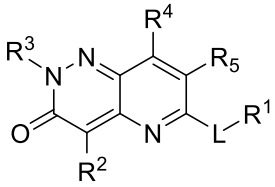
be indicative of a cancer at an early stage of development, whereas deletion of the genes encoding for p16 and MTAP was reported to be indicative of a cancer at a more advanced stage of tumor development. In some osteosarcoma patients, the MTAP gene was present at diagnosis but was deleted at a later 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.

[0009a] In an aspect, there is provided a compound according to Formula I:



(I)

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 1 - 6 deuterium;

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_2-C_6)alkynyl, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, - OC(O)R^A, -Si(C_1-C_6-alkyl)$_3$ and -CN;

R^4 is selected from the group consisting of H, C_1-C_6-alkyl (optionally substituted by one or more halo, hydroxy or 3- to 14-membered heterocycloalkoxy (wherein 1-4 heterocycloalkoxy members are independently selected from N, O, and S)), -O(C_1-C_6- alkyl) (optionally substituted by one or more halo), -OH, halo, -CN, -(C_1-C_6- alkyl)NR^AR^B, and -NR^AR^B;

R^5 is selected from the group consisting of H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, –CN, and -NR^CR^D;

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 deuterium, 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 substituent 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;

R^C and R^D are each independently selected from H and C_1-C_6-alkyl;

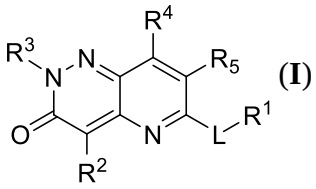
or a pharmaceutically acceptable salt thereof.

[0009b] In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0009c] In another aspect, there is provided a use of a MAT2A inhibitor compound or a pharmaceutically acceptable salt thereof as defined above, in the manufacture of a medicament for treating cancer.

[0009d] In another aspect, there is provided a MAT2A inhibitor compound or a pharmaceutically acceptable salt thereof as defined above, for use in therapy.

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



(I)

[0011] In Formula I, L is O, S, NR, or a bond. R is H or C_1-C_6-alkyl.

[0012] 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. In an ~~embodiment~~example, R^1 is optionally substituted by 1-6 halo or 1-6 deuterium.

[0013] Alternatively, in an ~~embodiment~~example, 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.

[0014] R^2 and R^3 are independently selected from the group consisting of C_2-C_6-alkynyl, 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). 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, $-C(O)OR^A$, $-C(O)NR^AR^B$, $-OC(O)R^A$, $-Si(C_1-C_6$-alkyl$)_3$ and -CN.

[0020] The disclosure provides in another ~~embodiment~~ example a pharmaceutical composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof as described herein, and a pharmaceutically acceptable carrier.

[0021] In another ~~embodiment~~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 compound as described herein.

[0022] Yet another ~~embodiment~~ example of the disclosure is 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.

[0023] The disclosure, in another ~~embodiment~~example, relates to a method for inhibiting the synthesis of S-adenosyl methionine (SAM) in a subject, comprising administering to the subject an effective amount of at least one compound or a salt, tautomer, and/or isotopologue thereof as described herein.

[0024] In an ~~embodiment~~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 comprising administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein.

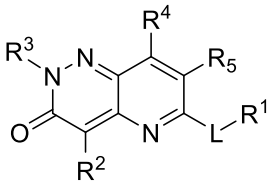
[0025] The disclosure also provides in another ~~embodiment~~ example a compound or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein, for inhibiting the synthesis of S-adenosyl methionine (SAM).

[0026] In still a further ~~embodiment~~example, the disclosure provides a compound or a pharmaceutically acceptable salt, tautomer, and/or isotopologue thereof, as described herein, for use in treating a cancer in a subject suffering therefrom.

[0027] 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.

WE CLAIM:

1. A compound according to Formula I:



(I)

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 1 - 6 deuterium;

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_2-C_6)alkynyl, 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^AR^B, -(C_1-C_6-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A, -Si(C_1-C_6-alkyl)$_3$ and -CN;

R^4 is selected from the group consisting of H, C_1-C_6-alkyl (optionally substituted by one or more halo, hydroxy or 3- to 14-membered heterocycloalkoxy (wherein 1-4 heterocycloalkoxy members are independently selected from N, O, and S)), -O(C_1-C_6-alkyl) (optionally substituted by one or more halo), -OH, halo, -CN, -(C_1-C_6-alkyl)NR^AR^B, and -NR^AR^B;

R^5 is selected from the group consisting of H, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo, –CN, and -NR^CR^D;

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 deuterium, 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 substituent 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;

R^C and R^D are each independently selected from H and C_1-C_6-alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein:

R^4 is selected from the group consisting of H, C_1-C_6-alkyl (optionally substituted by one or more halo, hydroxy or 3- to 14-membered heterocycloalkoxy (wherein 1-4 heterocycloalkoxy members are independently selected from N, O, and S)), -O(C_1-C_6-

alkyl), -(C_1-C_6-alkyl)NR^AR^B, and -NR^AR^B (wherein R^A and R^B are independently selected from H and C_1-C_6-alkyl); and

R^5 is selected from the group consisting of H, C_1-C_6-alkyl, C_1-C_6-alkoxy, and -NR^CR^D.

3. The compound according to claim 1 or 2, wherein:

(a) at least one of R^4 and R^5 is H~~.~~; and/or

~~4. The compound according to any one of claims 1 to 3, wherein~~(b) R^4 is H~~.~~; and/or

~~5. The compound according to any one of claims 1 to 4, wherein~~(c) R^5 is H~~.~~; and/or

~~6. The compound according to any one of claims 1 to 5, wherein~~ (d) each of R^4 and R^5 is H.

~~7~~4. The compound according to any one of claims 1 to ~~6~~3, wherein R^2 is optionally substituted C_6-C_{10}-aryl or optionally substituted 5- to 10-membered heteroaryl~~.~~, optionally

~~8. The compound according to claim 7,~~ wherein R^2 is:

(a) optionally substituted C_6-C_{10}-aryl~~.~~,

~~9. The compound according to claim 8,~~optionally wherein R^2 is optionally substituted phenyl~~.~~; or

~~10. The compound according to claim 7, wherein R^2 is~~ (b) optionally substituted 5- to 10-membered heteroaryl, and wherein 1 ring member is N~~.~~, optionally

~~11. The compound according to claim 10,~~ wherein:

(i) R^2 is optionally substituted 5- or 6-membered heteroaryl~~.~~; and/or

~~12. The compound according to claim 10 or 11, wherein~~(ii) R^2 is optionally substituted 6-membered heteroaryl~~.~~; and/or

~~13. The compound according to any one of claims 10 to 12, wherein~~(iii) R^2 is optionally substituted pyridyl.

~~14~~5. The compound according to any one of claims 1 to ~~12~~4, wherein R^3 is :

(a) optionally substituted 3- to 14-membered heterocycloalkyl or optionally substituted 5- to 10-membered heteroaryl~~.~~,

~~15. The compound according to claim 14,~~optionally wherein R^3 is selected from the group consisting of benzothiazolyl, benzoisothiazolyl, benzoxazolyl, pyridinyl, pyridinonyl, pyridazinyl, benzimidazolyl, benzotriazolyl, indazolyl, quinoxalinyl, quinolinyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, triazolopyridinyl, cinnolinyl, isoxazolyl, pyrazolyl, benzofuranyl, dihydrobenzofuranyl, dihydrobenzodioxinyl, and tetrahydrobenzodioxinyl, each of which may be optionally substituted~~.~~; or

~~16. The compound according to any one of claims 1 to 12, wherein R^3 is~~(b) optionally substituted C_6-C_{10}-aryl~~.~~,

~~17. The compound according to claim 16,~~optionally wherein R^3 is optionally substituted phenyl.

~~18~~6. The compound according to any one of claims 1 to ~~6~~3, 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.

~~19~~7. The compound according to any one of claims 1 to ~~18~~6, wherein L is O or NR~~.~~, optionally

~~20. The compound according to claim 19,~~ wherein R^1 is:

(a) optionally substituted C_1-C_6-alkyl or optionally substituted C_3-C_6-carbocyclyl~~.~~; and/or

~~21. The compound according to claim 19 or 20, wherein R^1 is~~ (b) C_1-C_3-alkyl that is optionally substituted by 1 - 3 F.

~~22~~8. The compound according to claim 1, 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;

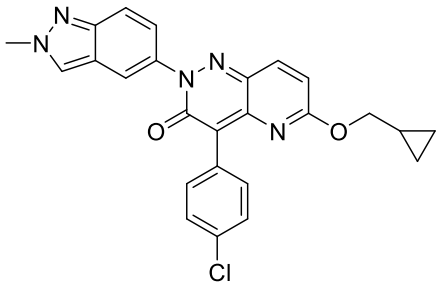
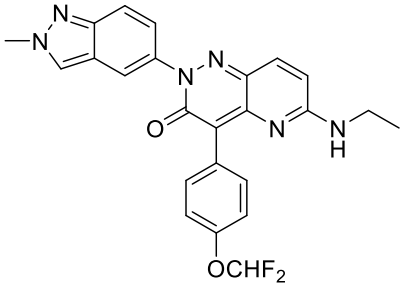
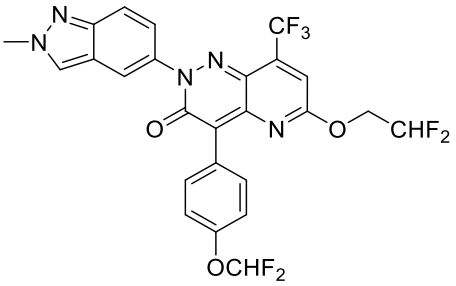
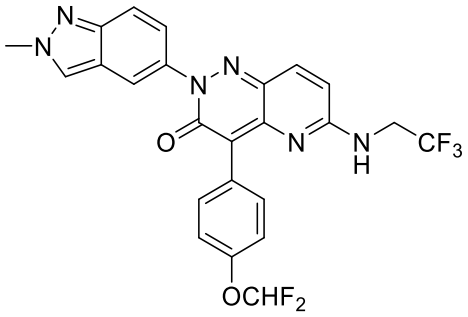
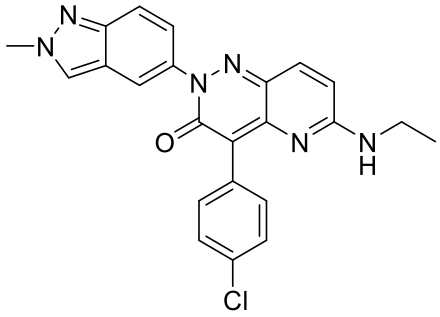
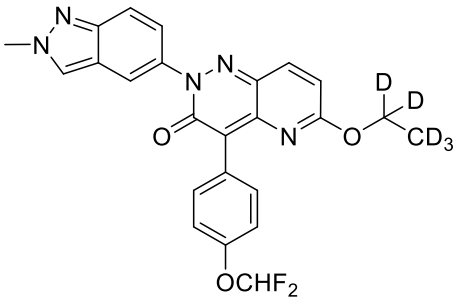
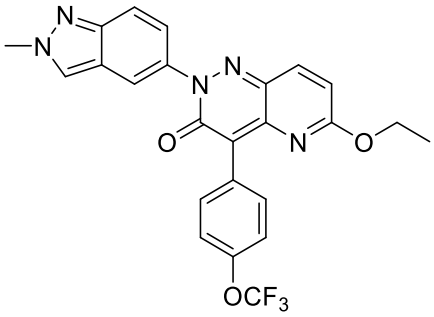
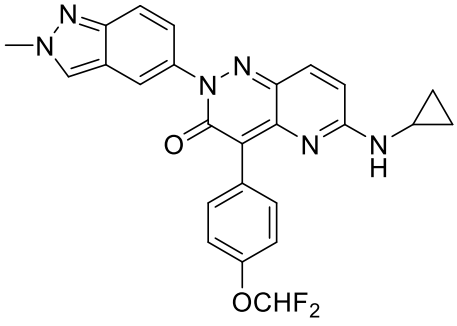
R^3 is optionally substituted 3- to 14-membered heterocycloalkyl or optionally substituted 5- to 10-membered heteroaryl wherein 1 to 3 heterocycloalkyl or heteroaryl members are independently selected from N, O, and S; and

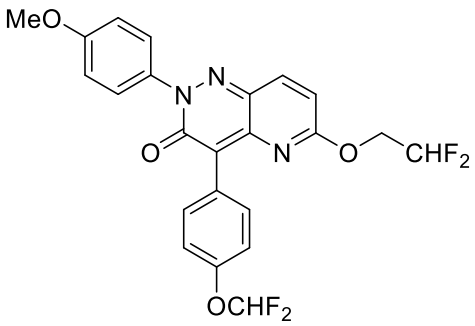
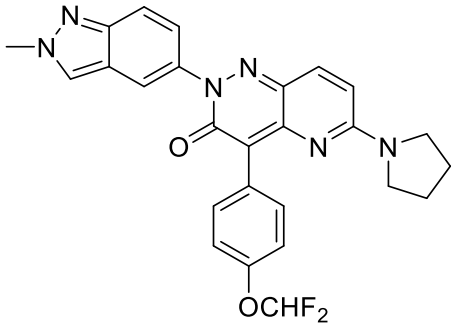
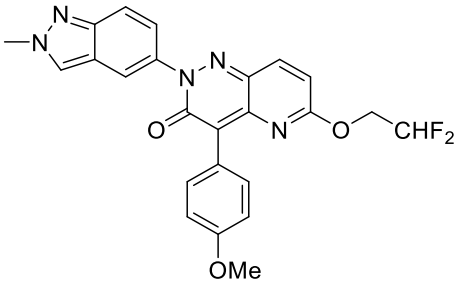
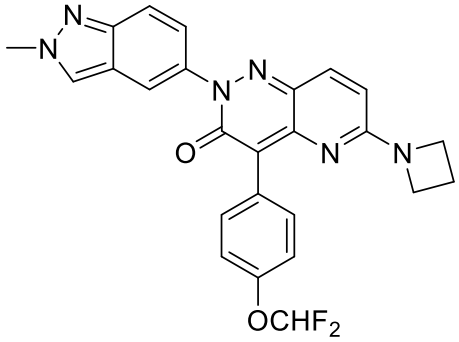
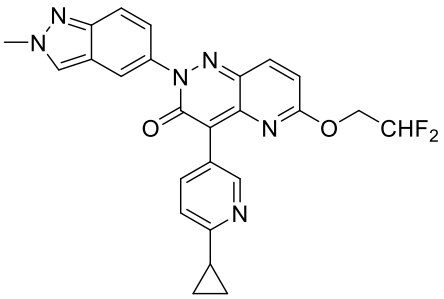
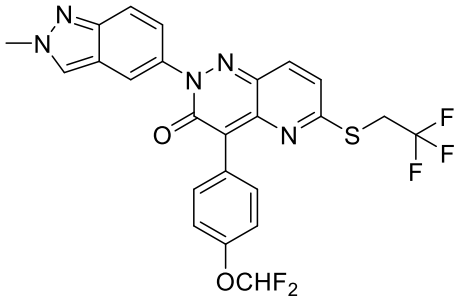
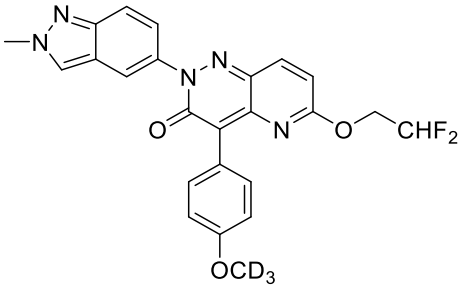
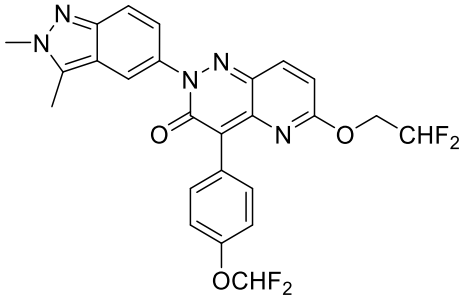
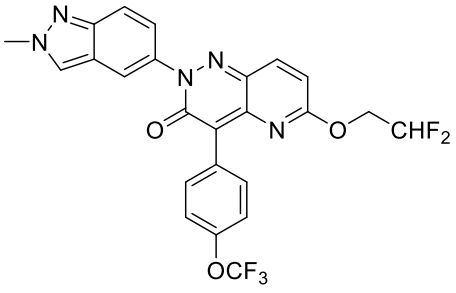
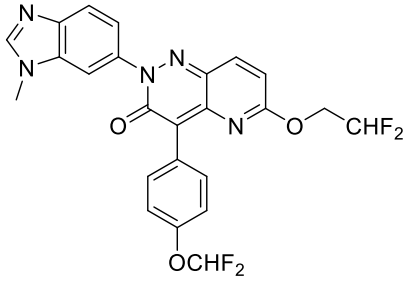
each of R^4 and R^5 is H~~,~~

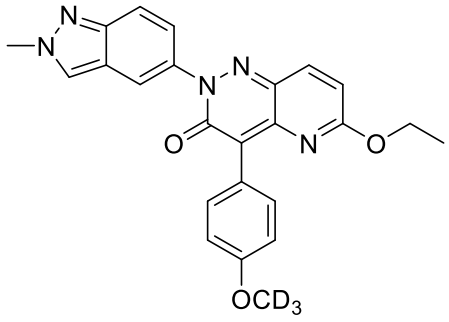
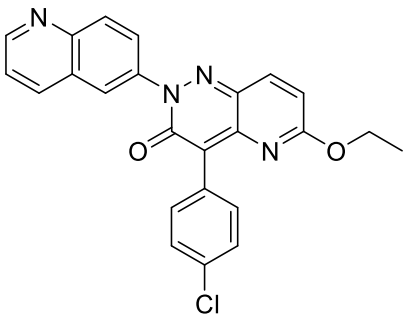
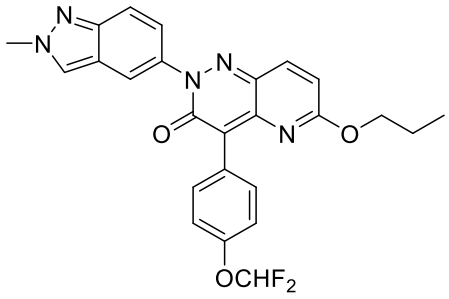
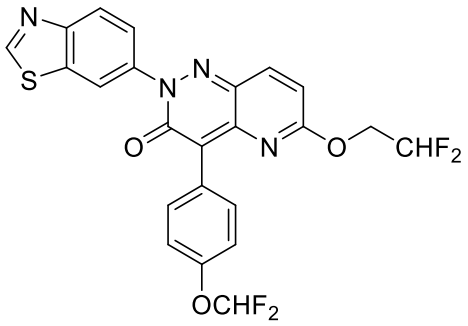
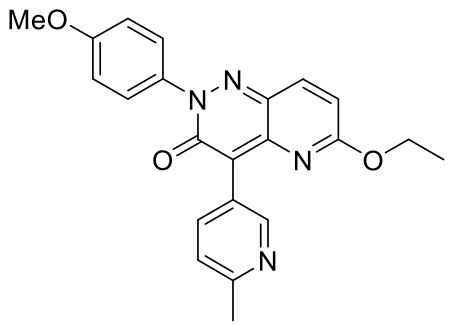
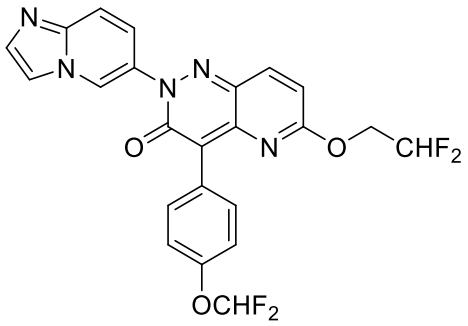
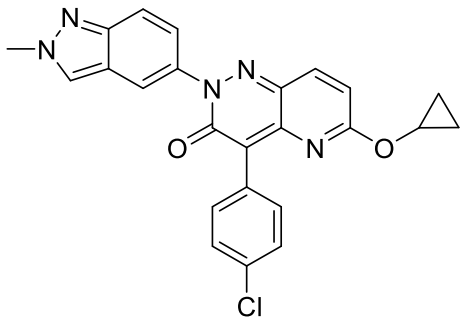
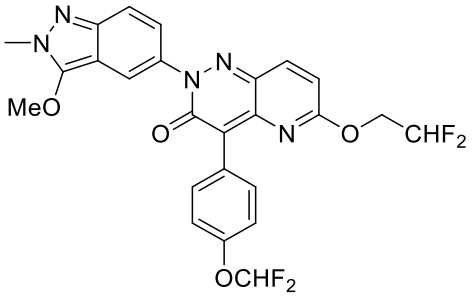
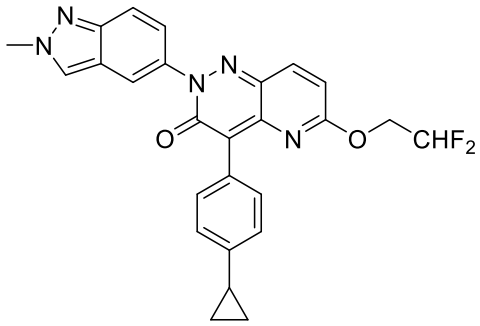
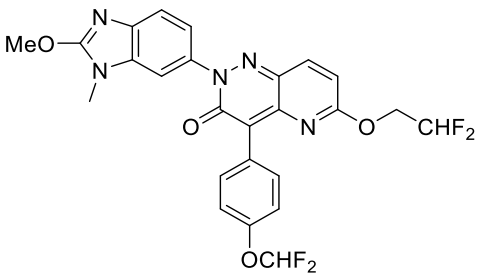
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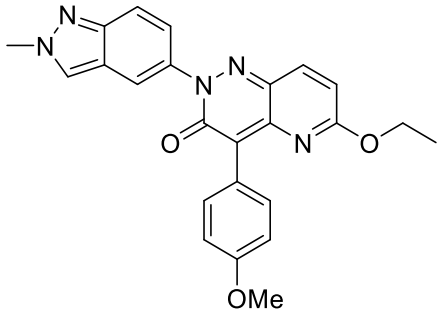
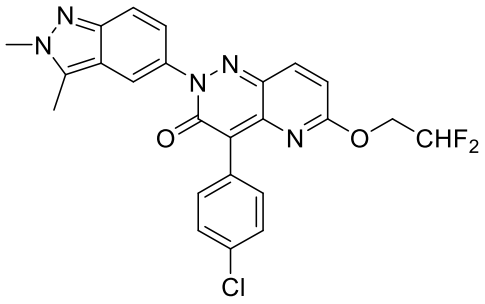
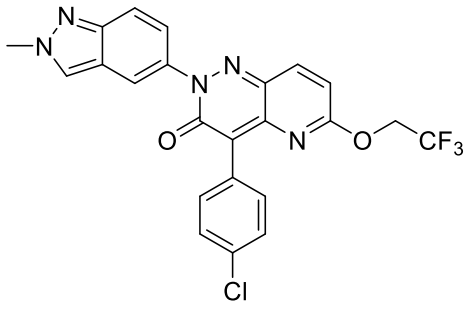
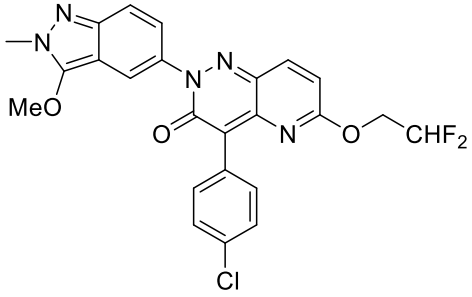
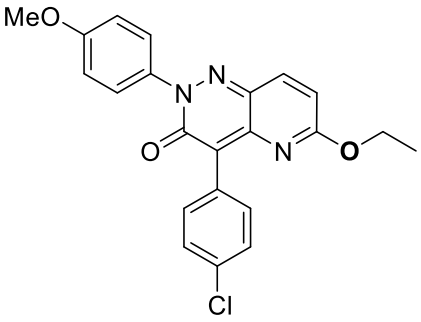
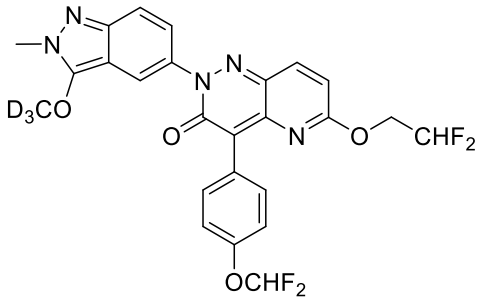
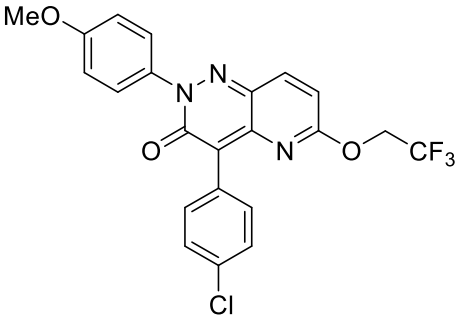
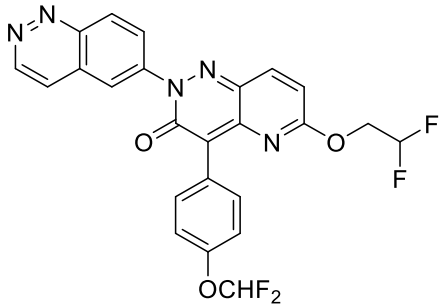
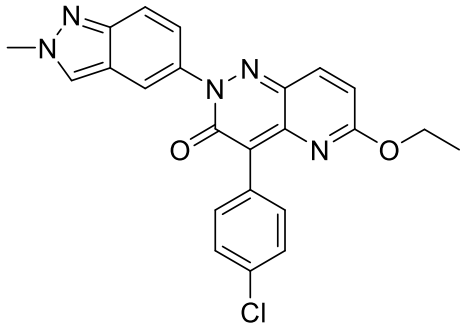
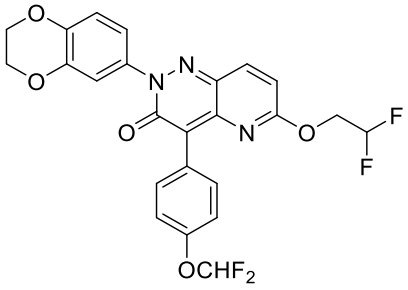
~~23. The compound according to claim 22,~~ wherein L is NR.

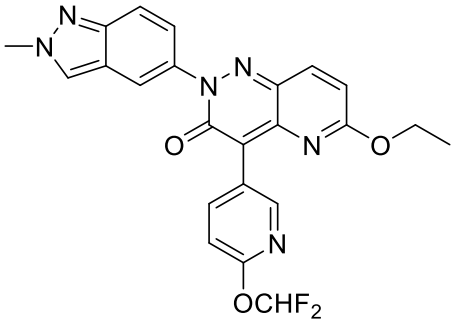
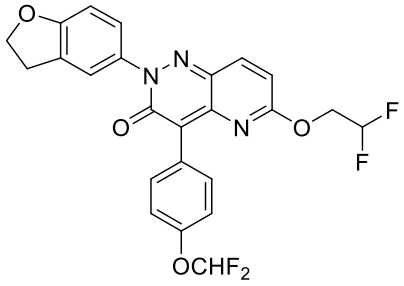
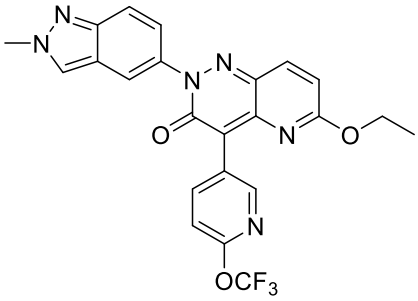
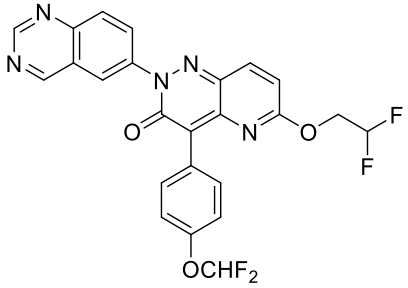
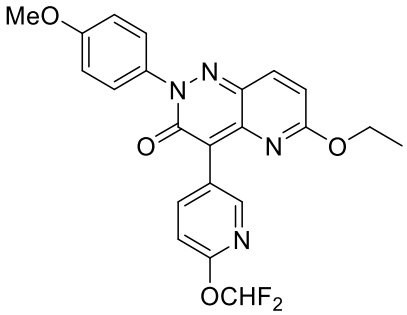
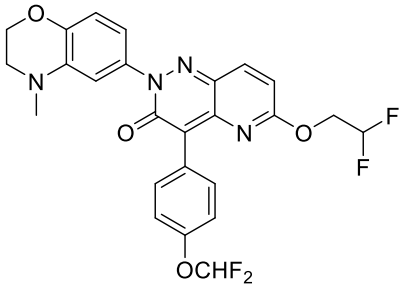
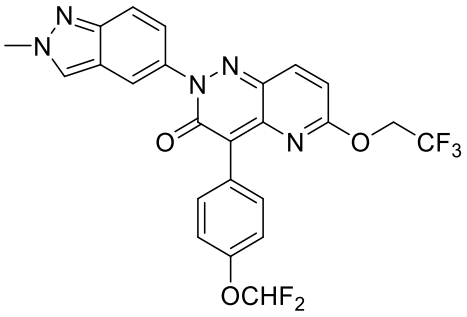
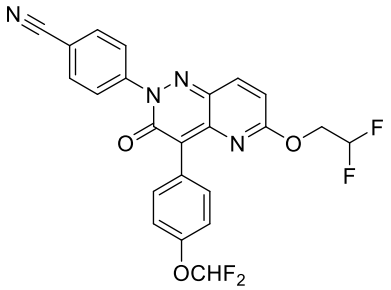
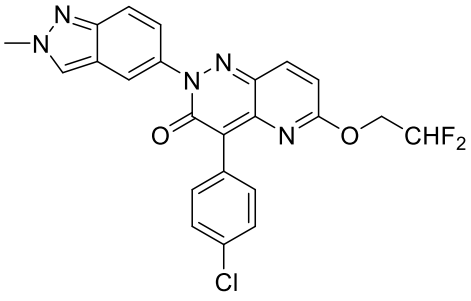
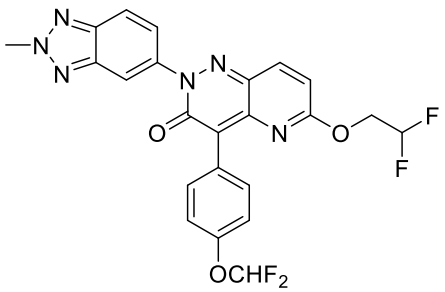
~~24~~9. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:

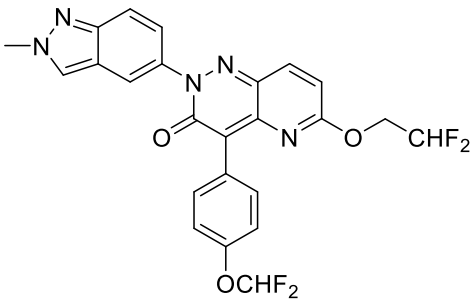
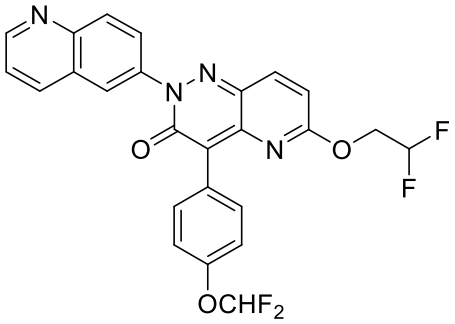
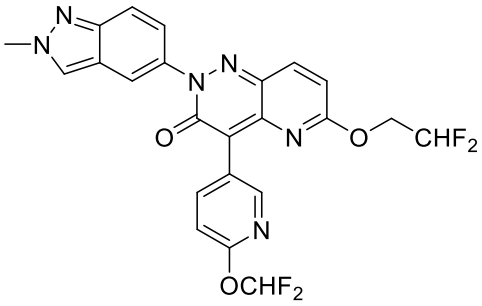
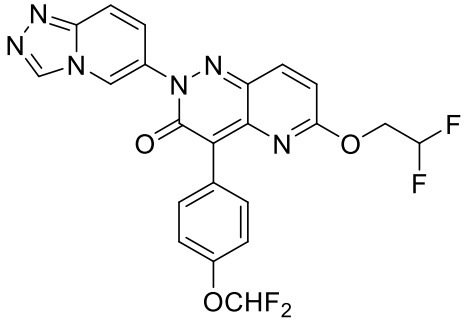
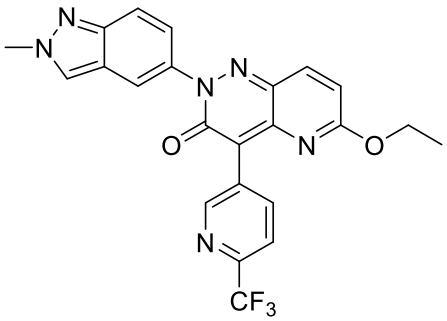
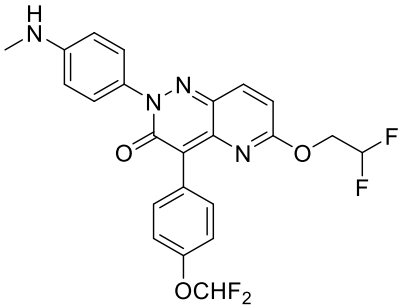
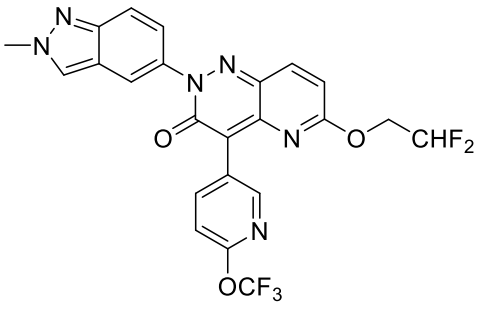
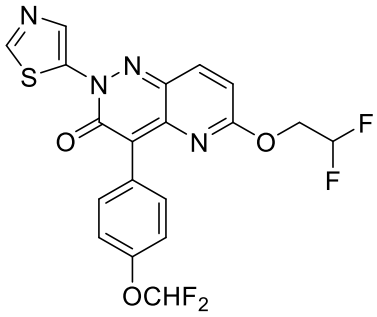
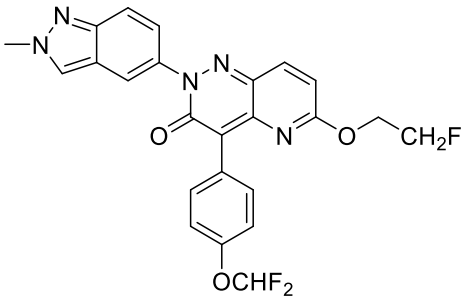
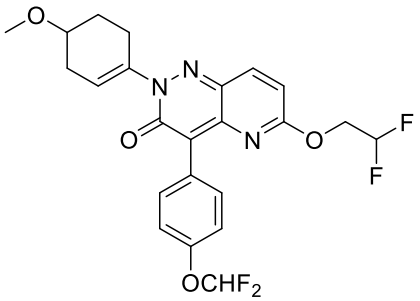
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104		**162**	

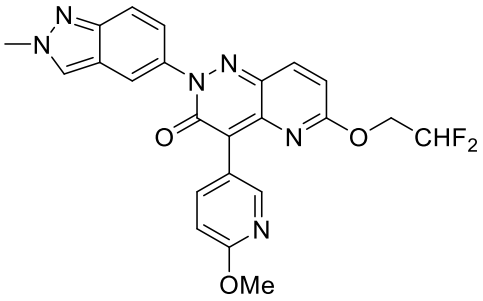
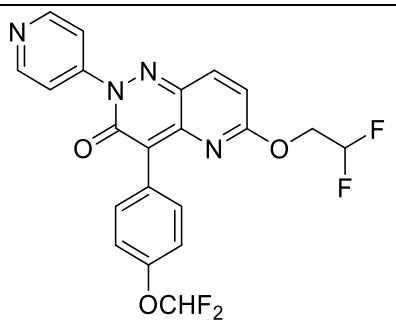
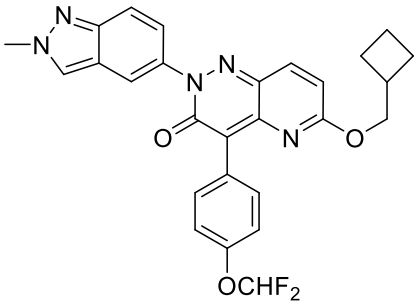
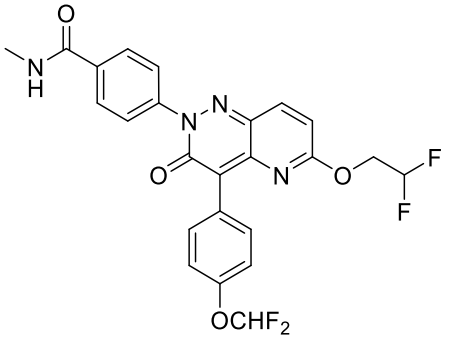
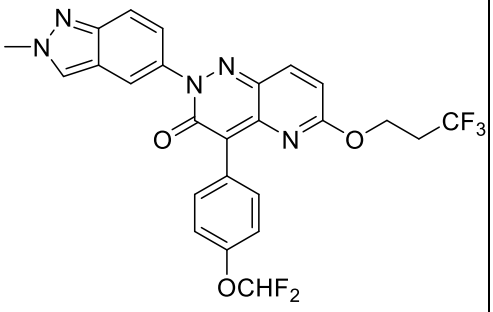
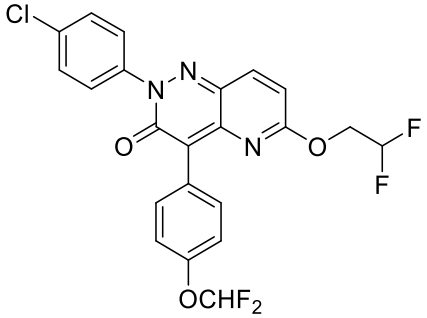
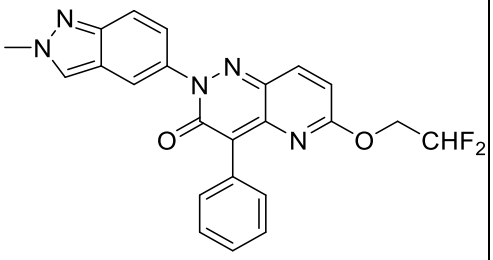
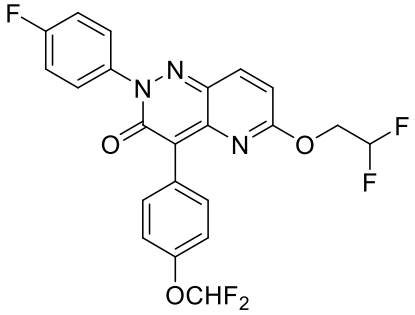
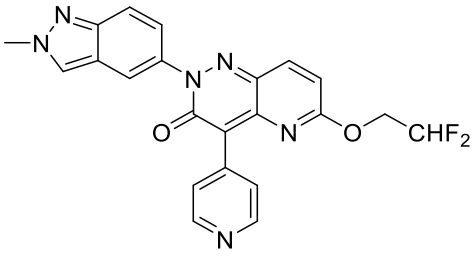
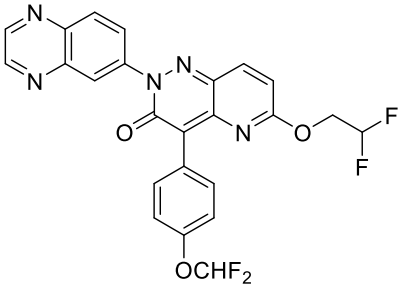
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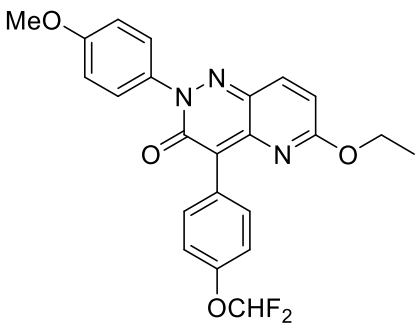
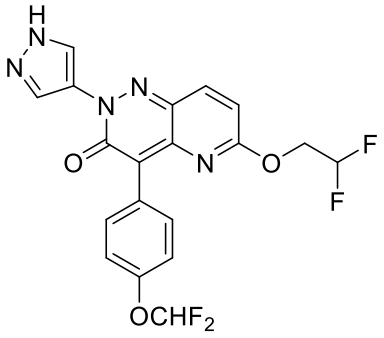
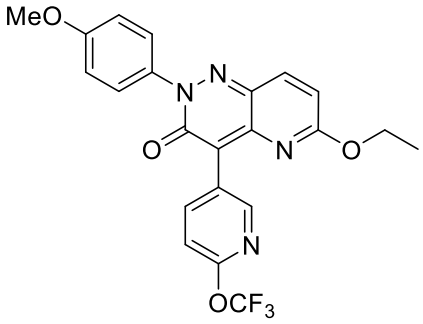
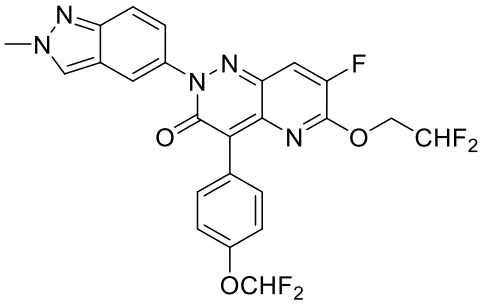
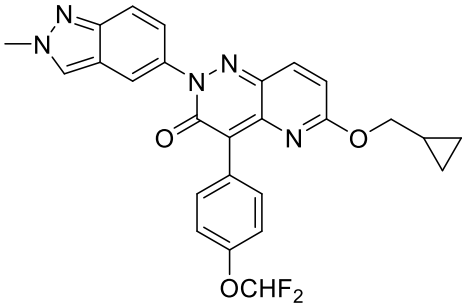
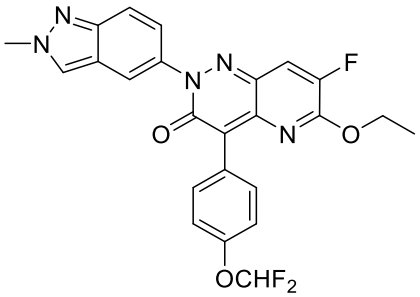
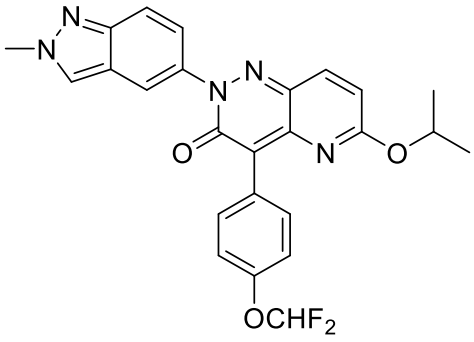
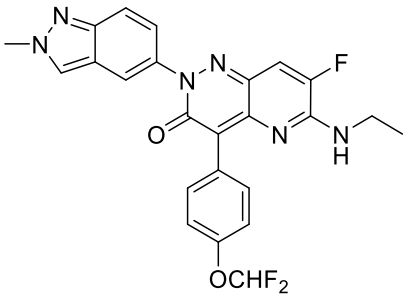
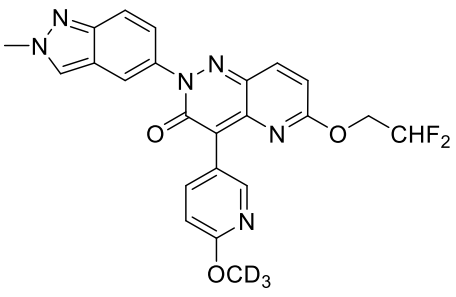
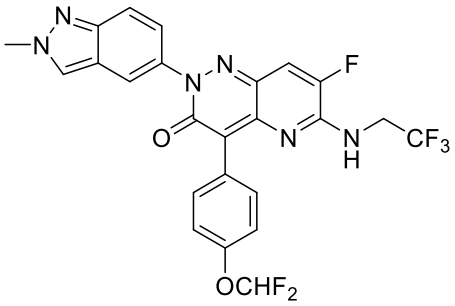
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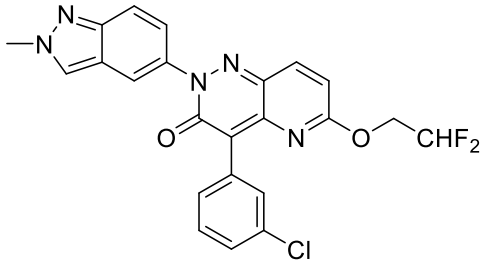
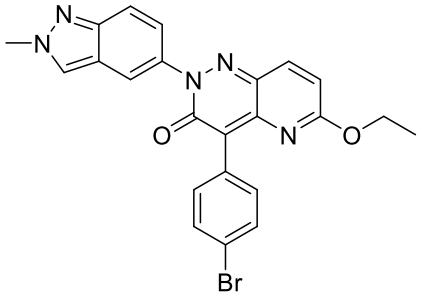
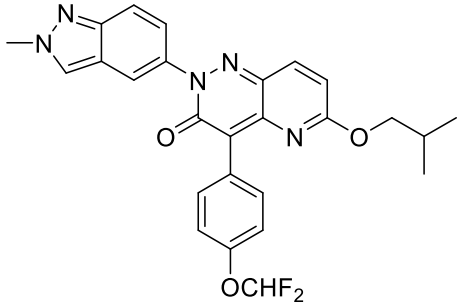
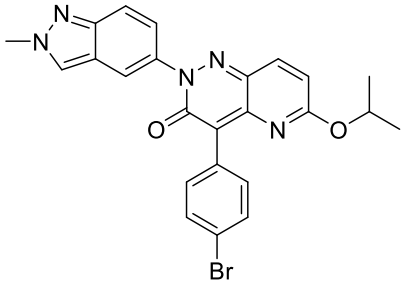
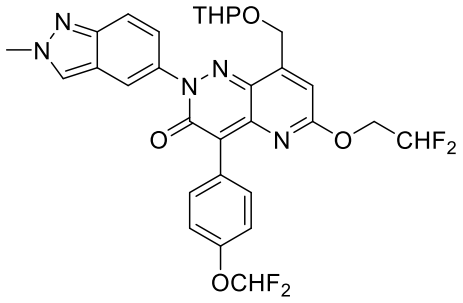
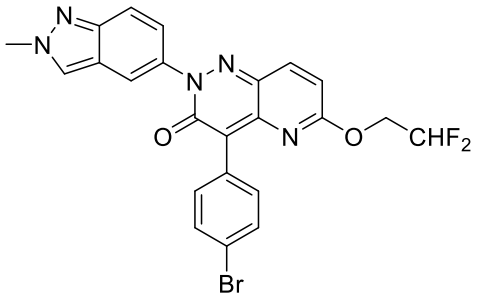
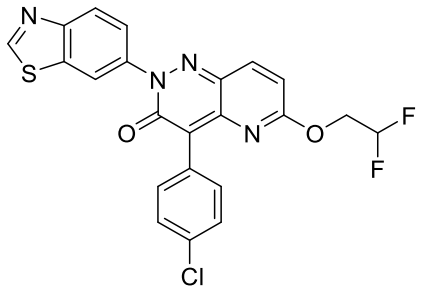
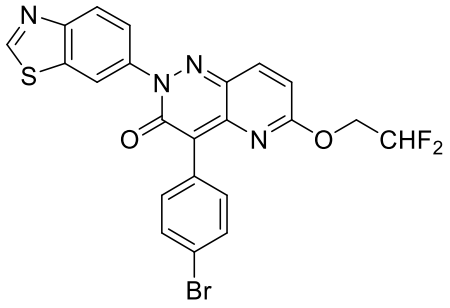
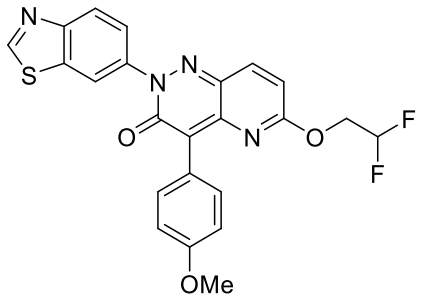
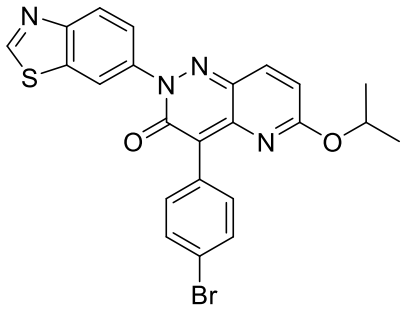
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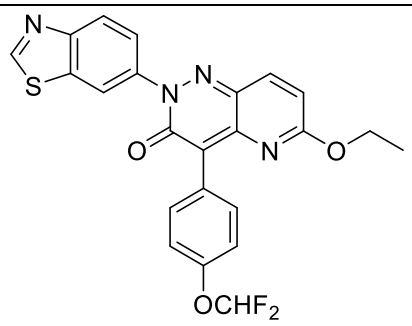
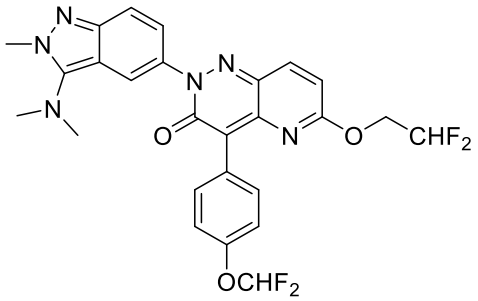
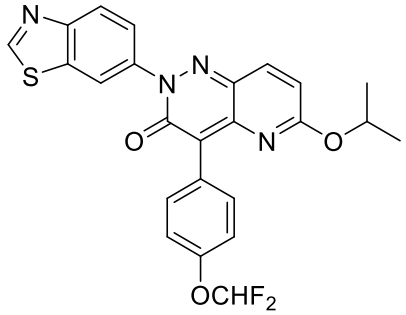
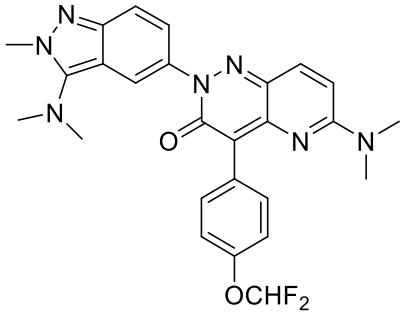
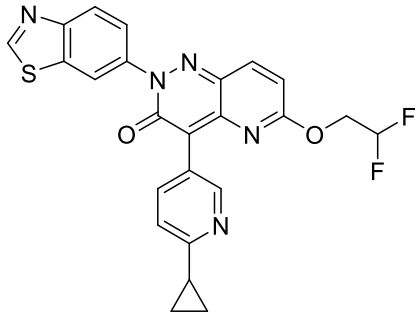
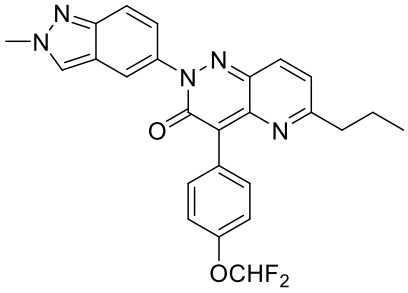
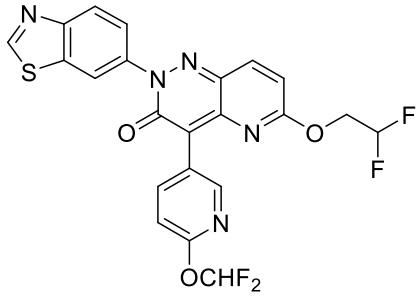
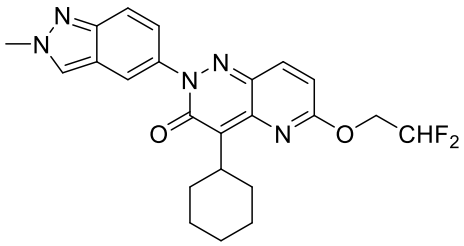
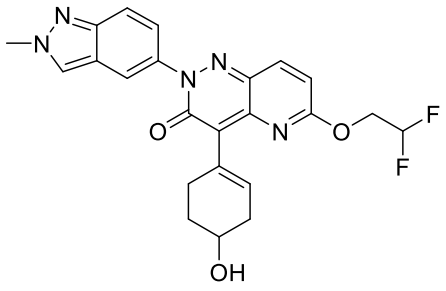
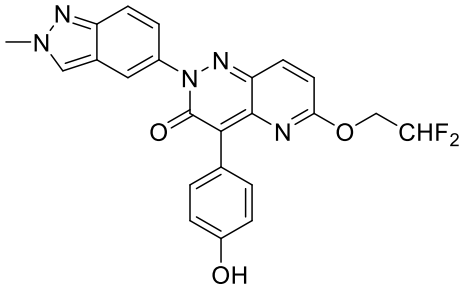
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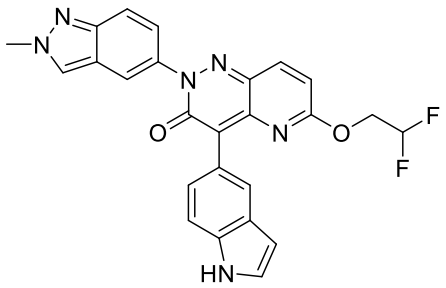
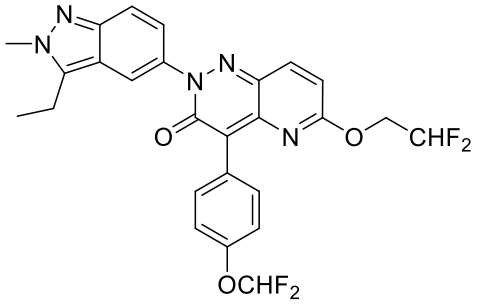
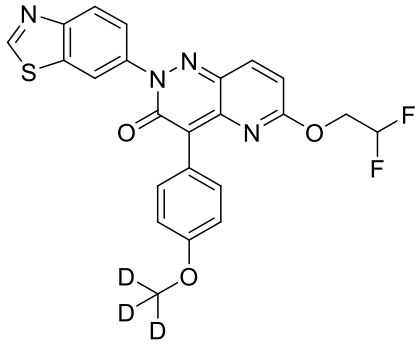
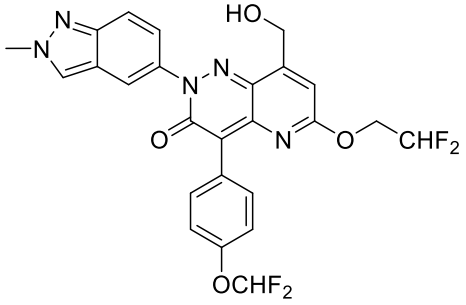
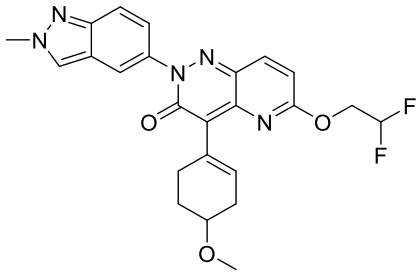
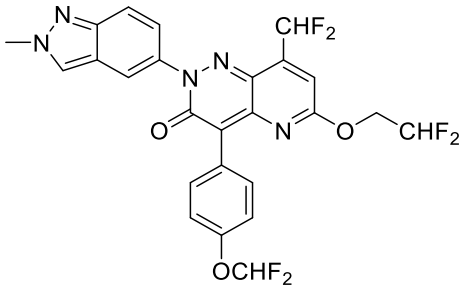
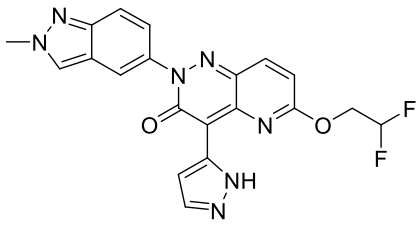
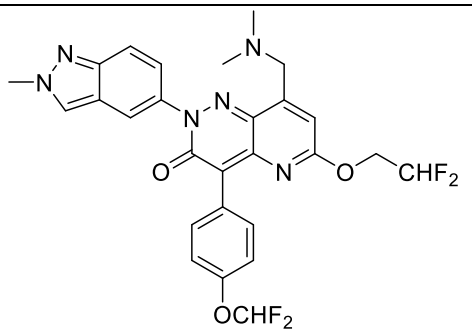
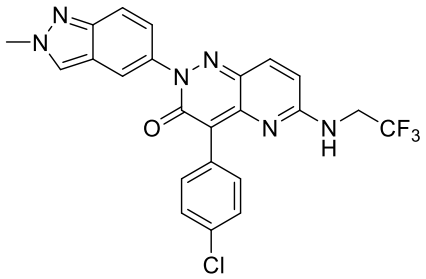
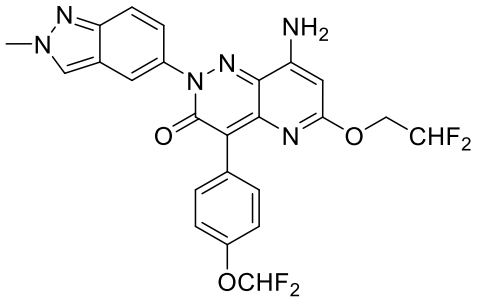
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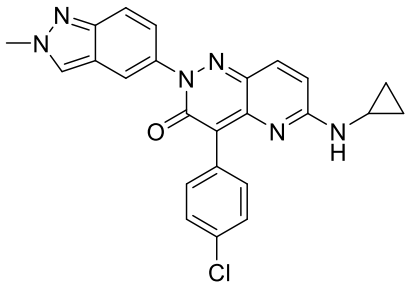
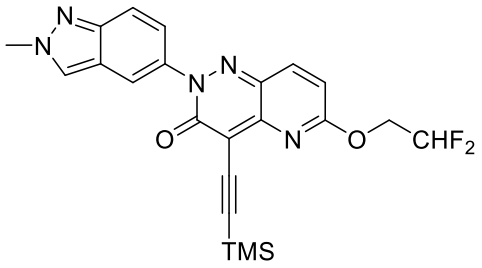
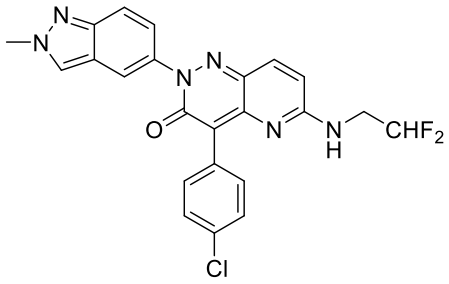
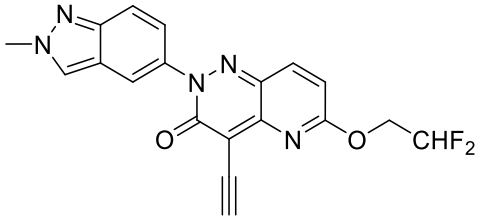
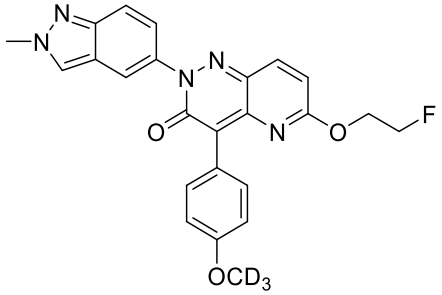
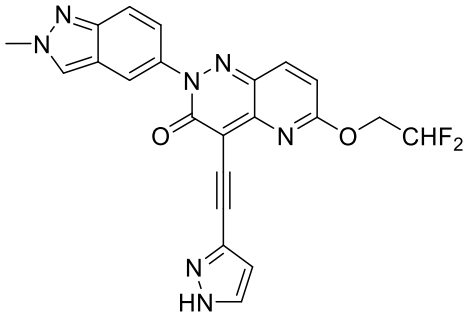
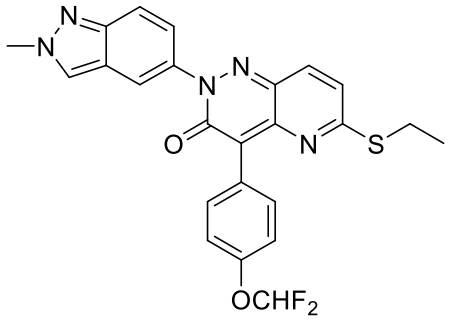
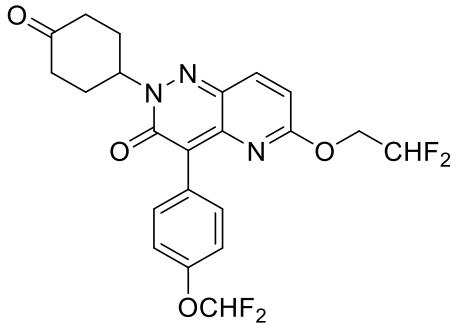
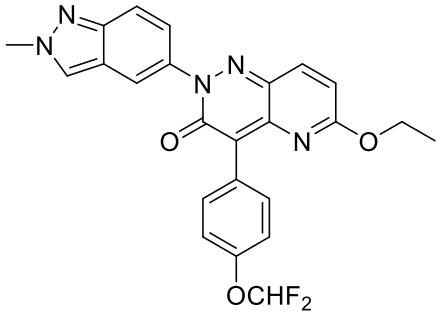
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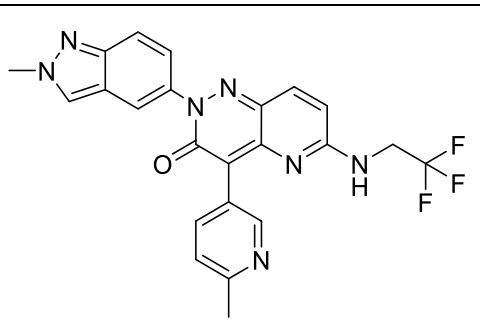
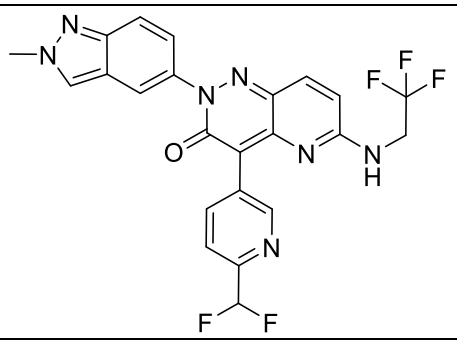
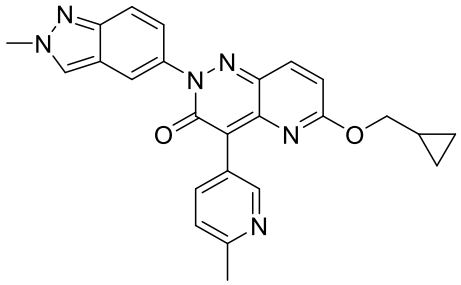
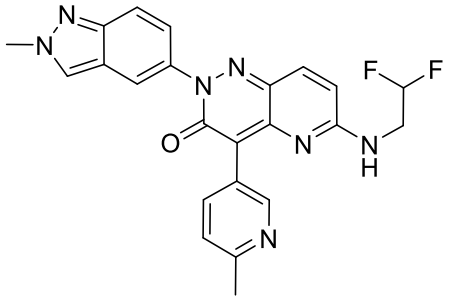
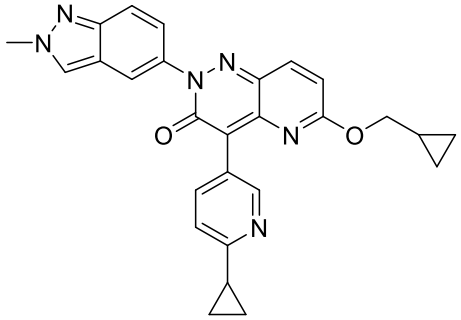
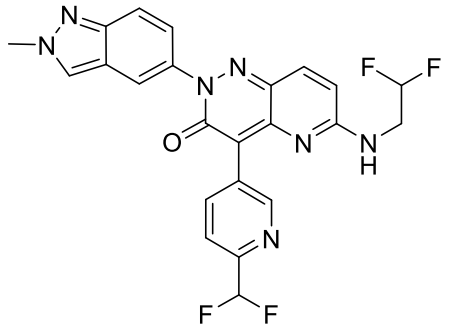
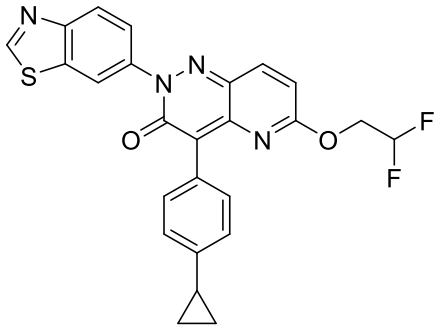
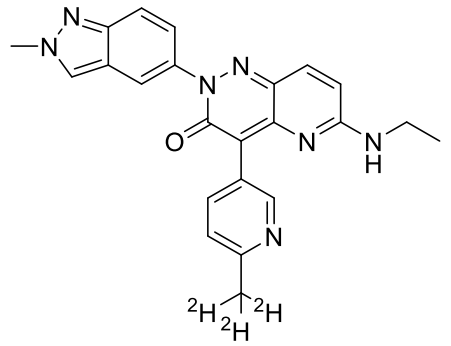
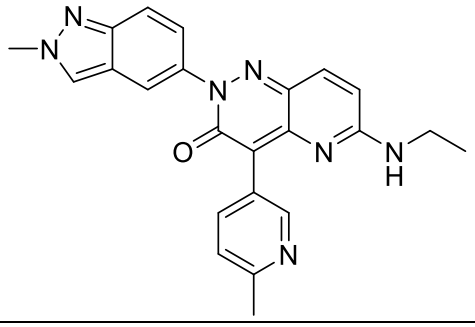
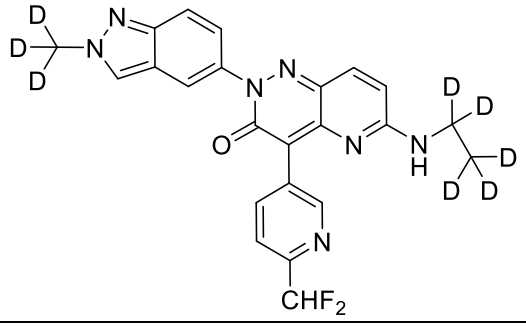
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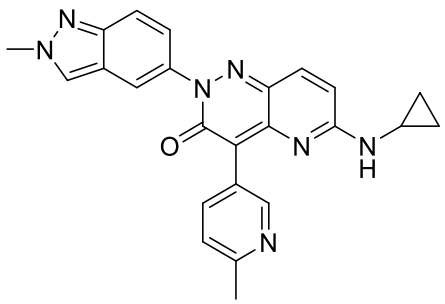
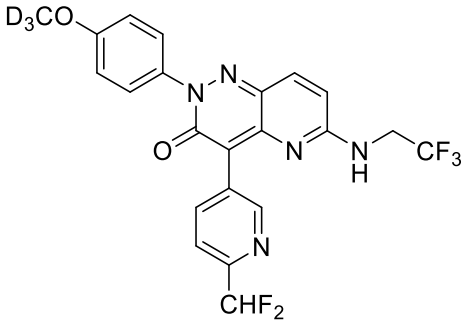
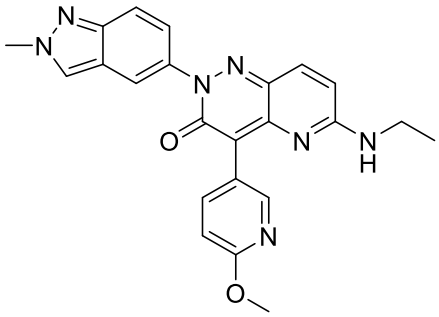
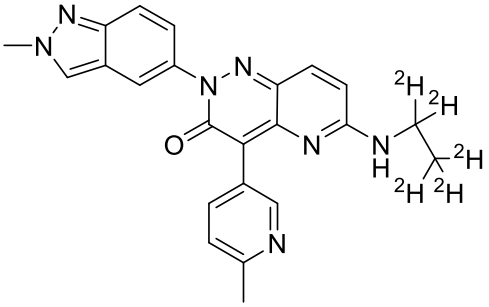
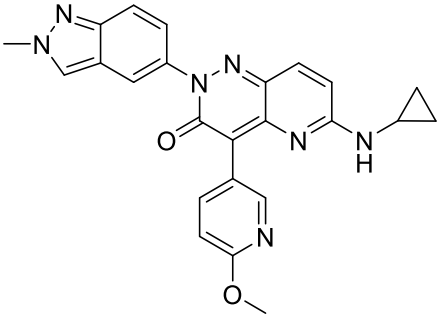
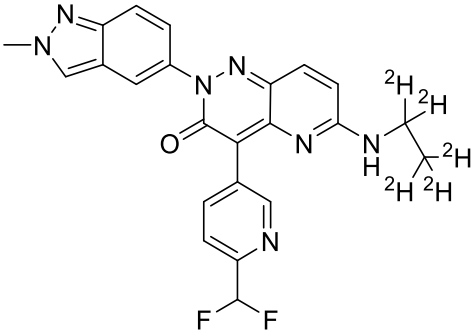
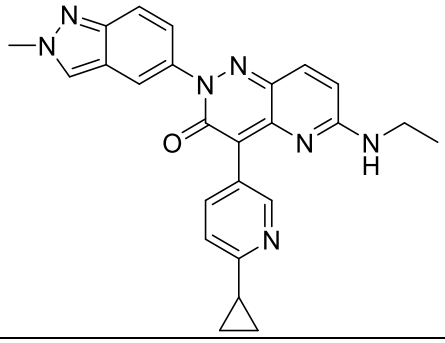
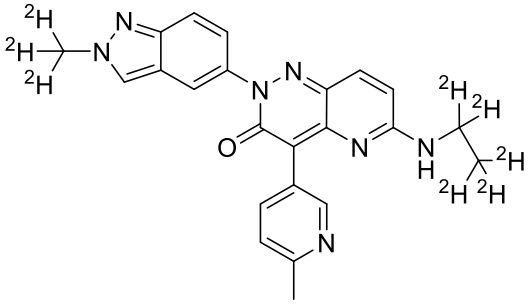
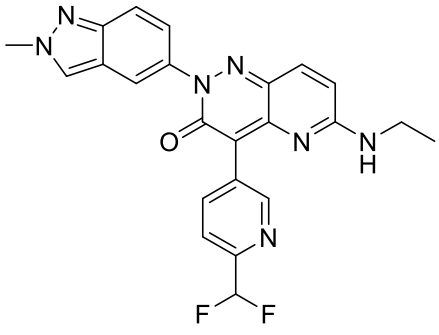
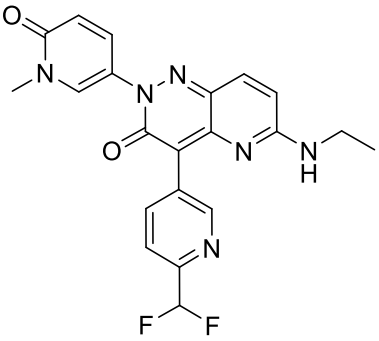
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146		**204**	
147		**205**	
148		**206**	
149		**207**	

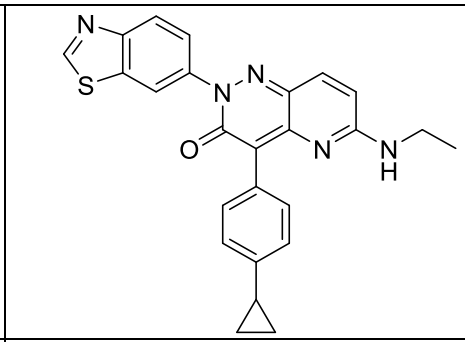
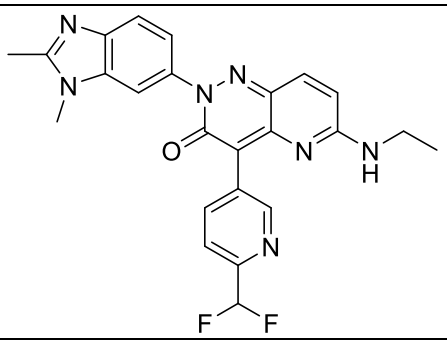
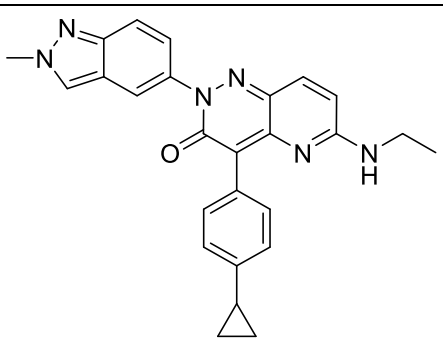
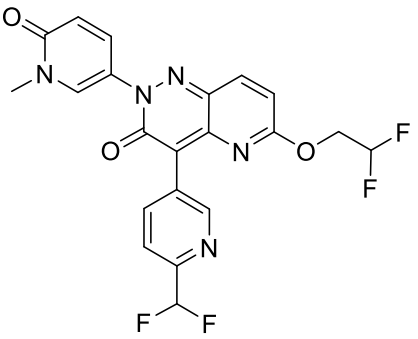
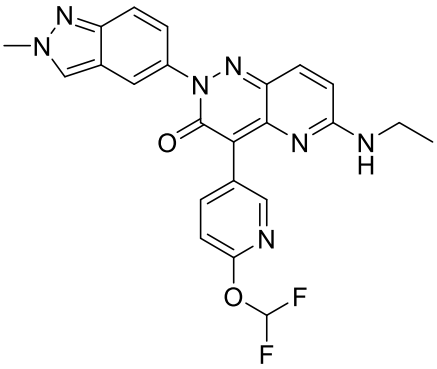
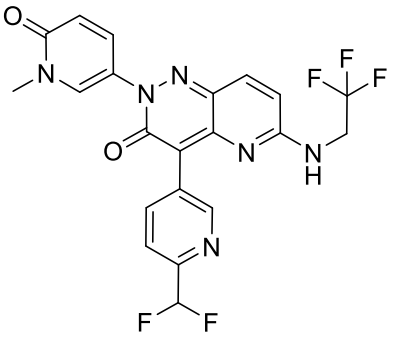
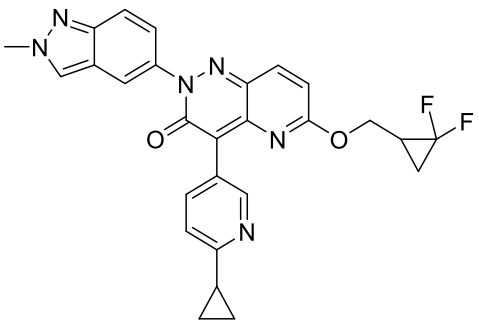
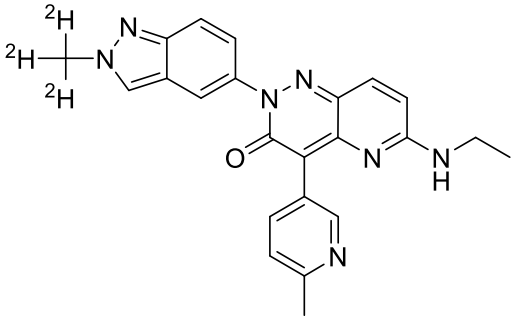
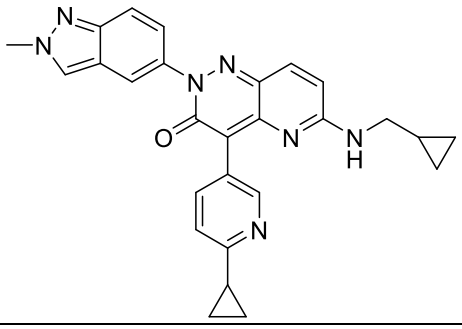
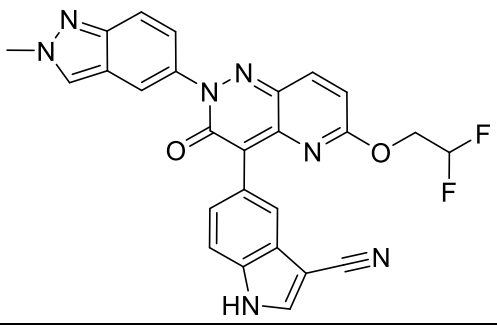
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151		**209**	
152		**210**	
153		**211**	
154		**212**	

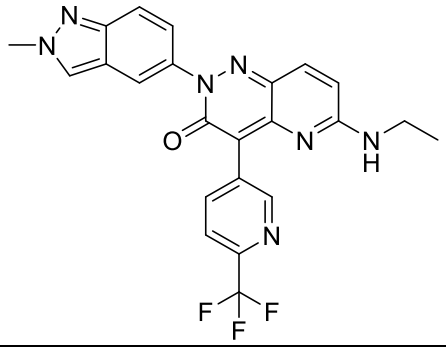
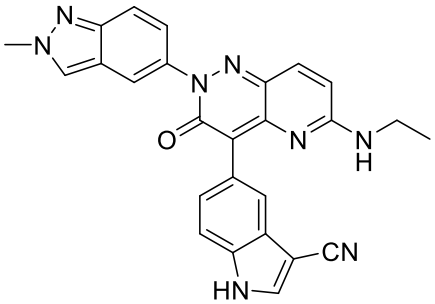
155		**213**	
156		**214**	
157		**215**	
158		**216**	
		217	

~~25. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:~~

301		**317**	
302		**318**	
303		**319**	
304		**320**	
305		**321**	

306		**322**	
307		**323**	
308		**324**	
309		**325**	
310		**326**	

311		**327**	
312		**328**	
313		**329**	
314		**330**	
315		**331**	

316		**332**	

~~26~~10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to ~~9~~25 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~27. A method for treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a MAT2A inhibitor compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 25.~~

~~28. The method according to claim 27, wherein the cancer is an MTAP-deleted cancer.~~

~~29. 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 thereof according to any one of claims 1 to 25.~~

~~30. The method according to claim 29, wherein the cancer is an MTAP-deleted cancer.~~

~~31. The method according to any one of claims 27 to 29, 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.~~

~~32. The method according to claim 29 or 30, 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.~~

~~33. The method according to claim 32, wherein the cancer is a lung cancer 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.~~

~~34. The method according to claim 32, wherein cancer is a brain tumor selected from the group consisting of glioma, glioblastoma, astrocytoma, meningioma, medulloblastoma, peripheral neuroectodermal tumors, and craniopharyngioma.~~

~~35. The method according to claim 32, wherein the cancer is triple negative breast cancer (TNBC).~~

~~36. The method according to claim 32, 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.~~

~~37. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, for use in treating a cancer in a subject suffering therefrom.~~

~~38. The compound according to claim 37, or a pharmaceutically acceptable salt thereof, wherein the cancer is an MTAP-deleted cancer.~~

~~39. The compound according to claim 37 or 38, or a pharmaceutically acceptable salt thereof, 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.~~

~~40. The compound according to claim 37 or 38, or a pharmaceutically acceptable salt thereof, 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.~~

~~41. The compound according to claim 40, or a pharmaceutically acceptable salt thereof, wherein the cancer is a lung cancer 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.~~

~~42. The compound according to claim 40, or a pharmaceutically acceptable salt thereof, wherein the cancer is triple negative breast cancer (TNBC).~~

~~43. The compound according to claim 40, or a pharmaceutically acceptable salt thereof, wherein the cancer is a brain tumor selected from the group consisting of glioma, glioblastoma, astrocytoma, meningioma, medulloblastoma, peripheral neuroectodermal tumors, and craniopharyngioma.~~

~~44. The compound according to any one of claims 37 to 39, or a pharmaceutically acceptable salt thereof, 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 (DLBCL), and adult T-cell leukemia/lymphoma.~~

~~45~~11. Use of a MAT2A inhibitor compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to ~~25~~9, ~~or a pharmaceutically acceptable salt thereof, for~~in the manufacture of a medicament for treating cancer.

~~46~~12. The use according to claim ~~45~~11, ~~or a pharmaceutically acceptable salt thereof,~~ wherein the cancer is an MTAP-deleted cancer.

~~47~~13. The use according to claim ~~45~~ 11 or ~~46~~12, or a pharmaceutically acceptable salt thereof, wherein the cancer is:

(a) an MTAP-deleted cancer; and/or

(b) 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~~.~~; and/or

~~48. The use according to claim 45 or 46, or a pharmaceutically acceptable salt thereof, wherein the cancer is~~ (c) 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~~.~~,

optionally wherein the cancer is:

~~49. The use according to claim 48, 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

~~50. The use according to claim 48, or a pharmaceutically acceptable salt thereof, wherein the cancer is~~(ii) triple negative breast cancer (TNBC)~~.~~; or

~~51. The use according to claim 48, or a pharmaceutically acceptable salt thereof, wherein the cancer is~~(iii) a brain tumor selected from the group consisting of glioma, glioblastoma, astrocytoma, meningioma, medulloblastoma, peripheral neuroectodermal tumors, and craniopharyngioma~~.~~; or

~~52. The use according to claim 48, or a pharmaceutically acceptable salt thereof, wherein the cancer is~~(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.

14. A MAT2A inhibitor compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, for use in therapy.