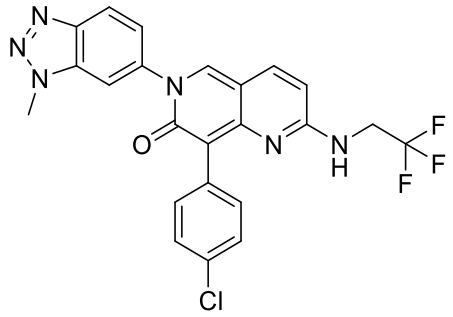
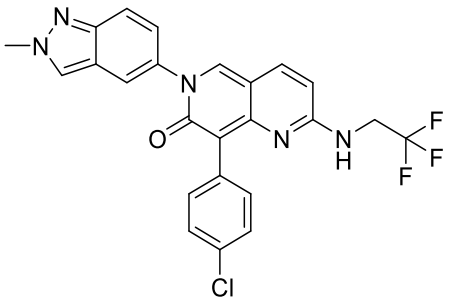
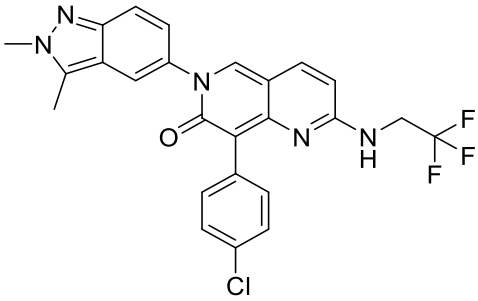
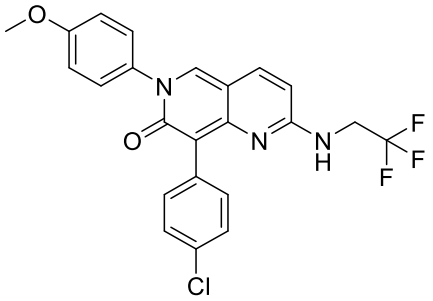
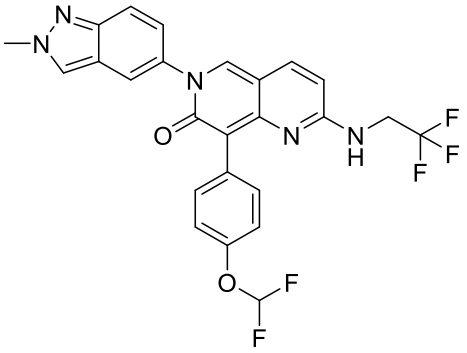
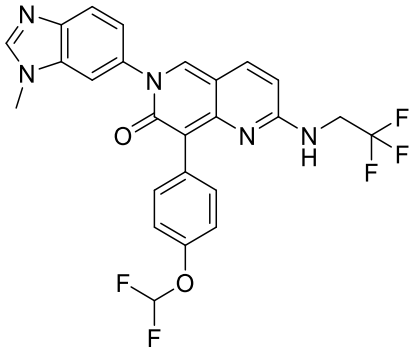
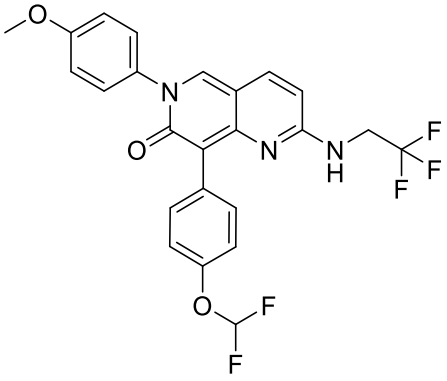
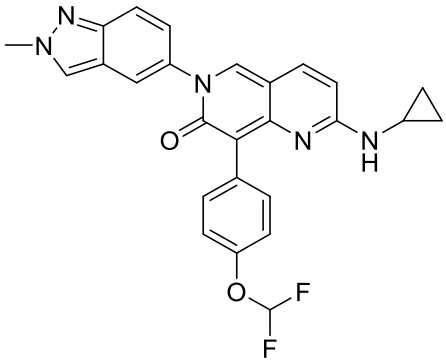
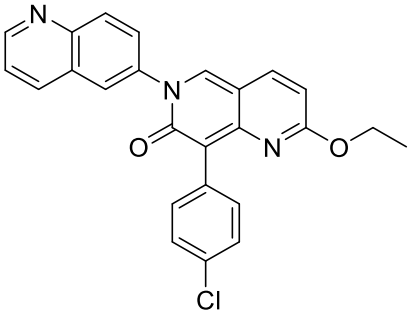
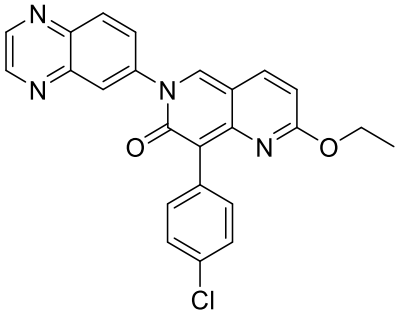
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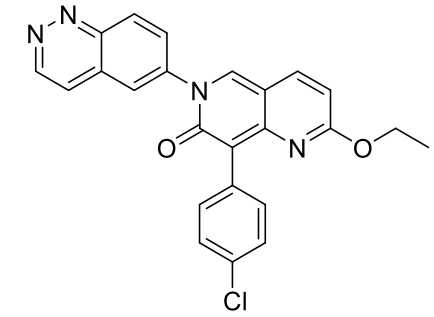
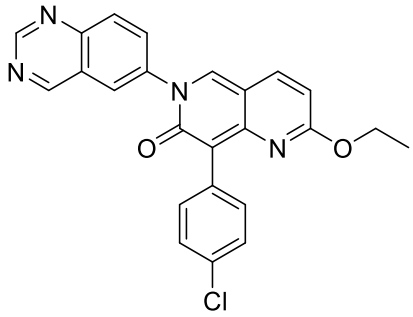
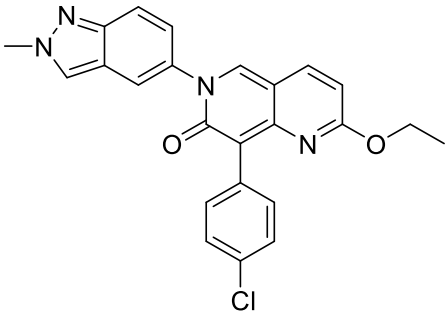
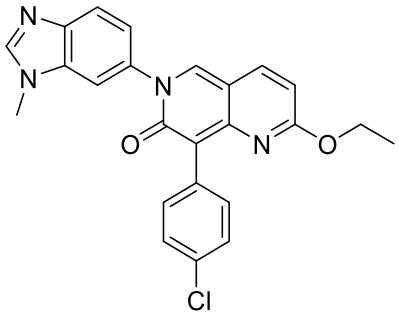
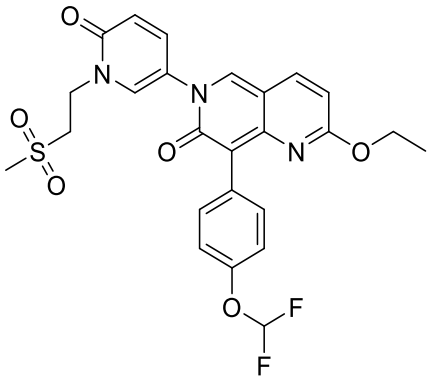
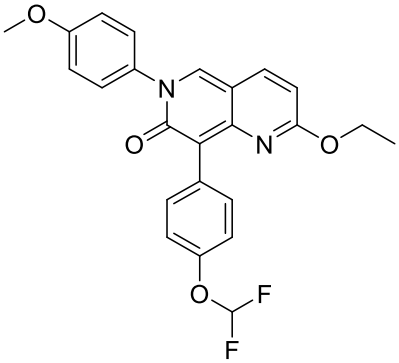
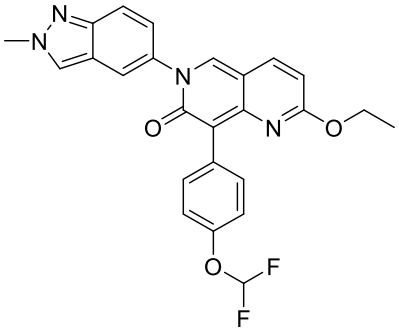
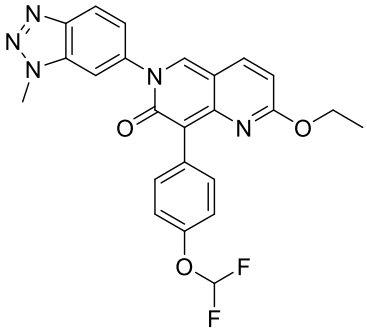
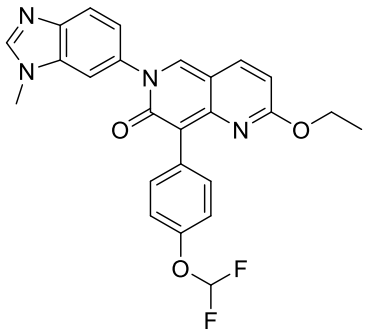
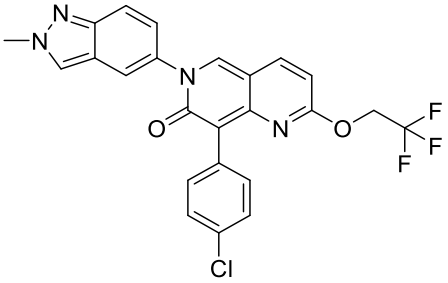
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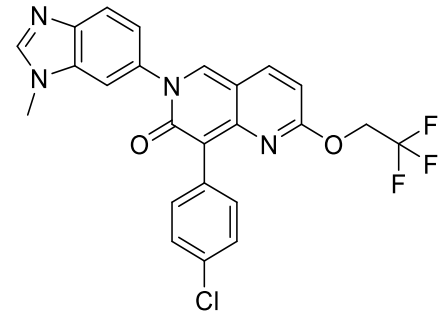
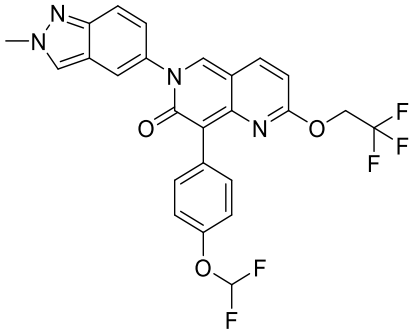
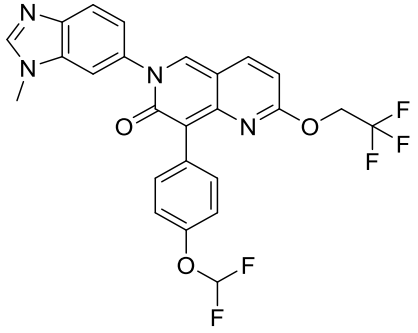
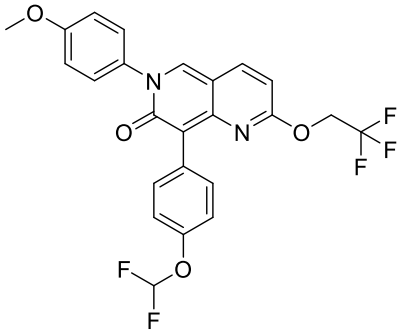
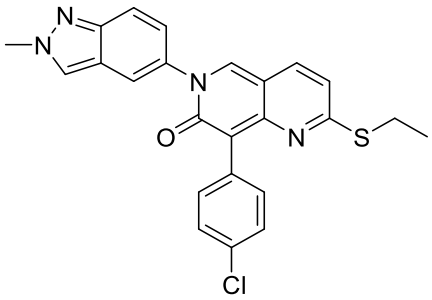
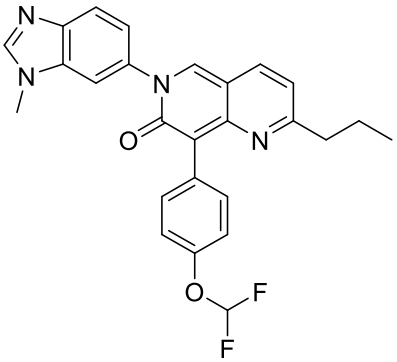
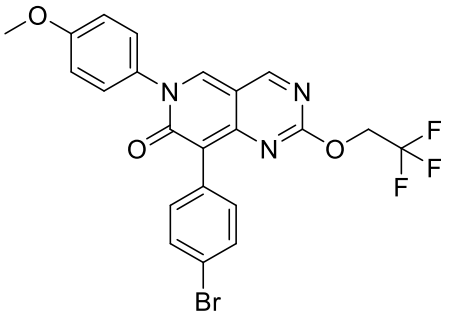
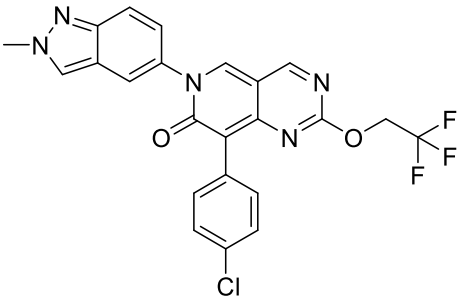
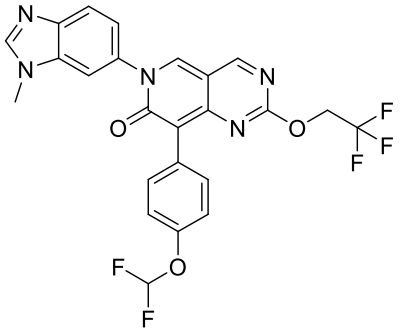
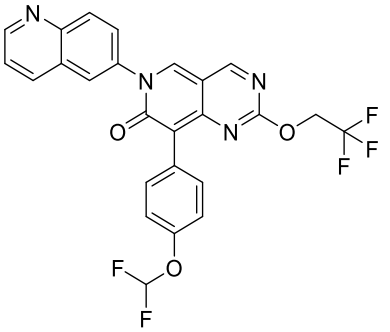
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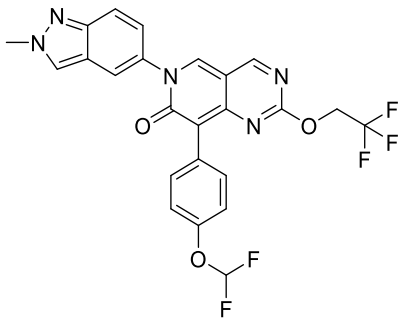
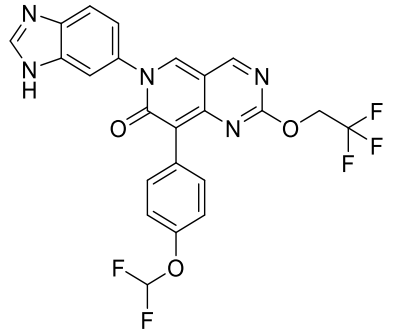
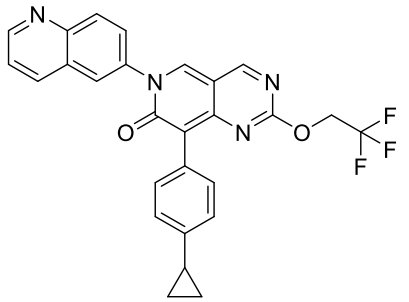
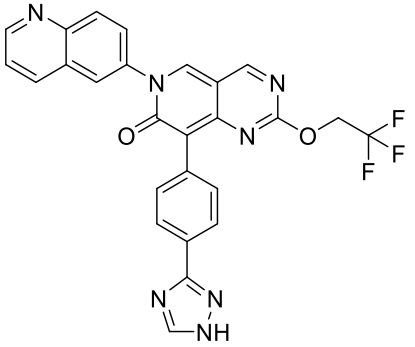
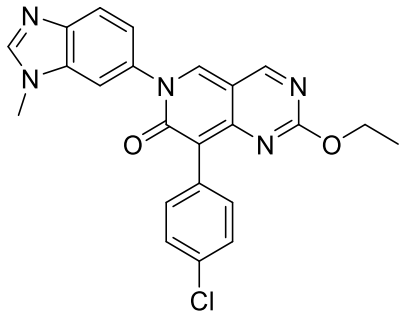
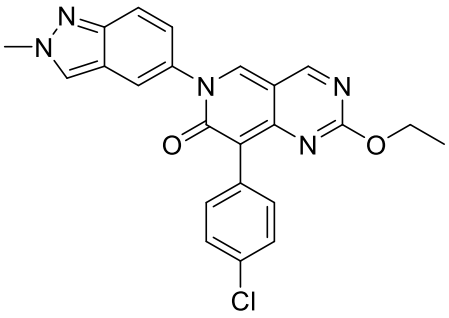
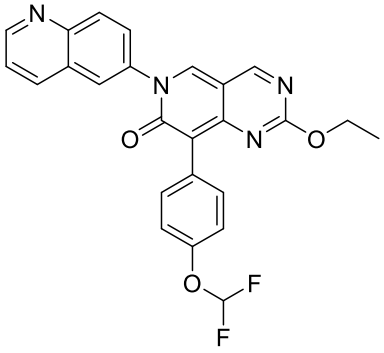
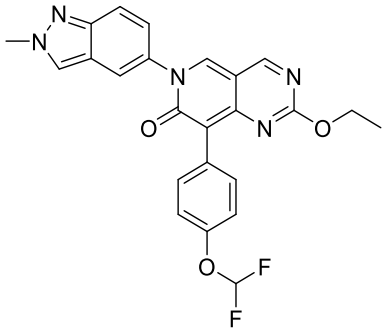
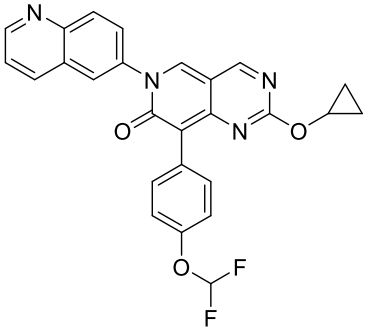
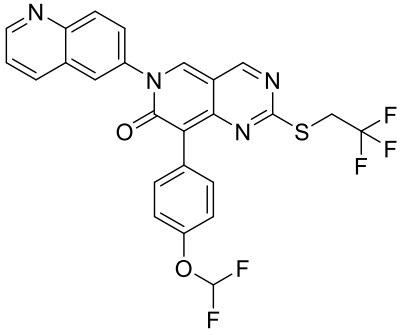
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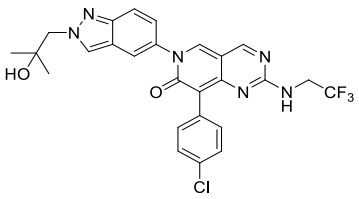
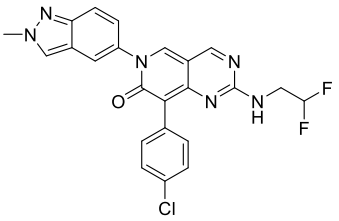
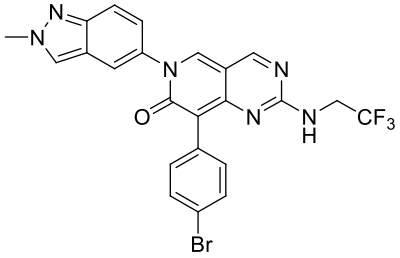
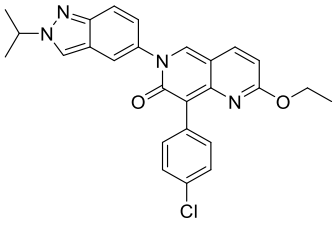
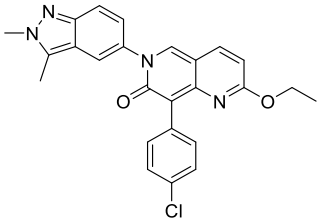
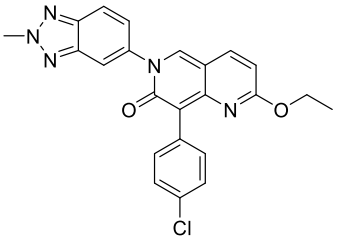
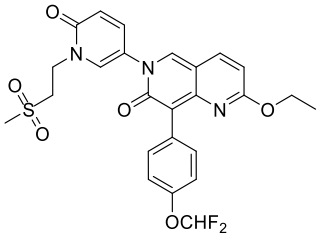
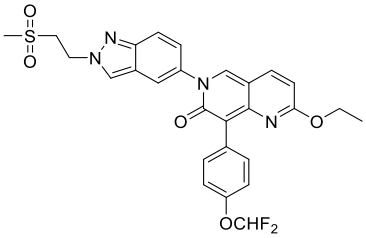
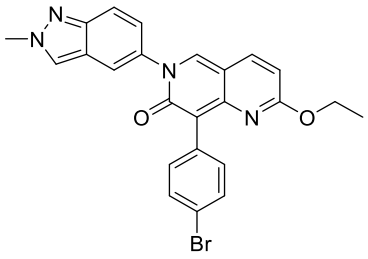
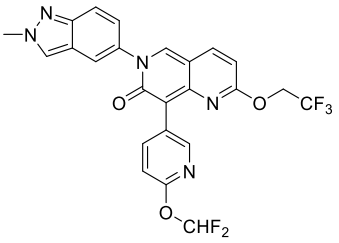
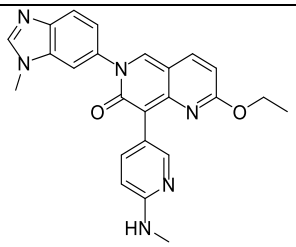
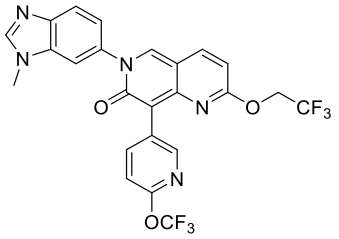
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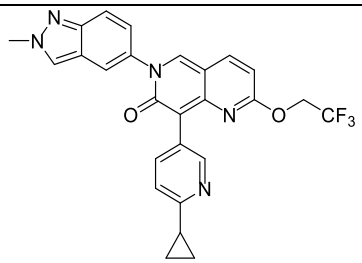
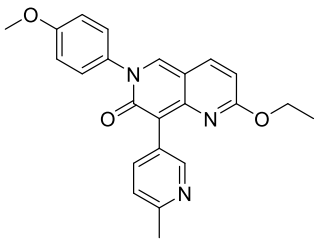
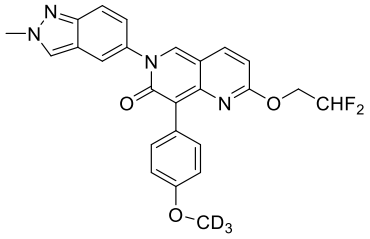
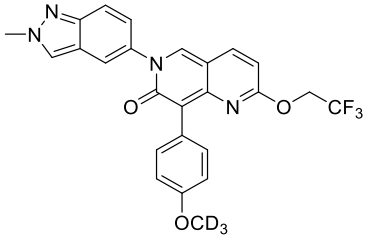
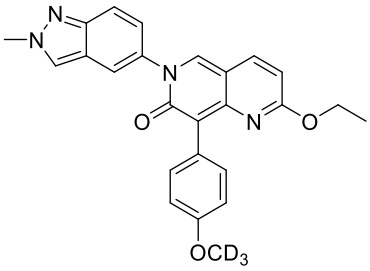
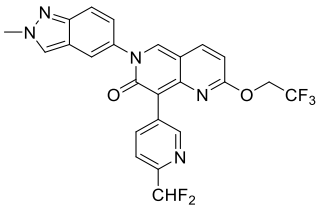
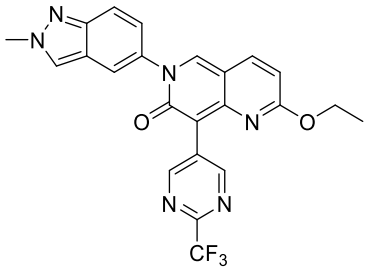
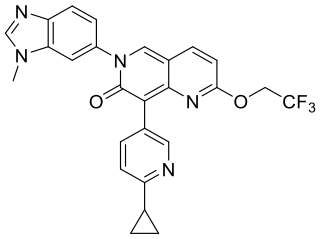
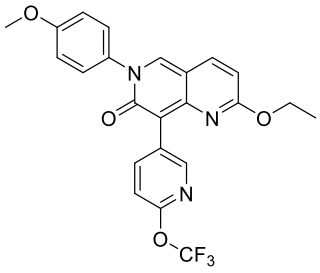
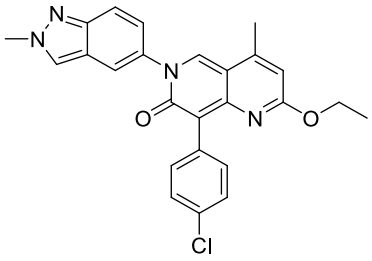
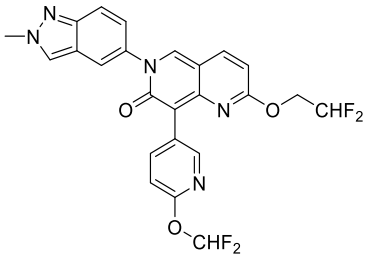
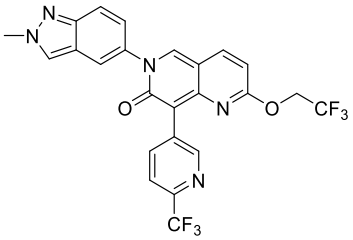
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257		**258**	
259		**260**	
261		**262**	
263		**264**	

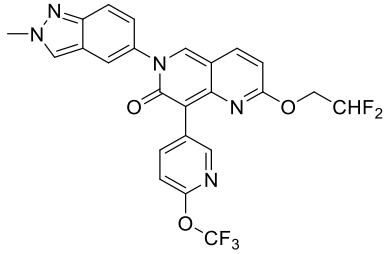
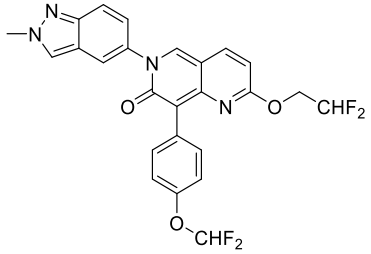
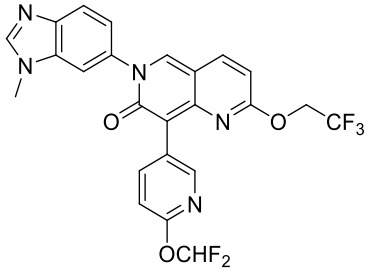
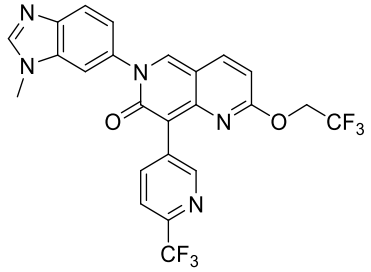
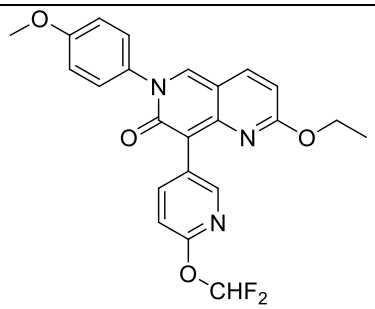
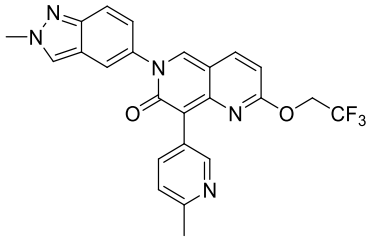
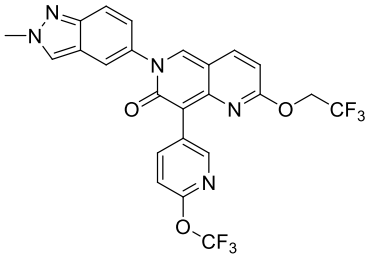
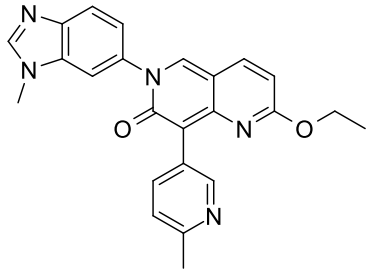
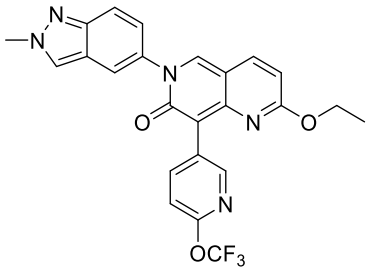
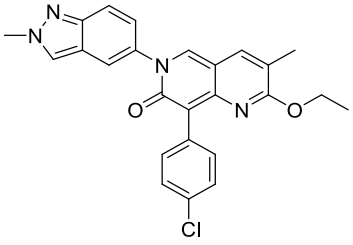
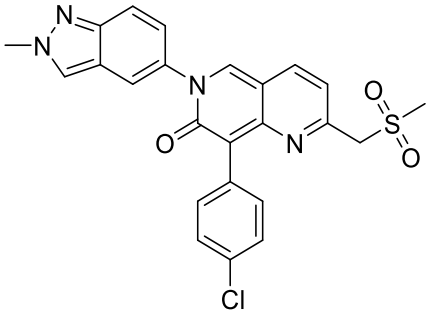
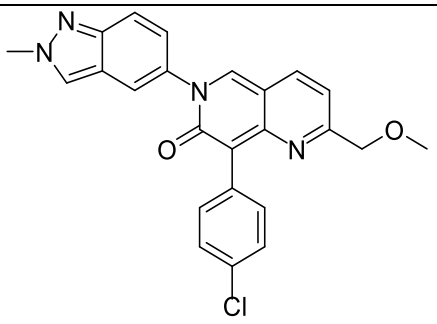
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267		**268**	
269		**270**	
271		**272**	
273		**274**	

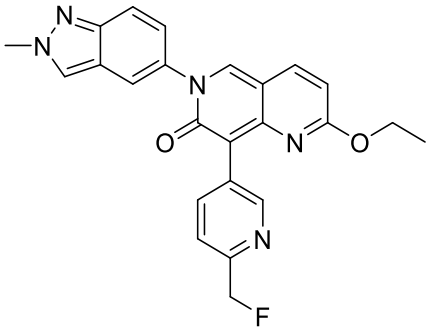
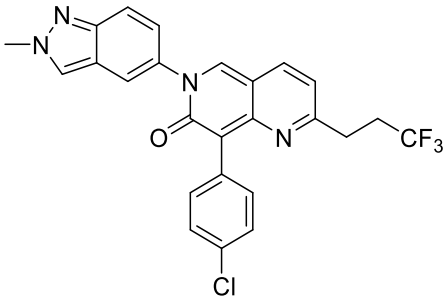
or a pharmaceutically acceptable salt thereof.

22. The compound according to claim **Error! Reference source not found.** or 2, wherein the compound is selected from the following table:

101-A		**102-A**	
103-A		**104-A**	
105-A		**106-A**	
107-A		**108-A**	
109-A		**110-A**	
111-A		**112-A**	

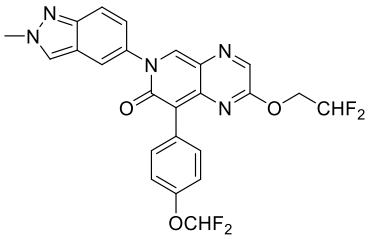
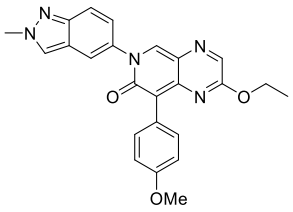
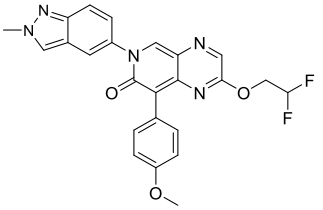
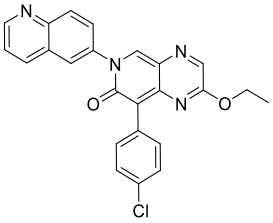
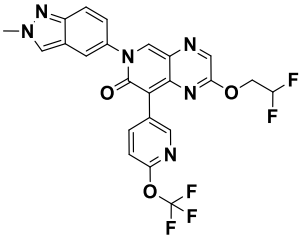
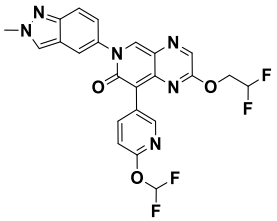
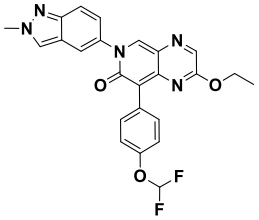
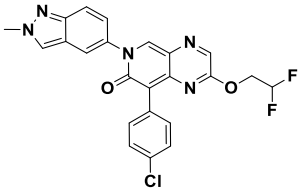
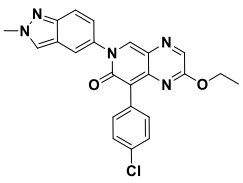
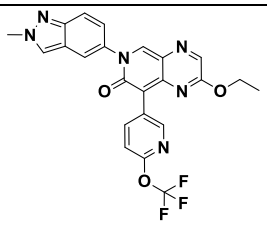
113-A		**114-A**	
115-A		**116-A**	
117-A		**118-A**	
119-A		**120-A**	
121-A		**122-A**	
123-A		**124-A**	

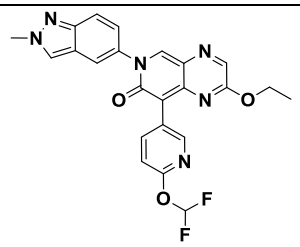
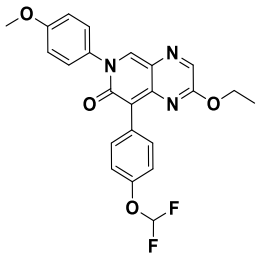
125-A		**126-A**	
127-A		**128-A**	
129-A		**130-A**	
131-A		**132-A**	
133-A		**134-A**	
135-A		**136-A**	

137-A		**138-A**	

or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 3, wherein the compound is selected from the following table:

139-A		**140-A**	
141-A		**142-A**	
143-A		**144-A**	
145-A		**146-A**	
147-A		**148-A**	

149-A		**150-A**	

or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims **Error! Reference source not found.** to 23 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25. An *in vitro* 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 thereof, according to any one of claims **Error! Reference source not found.** to 23.

26. Use of a compound according to any one of claims 1-23 in the manufacture of a medicament for treating a cancer in a subject suffering therefrom, wherein an effective amount of the compound is to be administered to the subject .

27. The use according to claim 26, wherein the cancer is an MTAP-deleted cancer.

28. The use according to claim 26, or 27, wherein the cancer is selected from the group consisting of mesothelioma, neuroblastoma, rectum carcinoma, colon carcinoma, familiary 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 thyroidea carcinoma, papillary thyroidea carcinoma, renal carcinoma, kidney parenchym 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, choroidea melanoma, seminoma, rhabdomyo sarcoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma.

29. The use according to claims 26 or 27, wherein the cancer is selected from the group consisting of 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, wherein the 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.

31. The use according to claim 29, wherein the brain cancer is a brain tumor selected from the group consisting of glioma, glioblastoma, astrocytoma, meningioma, medulloblastoma, peripheral neuroectodermal tumors, and craniopharyngioma.

32. The use according to claim 29, wherein the breast cancer is triple negative breast cancer (TNBC).

33. The use according to claim 29, wherein the cancer is a lymphoma selected from the group consisting of mantle cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, and adult T-cell leukemia/lymphoma.

34. Use of a compound according to any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament 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, wherein a therapeutically effective amount of a compound is to be administered to the subject.